Conclusion

Embolization of cerebral AVMs was performed with a high degree of safety and a low rate of symptomatic complications in Japan.

Acknowledgements

Conflicts of Interest Disclosure

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Real-world Experience of Carotid Artery Stenting in Japan: Analysis of 7,134 Cases from JR-NET1 and 2 Nationwide Retrospective Multi-center Registries

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Abstract

The present study aimed to demonstrate the "real-world" experiences of carotid artery stenting (CAS) in Japan using Japanese Registry of Neuroendovascular Therapy (JR-NET) 1 and 2, retrospective nationwide multi-center surveillances. JR-NET1 and 2 registries are retrospective surveillances conducted between January 2005 and December 2007 and January 2008 and December 2009, respectively, in Japan regarding neuroendovascular therapy. A total of 7,134 procedures (1,943 for JR-NET1 and 5,191 for JR-NET2) were included in this study and retrieved data were analyzed retrospectively. Treatment results of two surveillance periods were similar. In JR-NET2 registry, total of 5,191 lesions were treated by CAS and 5,008 of 5,191 procedures (96.5%) were performed by the board-certified surgeons of Japanese Society of Neuroendovascular Therapy. The rate of technical success was extremely high (99.99%), and the rate of clinically significant complication was low (3.2%). These results were comparable to a previous large study in Japan. Multivariate logistic analysis revealed that age [odds ratio (OR), 1.04 per year; 95% confidence interval (CI), 1.02–1.07; p = 0.0004], symptomatic lesion (OR, 1.87; 95% CI; p = 0.0004), and the use of closed-cell type stent (OR, 0.58; 95% CT, 0.32–1.00; p = 0.05) were independently associated with clinically significant complications. It was revealed that good clinical results were achieved in patients who underwent CAS in Japan. It is expected that the evolution of devices and increasing experiences of surgeons would lead to further improvement of the clinical results, and further investigation would be required to clarify the optimal treatment strategy and therapeutic efficacy of CAS, especially in symptomatic lesions.

Keywords: carotid artery stenosis, nationwide surveillance, stenting, treatment results

Introduction

Carotid artery stenting (CAS) has been widely accepted as a valuable therapeutic alternative to carotid endarterectomy (CEA) for the treatment of atherosclerotic stenosis of cervical internal carotid artery. In 2005, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial demonstrated that CAS carried a better outcome than CEA in patients with CEA high-risk characteristics.[1] However, the succeeding randomized controlled trials, Symptomatic Severe Carotid Stenosis trial (EVA-3S),[2] Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial,[3] and International Carotid Stenting Study (ICSS)[4] failed to prove the non-inferiority of CAS compared to CEA. Together with these results, the safety and efficacy of CAS compared to CEA still remains questioned, and CEA has been considered to the first-line treatment of carotid stenosis in

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worldwide. On the other hand, CAS was officially approved in Japan in April 2008, and the number of patients undergoing CAS has been increasing because of its less-invasiveness. Carotid revascularization was performed in approximately 7,500–8,500 cases per year in 2007–2009, and CAS is performed nearly 1.5–2 times more often than CEA in Japan.[5] The present study aimed to demonstrate the "real-world" experiences of CAS in Japan using the Japanese Registry of Neuroendovascular Therapy (JR-NET) 1 and 2 retrospective nationwide surveillances.

Materials and Methods

I. Patient population

JR-NET1 and 2 registries are retrospective surveillances conducted between January 2005 and December 2007 and January 2008 and December 2009, respectively, in Japan regarding neuroendovascular therapy. A total of 7,821 procedures of CAS in Japan were registered with JR-NET1 and JR-NET2 registries (2,323 for JR-NET1 and 5,498 for JR-NET2). Among these 7,821 procedures, 687 were excluded, and the remaining 7,134 procedures (1,943 for JR-NET1 and 5,191 for JR-NET2) were included in this study and retrieved data were analyzed retrospectively. The reasons of exclusion from this study were as follows: 66 procedures had undergone CAS not for atherosclerotic carotid stenosis, 261 procedures simultaneously performed other disorders, and the details of 360 procedures were not available. In the present study, we mainly focused and analyzed the data from JR-NET2 because CAS has been officially approved since April 2008 in Japan, and JR-NET2 registry mainly covered this period.

II. Analysis of characteristics of patients and CAS procedures

First, to determine the characteristics and background of patients who underwent CAS, age, gender, CEA high-risk characteristics according to SAPPHIRE trial,[1] presentation of symptoms, and degree of stenosis were analyzed. Next, procedural success, periprocedural antiplatelet use, embolic protection device (EPD) use, the type of stent strut (open-cell or closed-cell), the execution of pre- or post balloon dilatation, and procedure-related complications were analyzed to clarify the current strategy and the treatment results of CAS. Degree of stenosis was measured in accordance with North American Symptomatic Carotid Endarterectomy Trial (NASCET) method.[6] "Procedural success" was defined as the achievement of sufficient dilatation of stenotic site by stent placement. Procedure-related complications

were defined as distal embolism, vascular perforation, arterial dissection, hyperperfusion, acute thrombosis, myocardial infarction, and any other complications occurred within 30 days after procedure that related to the CAS procedure.

III. Clinical evaluation

The modified Rankin Scale (mRS) score of disability was used to evaluate the pre- and postprocedural neurological conditions of the patients. "Morbidity" was defined as worsening of mRS score between onset and at 30 days after CAS procedure, and "clinically significant complication" was defined as any morbidity related to the CAS procedure. "Minor morbidity" was defined as 1 point worsening of mRS score, and "major morbidity" was defined as 2 or more points worsening of mRS score.

IV. Statistical analysis

All quantitative variables are expressed as mean ± standard deviation (SD). The statistical significance of intergroup differences was assessed using the Chi-square test for categorical variables and the Student's t-test for quantitative variables. The retrieved clinical variables were interrogated using univariate and multivariate logistic analysis to identify risk factors for clinically significant complications. P-values less than 0.05 were considered statistically significant. The odds ratio (OR) and 95% confidential interval (CI) were also determined. Commercially available software (JMP 7 for Macintosh; SAS Institute Inc., Cary, North Carolina, USA) was used for all statistical analysis.

Results

I. Baseline characteristics of patients and lesions (JR-NET2)

Among a total of 5,191 CAS procedures included in JRNET-2 registry, 5,008 (96.5%) were performed by the board-certified surgeon of Japanese Society of Neuroendovascular Therapy (JSNT).

Characteristics of patients are shown in Table 1. Total of 5,191 lesions with a mean age of 71.6 ± 7.6 years (range 16–95 years) and a mean degree of stenosis of 78.1 ± 12.5% according to NASCET method were treated by CAS in JR-NET2 surveillance. Among these 5,191 procedures, 4,871 (93.9%) were performed for the patients who scored as good clinical status (mRS 0 to 2 at CAS procedure), and 4,262 (84.4%) were performed for the patients who had CEA high-risk characteristics. Symptomatic lesions were 3,075 (59.3%) and asymptomatic lesions were 2,114 (40.7%). Detailed presentations of treated lesions were as follows: 226 (4.4%) were amaurosis

Table 1 Patient and lesion characteristics (JR-NET2)

Age, mean ± SD	71.6 ± 7.6
Range	16–95
Age ≥ 70 years, n (%)	3,358 (64.7)
mRS 0–2 at procedure	4,871 (93.9)
Male gender, n (%)	4,496 (86.6)
Degree of stenosis, %, mean ± SD	78.1 ± 12.5
CEA high risk characteristics, n (%)	4,262 (84.4)
Presentation, n (%)	
Symptomatic	3,075 (59.3)
Amaurosis fugax	226 (4.4)
TIA	679 (13.1)
Minor completed stroke	1,617 (31.2)
Major stroke	371 (7.1)
Progressing stroke	100 (1.9)
Asymptomatic	2,114 (40.7)

CEA: carotid endarterectomy, JR-NET: Japanese Registry of Neuroendovascular Therapy, mRS: modified Rankin Scale, TIA: transient ischemic attack.

fugax, 679 (13.1%) were transient ischemic attack (TIA), 1,617 (31.2%) were minor completed stroke, 371 (7.1%) were major stroke, and 100 (1.9%) were progressing stroke.

II. Results of CAS and procedure-related complications (JR-NET1 and 2)

The clinical results of CAS in each surveillance period are presented in Table 2. At 30 days after CAS procedure, 1,815 of 1,943 (93.4%) and 4,770 (93.0%) of 5,191 of treated patients scored as mRS 0–2, and 13 (0.7%) and 14 (0.3%) patients died in JR-NET1 and 2, respectively. Procedure-related complications occurred in 174 (9.0%) and 508 (9.8) procedures, and in 58 (3.0%) and 166 (3.2%) the complications were clinically significant. Major morbidity occurred in 32 (1.7%) and 81 (1.6%), and minor morbidity occurred in 18 (0.9%) and 78 (1.5%) after CAS procedure in JR-NET1 and 2, respectively.

III. Details of current CAS procedure in Japan

Table 3A shows the details of current strategy of CAS determined by JR-NET2. Antiplatelet agents were used in 5,093 (99.3%) procedures; dual or triple antiplatelet agents were employed in 4,504 procedures (93.4%). Aspirin was most widely used and Cilostazol or Thienopyridine derivatives (Ticropidine or Clopidogrel) were combined in most cases in this study. Procedural success was achieved in

Table 2 Results of CAS and procedure-related complications (JR-NET1 & 2)

	JR-NET1 (n = 1,943)	JR-NET2 (n = 5,191)
mRS 0–2	1,815 (93.4)	4,770 (93.0)
Any death, n (%)	13 (0.7)	14 (0.3)
Any morbidity, n (%)	106 (5.5)	397 (7.8)
Any procedure related complication, n (%)	174 (9.0)	508 (9.8)
Clinically significant complication, n (%)	58 (3.0)	166 (3.2)
Death	8 (0.4)	7 (0.1)
Major morbidity	32 (1.7)	81 (1.6)
Minor morbidity	18 (0.9)	78 (1.5)

CAS: carotid artery stenting, mRS: modified Rankin Scale, JR-NET: Japanese Registry of Neuroendovascular Therapy.

Table 3A Details of current CAS procedure in Japan (JR-NET2)

Antiplatelet use, n (%)	5,093 (99.3)
Dual/Triple antiplatelet	4,504 (93.4)
Aspirin	4,349 (90.2)
Ticropidine/Clopidogrel	2,315 (48.0)
Cilostazol	3,046 (63.2)
Technical characteristics, n (%)	
Procedural success	5,186 (99.99)
EPD use	5,161 (99.6)
Distal filter	2,683 (52.1)
Distal balloon	1,972 (38.3)
Proximal/combined protection	492 (9.5)
Stents	
Open-cell type	4,373 (84.5)
Closed-cell type	762 (14.7)
Combined	14 (0.3)

CAS: carotid artery stenting, EPD: embolic protection device, JR-NET: Japanese Registry of Neuroendovascular Therapy.

5,186 (99.99%) procedures. Most procedures (5,161 procedures, 99.6%) were performed using EPDs, and used EPDs were as follows: 2,683 (52.1%) with distal filter protection device; 1,972 (38.3%) with distal balloon protection; and 492 (9.5%) with proximal or combined protection. Open-cell type stent was used in 4,373 (84.5%) procedures, and closed-cell type stent was used in 762 (14.7%) procedures.

Table 3B shows the comparison of technical characteristics between asymptomatic and symptomatic

Table 3B Comparison of technical characteristics between symptomatic and asymptomatic lesions (JR-NET2)

Variables	Asymptomatic (n = 2,114)	Symptomatic (n = 3,075)	p value
Dual/Triple antiplatelet use, n (%)	1,840 (93.4)	2,664 (93.4)	0.95
Aspirin	1,792 (90.1)	2,557 (86.7)	0.15
Ticlopidine/ Clopidogrel	960 (48.7)	1,355 (47.5)	0.41
Cilostazol	1,217 (61.8)	1,829 (64.2)	0.09
Technical characteristics, n (%)			
Distal filter protection	1,220 (58.2)	1,462 (47.9)	< 0.0001
Distal balloon protection	743 (35.4)	1,229 (40.2)	< 0.001
Proximal/ combined protection	132 (6.3)	360 (11.8)	< 0.0001
Stents			
Closed-cell type	295 (14.0)	482 (15.8)	0.08
Clinically significant complication	42 (2.0)	124 (4.1)	< 0.0001

JR-NET: Japanese Registry of Neuroendovascular Therapy.

lesions. Distal filter protection was less frequently used in symptomatic lesions than asymptomatic lesions (47.9% vs. 58.2%, p < 0.0001). Instead, distal balloon protection was more frequently used in symptomatic lesions than asymptomatic lesions (40.2% vs. 35.4%, p < 0.001). Furthermore, proximal/combined protection was used about two times frequency in symptomatic lesions (11.8% vs. 6.3%, p < 0.0001). The rate of clinically significant complication was significantly higher in symptomatic lesions than those of asymptomartic lesions (4.1% vs. 2.0%, p < 0.0001).

IV. Risk factors for clinically significant complications following CAS

Clinically significant complication related to CAS occurred in 166 (3.2%) procedures in JR-NET2. Age (OR, 1.05 per year; 95% CI, 1.02–1.07; p < 0.0001) and symptomatic lesion (OR, 2.05; 95% CI, 1.45–2.90; p < 0.0001) were determined as risk factors for clinically significant complications by univariate logistic analysis. Multivariate analysis showed that age (OR, 1.04 per year; 95% CI, 1.02–1.07; p = 0.0004), symptomatic lesion (OR, 1.87; 95% CI, 1.31–2.71; p = 0.0004), and the use of closed-cell stent (OR, 0.58; 95% CI, 0.32–1.00; p = 0.05) were independently associated with clinically significant

Table 4 Risk factors for clinically significant complication related to CAS procedure (JR-NET2)

Variables	Significant complication (n = 166)	Univariate analysis		Multivariate analysis	
	mean ± SD or n (%)	OR [95% CI]	P value	OR [95% CI]	P value
Age, years	73.8 ± 6.2	1.05 [1.02–1.07]	< 0.0001*	1.04 [1.02–1.07]	0.0004*
Male gender	145 (87.4)	0.93 [0.57–1.45]	0.77	0.86 [0.51–1.39]	0.56
Symptomatic lesion	124 (74.7)	2.05 [1.45–2.90]	<0.0001*	1.87 [1.31–2.71]	0.0004*
Degree of stenosis, %	77.6 ± 13.0	1.00 [0.98–1.01]	0.64	0.99 [0.98–1.01]	0.46
Antiplatelet use	165 (100)	–	0.63	–	
Dual/triple antiplatelet	149 (91.4)	0.74 [0.44–1.36]	0.31	0.86 [0.36–2.17]	0.75
Aspirin	145 (89.0)	0.87 [0.54–1.49]	0.60	0.98 [0.46–2.14]	0.96
Ticropidine/Clopidogrel	73 (44.8)	0.88 [0.64–1.20]	0.41	0.85 [0.46–1.49]	0.59
Cilostazol	104 (63.8)	1.02 [0.75–1.43]	0.86	1.01 [0.54–1.81]	0.98
EPD use	164 (98.8)	0.32 [0.09–1.21]	0.14	–	
Distal filter protection	88 (54.3)	1.10 [0.81–1.51]	0.54	0.97 [0.67–1.41]	0.85
Proximal/combined protection	14 (8.6)	0.89 [0.49–1.50]	0.68	0.58 [0.27–1.10]	0.10
Predilatation	140 (84.9)	1.08 [0.71–1.65]	0.83	1.12 [0.70–1.89]	0.64
Postdilatation	151 (91.5)	0.97 [0.56–1.66]	0.89	1.15 [0.62–2.37]	0.68
Closed-cell stent	17 (10.4)	0.64 [0.37–1.04]	0.07	0.58 [0.32–1.00]	0.05*

*indicates statistical significance. CAS: carotid artery stenting, CI: confidence interval, EPD: embolic protection device, JR-NET: Japanese Registry of Neuroendovascular Therapy, OR: odds ratio, SD: standard deviation.

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Table 5A Risk factors for clinically significant complications in symptomatic lesions (JR-NET 2)

Variables	Univariate analysis		Multivariate analysis	
	OR [95% CI]	P value	OR [95% CI]	P value
Age, years	1.05 [1.02–1.08]	0.0002*	1.04 [1.02–1.08]	0.0008*
Male gender	0.90 [0.55–1.11]	0.69	1.02 [0.56–1.73]	0.95
Acute intervention (within 14 days)	1.63 [1.02–2.51]	0.04*	1.69 [1.02–2.70]	0.04*
Degree of stenosis, %	1.00 [0.99–1.01]	0.95	0.99 [0.97–1.00]	0.13
Dual/Triple antiplatelet	0.77 [0.42–1.69]	0.46	1.58 [0.54–5.13]	0.42
Aspirin	0.81 [0.48–1.46]	0.46	0.72 [0.30–1.81]	0.47
Ticropidine/Clopidogrel	0.86 [0.59–1.17]	0.41	0.73 [0.34–1.43]	0.37
Cilostazol	1.05 [0.72–1.55]	0.79	0.85 [0.40–1.74]	0.67
EPD use	0.15 [0.04–1.00]	0.05	–	
Distal filter protection	1.14 [0.79–1.65]	0.49	0.97 [0.63–1.53]	0.91
Proximal/combined protection	0.90 [0.47–1.56]	0.73	0.64 [0.29–1.29]	0.22
Predilatation	1.47 [0.85–2.76]	0.17	2.41 [1.22–5.34]	0.01*
Postdilatation	1.02 [0.57–2.03]	0.95	1.69 [0.74–4.85]	0.23
Closed-cell stent	0.68 [0.37–1.16]	0.16	0.66 [0.33–1.22]	0.19

*indicates statistical significance. EPD: embolic protection device, JR-NET: Japanese Registry of Neuroendovascular Therapy, OR: odds ratio, CI: confidence interval.

complication (Table 4).

V. Risk factors for clinically significant complications in asymptomatic and symptomatic lesions

Table 5A demonstrates the risk factors for clinically significant complications in symptomatic lesions. Age (OR, 1.05 per year; 95% CI, 1.02–1.08; p = 0.0002) and acute intervention (within 14 days after symptom onset) (OR, 1.63; 95% CI, 1.02–2.51; p = 0.04) were determined as risk factors for clinically significant complications by univariate logstic analysis. In multivariate analysis, age (OR, 1.04 per year; 95% CI, 1.02–1.08; p = 0.0008), acute intervention (OR, 1.69; 95% CI, 1.02–2.70; p = 0.04), and performing predilatation (OR, 2.41; 95% CI, 1.22–3.54; p = 0.01) were determined as independent risk factors for clinically significant complication. On the other hand, in asymptomatic lesions, any variables were not estimated as the significant risk factors for clinically significant complication (Table 5B).

Discussion

In the present study, we demonstrated the current strategy and the treatment results of CAS in Japan. From these results, it was considered that almost all procedures were conducted in accordance with current recommendation guidelines, and that the

Table 5B Risk factors for clinically significant complications in asymptomatic lesions (JR-NET2)

Variables	OR [95% CI]	P value
Age, years	1.02 [0.98–1.08]	0.23
Male gender	0.48 [0.11–1.35]	0.18
Degree of stenosis, %	0.99 [0.96–1.01]	0.35
Dual antiplatelet	0.66 [0.26–5.42]	0.46
Aspirin	1.30 [0.47–1.49]	0.65
Ticropidine/Clopidogrel	0.96 [0.51–1.77]	0.88
Cilostazol	0.91 [0.49–1.72]	0.76
EPD use	–	0.5
Distal filter protection	1.31 [0.70–2.53]	0.4
Proximal/combined protection	0.36 [0.02–1.67]	0.23
Predilatation	0.56 [0.29–1.15]	0.11
Postdilatation	0.97 [0.34–4.06]	0.96
Closed-cell stent	0.46 [0.11–1.29]	0.16

CI: confidence interval, EPD: embolic protection device, JR-NET: Japanese Registry of Neuroendovascular Therapy, OR: odds ratio.

rates of technical success (99.99%) and clinically significant complication (approximately 3%) were good ones. We thought that there were several reasons leading to these favorable results of CAS in Japan.

First, it was proved that almost all cases of CAS (5,008/5,191; 96.5%) were performed by board-certified surgeons of JSNT. There is no doubt that adequate training and experience of surgeons is an important factor to maintain the quality and the treatment results of CAS, and this issue has been discussed in many reports following the results of the European randomized controlled trials (RCTs).[7] In Japan, the training and experiences of CAS is strictly regulated by the concerned societies, and sectional seminars and society-oriented continuing education are frequently held to educate surgeons not only about technical aspects, but also about periorerative management.[5] These systems would certainly contribute to improve the rate of technical success without perioperarive complications.

Second, it was suggested that Japanese CAS surgeons selected optimal strategy for each case, especially in protection methods, in accordance with preoperative risk evaluation. One of the major concerns associated with CAS is the potential of embolic infarction during the procedure. Plaque components of stenotic site, especially lipid core and intraplaque hemorrhage is associated with an increasing number of embolic infarction after CAS.[8] In most Japanese institutions, the patients who elected CAS routinely underwent plaque imaging by magnetic resonance imaging (MRI) and/or carotid ultrasound to predict the potential of embolic infarction.[9–11] In JR-NET2 registry, distal filter protection device were most widely used (52.1%) because distal filter protection device (Angioguard XP; Cordis/Johnson & Johnson, Miami, Florida, USA) was the only EPD which was officially approved for carotid use in the latter half of JR-NET2 surveillance period (between April 2008 and December 2009). However, distal filter protection systems have some limitations owing to its structure.[5] It has been considered that distal balloon protection is more effective for debris collection without leakage through the occlusion site.[12] Moreover, it was reported that proximal protection resulted in a significant reduction in the incidence and volume of new ischemic lesion during CAS compared to distal filter protection.[13] Based on these data and risk evaluation, Japanese CAS surgeons more frequently used proximal or combined protection system in symptomatic lesions than in asymptomatic lesions (11.8% vs. 6.3%, p < 0.001) in spite of limitation of available devices. In the present study, it was demonstrated that use of closed-cell type stent significantly reduced the rate of clinically significant complications. Recently, similar results were reported by Park, et al.; ischemic lesions detected by diffusion-weighted MR imaging were more frequent in the open-cell stent than in the

closed-cell stent.[14] These results also indicated the importance of optimal therapeutic strategy in order to reduce the rate of perioperative complication. After this surveillance periods, several different EPDs (distal balloon protection and proximal protection devices) or stents were approved in succession. It is expected that the introduction of new devices would lead to further improvement of the clinical results of CAS.

The rate of clinically significant complication (approximately 3%) in this study period was comparable to another Japanese large study,[5] and this rate was considered as a good one. Similar to the above-mentioned report, the rate of clinically significant complications was significantly higher in symptomatic lesions than those of asymptomatic lesions (4.2% vs. 2.0%, p < 0.0001). In the symptomatic lesions, age and acute intervention (within 2 weeks after symptom onset) were determined as the significant risk factors for clinically significant complications. It has been reported that the timing of intervention influences the benefit in patients with symptomatic carotid stenosis, and CEA surgery was most effective when performed within the first 2 weeks after symptom onset.[15] On the other hand, the ideal timing of CAS in the symptomatic lesions still remains unclear. Recent study showed that the patients with symptomatic carotid stenosis treated with CAS within 7 days after onset had remarkably higher risk of periprocedural stroke or death compared to the similar patients treated with CEA (9.4% vs. 2.8%, respectively).[16] Our results also demonstrated the risk of early CAS within 2 weeks after symptoms (OR, 1.69; 95% CI, 1.02–2.70; p = 0.04). Interestingly, performing predilatation was determined as one of the independent risk factor for clinically significant complication in symptomatic lesions (OR, 2.41; 95% CI, 1.22–3.54; p = 0.01). Although cerebral embolism may occur throughout the procedure, it has been still controversial as to which part of procedure most frequently causes the embolism. One previous study reported that the highest embolic loads occurred during predilatation.[17] However, another study indicated that most embolsm were produced by postdilatation.[18] Further investigations would be necessary to determine the optimal timing and the procedural strategy in patients with symptomatic carotid stenosis.

In contrast, in asymptomatic lesions, the rate of clinically significant complications was low (2.0%), and no significant risk factors for clinically significant complications were identified. These data confirmed that CAS is a beneficial therapeutic alternative to CEA in patients with asymptomatic carotid stenosis, as previously described.[5,19]

This study includes several limitations. This study was conducted in a retrospective way. The treatment strategy, the determination of complications, and the outcome measurements were independently made by each interventional team. Further investigation with standardized treatment protocol and clinical evaluation are required to clarify the optimal treatment strategy and therapeutic efficacy of CAS.

Conclusion

We demonstrated the current strategy and the therapeutic results of CAS in Japan. Relatively favorable clinical results were obtained because of tailor-made strategy based on perioperative risk evaluation. It is expected that the evolution of devices and increasing experiences of surgeons would lead to further improvement of the clinical results, and further investigation would be required to clarify the optimal treatment strategy and therapeutic efficacy of CAS, especially in symptomatic lesions.

Acknowledgments

Conflicts of Interest Disclosure

All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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

Japanese Registry of Neuroendovascular Therapy: Extracranial Steno-occlusive Diseases except for Internal Carotid Artery Stenosis

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Abstract

Although utilization of endovascular treatment of extracranial steno-occlusive lesions except for internal carotid artery stenosis continues to increase, there is no consensus regarding the natural course and standard treatment of these lesions. The aim of this study was to characterize the utility of endovascular treatment for extracranial steno-occlusive lesions except for internal carotid artery stenosis. A total of 1249 procedures for extracranial steno-occlusive lesions were identified from the Japanese Registry of Neuroendovascular Therapy (JR-NET) and JR-NET2. Excluding the cases of carotid lesions (290 cases), endovascular procedures were performed for 471 (37.7%) subclavian artery stenoses, 404 (32.3%) extracranial vertebral artery stenoses, and 38 (3.0%) innominate artery stenoses with a technical success rate of 97.2%. A stent was placed for 783 lesions and percutaneous transluminal angioplasty was performed for 183 lesions. Forty complications were reported in this cohort. Among these, ischemic complications were the most frequent (12 cases). Comparison between JR-NET1 and JR-NET2 demonstrated a marked increase in the number of procedures, a change in the utilization of antiplatelet therapy, and an increased rate of favorable outcome. We conclude that the endovascular treatment for extracranial steno-occlusive lesions is relatively safe. Continuous efforts should be made to reduce the complication rate, and further trials are needed to validate the beneficial effect of this procedure.

Key words: Japanese Registry of Neuroendovascular Therapy (JR-NET), subclavian artery stenosis, vertebral artery stenosis, stent

Introduction

Stenosis and occlusion of the extracranial subclavian and vertebral arteries are frequent findings among patients who undergo cerebrovascular imaging.[1,2] While there is no clear consensus on the natural course and best management of these lesions, recent reports have demonstrated that these lesions can cause vertebrobasilar ischemic events.[3,4] Recent advancements in medical therapy and endovascular devices have resulted in an increased utilization of these modalities for the management of extracranial steno-occlusive lesions.[5,6] The aim of this study was to characterize the utility of endovascular treatment for extracranial steno-occlusive lesions except for internal carotid artery stenosis in Japan.

Methods

The database of the Japanese Registry of Neuroendovascular Therapy (JR-NET) and the Japanese Registry of Neuroendovascular Therapy 2 (JR-NET2) were used
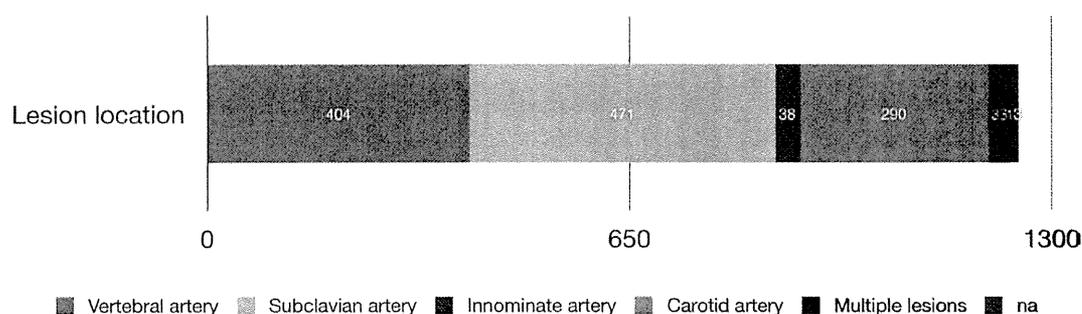
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Fig. 1 Distribution of lesion that was treated among patients registered with Japanese Registry of Neuroendo-vascular Therapy (JR-NET) and JR-NET2. na: not available.

to identify the patients. All patients who underwent endovascular procedures performed by the Japanese Society of Neuroendovascular therapy specialists from January 2005 to December 2006 (JR-NET) and from January 2007 to December 2009 (JR-NET2) were included in these registries. Patients who had extracranial steno-occlusive diseases except for internal carotid artery stenosis were extracted from these registries and analyzed. Patient demographics, procedural parameters, and 30-day outcomes were investigated. Favorable outcome was defined as a modified Rankin Scale (mRS) score of 0 or 1 at 30 days after the procedure. Statistical analyses were performed using the R version 2.15.1 software package (R Core Team, 2012; Foundation for Statistical Computing, Vienna, Austria; ISBN 3-900051-07-0; URL: http://www.R-project.org/). The chi-square test was used to compare categorical variables between groups. A value of $p < 0.05$ was considered to indicate statistical significance.

Results

I. General review

A total of 1477 percutaneous transluminal angioplasty (PTA) or stenting procedures for extracranial steno-occlusive lesions (except for internal carotid artery stenosis) were identified from JR-NET and JR-NET2 (660 procedures in JR-NET and 817 procedures in JR-NET2). Among these cases, detailed information was available for 442 JR-NET patients and 807 JR-NET2 patients. These 1249 cases were subjected to subsequent analysis. In this cohort, there were 471 (37.7%) cases of subclavian artery stenosis, 38 (3.0%) cases of innominate artery stenosis, 404 (32.3%) cases of extracranial vertebral artery stenosis, and 290 (23.2%) cases of carotid artery stenosis (Fig. 1). We excluded cases of carotid artery stenosis because this group might
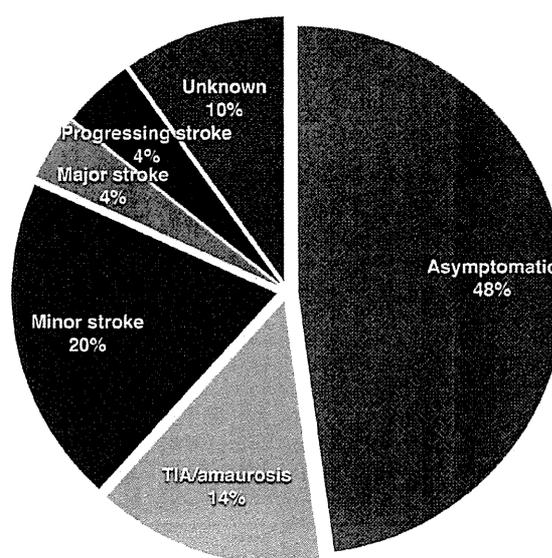
Fig. 2 Symptoms of the patients harboring extracranial stenoses (vertebral artery, subclavian artery, and innominate artery lesions) at presentation. TIA: transient ischemic attack.

share common characteristics with internal carotid artery stenosis. As a result, 959 cases were subjected to the later analysis. The technical success rate was 97.2% (324 cases in JR-NET and 608 cases in JR-NET2). Periprocedural complications were documented in 4.2% (20 cases in JR-NET and 20 cases in JR-NET2).

II. Detailed analysis

Patient characteristics: In JR-NET and JR-NET2, a total of 900 patients (93.8%) had atherosclerotic lesions. A total of 19 patients (2.0%) were treated for lesions associated with aortitis and 12 patients

(1.3%) were treated for dissections related to iatrogenic, traumatic, or idiopathic causes. Half of these cases were asymptomatic (459 cases, 47.9%) while the remaining had minor stroke (192 cases, 20.0%) and transient ischemic attack including amaurosis fugax (133 cases, 13.9%) (Fig. 2). Timing of the treatment was available only for patients registered with JR-NET2; symptomatic cases were treated within 24 h in 12 cases (4.0%); within 14 days in 49 cases (18.0%); and at more than 15 days after the events in 214 cases (78.0%). The degree of stenosis was documented as 100% (occluded) in 82 cases (8.6%), 70–99% in 728 cases (75.9%), and 50–69% in 121 cases (12.6%).

Procedures: Stenting was attempted for 783 lesions. The PTA alone was attempted for 183 lesions. Protection against distal embolism was used in 334 cases (34.8%). In this group, distal balloon protection was used in 287 procedures (85.9%). Other protection was used in 44 procedures (16 procedures in JR-NET and 28 procedures in JR-NET2). The details of the "other protection method" were available only for patients registered with JR-NET2. Distal filter protection was used in 17 procedures (7.7%), and proximal protection was used in 6 procedures (2.7%). A total of 775 stents were placed. In this stented group, poststenting dilatation was performed in 455 procedures (59.3%). The stents used in JR-NET were balloon expandable in 141 cases (53.4%), self-expandable/closed cell in 14 cases (5.3%), self-expandable/open cell in 37 cases (14.0%), and coronary stents in 62 cases (23.5%). In JR-NET2, an open-cell stent was used in 317 cases (62.0%), and a closed-cell stent was used in 159 cases (29.0%). More detailed information regarding

stent characteristics was not available for patients registered with JR-NET2.

Antithrombotics: Anticoagulants were administered postoperatively in 468 cases (48.0%). The anticoagulant was argatroban in 306 cases (54.4%) and heparin in 256 cases (45.6%). Antiplatelets were administered preoperatively in 921 cases for both before and after procedures. Single antiplatelet therapy was administered in 134 cases (14.5%), dual antiplatelet therapy was administered in 683 cases (74.2%), and triple antiplatelet therapy was administered in 36 cases (3.9%) preoperatively. The number of antiplatelet agents was not significantly different when comparing patients preoperatively vs. postoperatively (p = 0.317). The preoperative combination of antiplatelets most frequently employed was aspirin and thienopyridine (443 cases, 48.1%) followed by aspirin and cilostazol (210 cases, 22.8%). Details of the antiplatelet use are included in Fig. 3.

Outcomes: The mRS of 959 patients at 30 days after treatment was 0 in 660 patients (69.5%), 1 in 159 patients (16.7%), 2 in 69 patients (7.3%), 3 in 46 patients (4.8%), 4 in 11 patients (1.2%), 5 in 2 patients (0.2%), and 6 in 3 patients (0.3%). The overall outcome was good (mRS 0–1) in 85.4% of the patients. The mRS did not differ significantly between the preoperative and postoperative assessments (p = 0.128). Death occurred in three cases; one of them [a case of vertebral artery (VA) stenosis in JR-NET] was deemed as possibly related to the procedure. The mRS deteriorated after the procedures by more than 2 points in 22 patients (2.3%, Fig. 4A).

Complications: A total of 40 complications were documented (4.2%). The most common complication
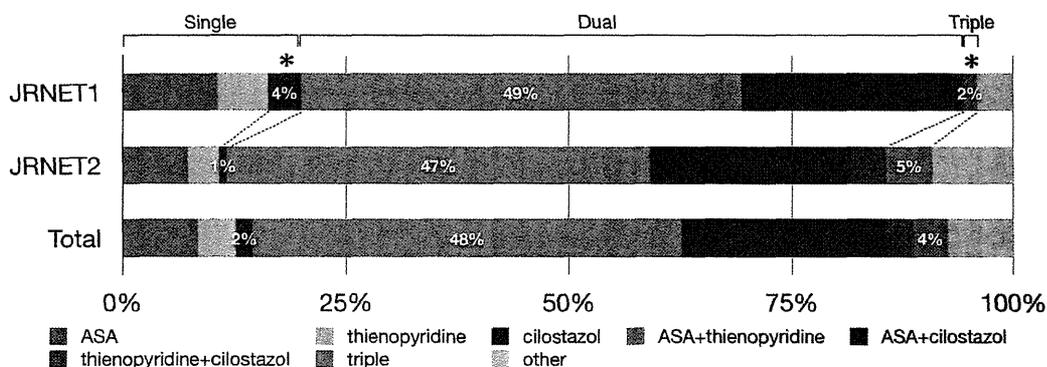

Fig. 3   Number and kinds of antiplatelets administered preoperatively. Asterisks indicate the items showing significant changes between Japanese Registry of Neuroendovascular Therapy (JR-NET) and JR-NET2. ASA: aspirin, triple: triple antiplatelet therapy.
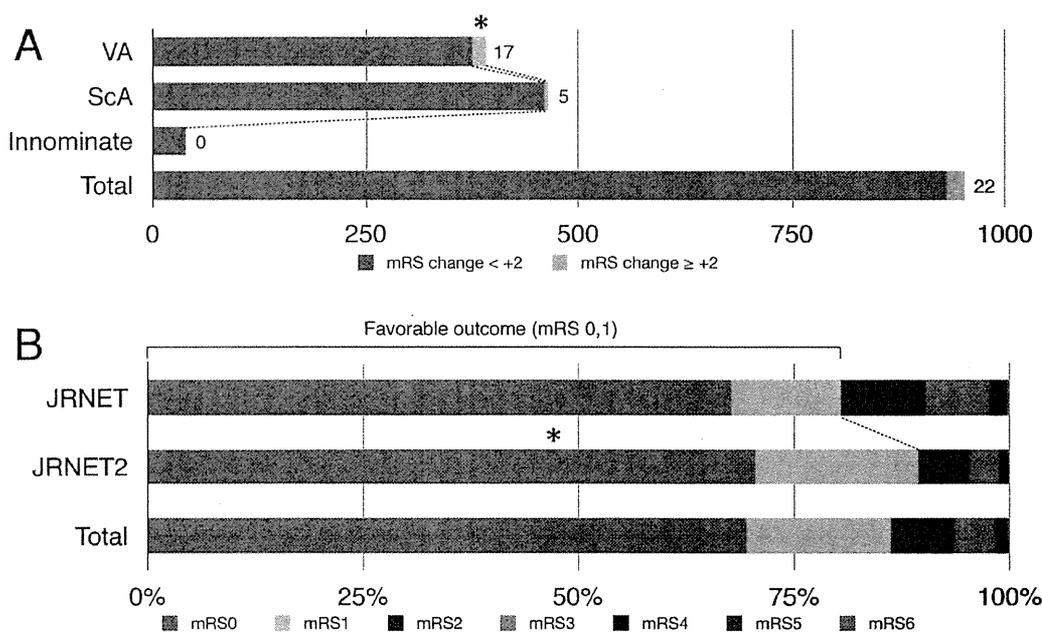
Fig. 4 A: Modified Rankin Scale (mRS) change after procedure in each location. The number of patients whose mRS deteriorated more than two points is shown. Significantly larger number of patients deteriorated postoperatively in VA stenosis (*asterisk*). B: Postoperative mRS in Japanese Registry of Neuroendovascular Therapy (JR-NET) and JR-NET2. Asterisks indicate the item showing significant change between JR-NET and JR-NET2. VA: vertebral artery, ScA: subclavian artery, innominate: innominate artery.

was distal embolism (12 cases, 30.0%) followed by vessel dissection (10 cases, 25.0%). Details regarding these complications were available only for patients registered with JR-NET2. In JR-NET2, complications occurred during the procedure in 12 cases (60.0%) and occurred within 24h postoperatively in 7 cases (35.0%). Although most patients (13 of 20 cases, 65.0%) experiencing complications were treated conservatively, endovascular treatment (three cases of subclavian artery stenosis, one case of VA stenosis, one case of innominate artery stenosis) or direct surgery (one case of subclavian artery stenosis) was needed for some patients. Morbidity (including transient symptoms, 19 patients) and mortality (3 patients) related to the procedure were calculated as 2.0% and 0.3%, respectively.

III. Differences according to the location of the lesion

Comparison between groups of patients (VA stenosis, subclavian artery stenosis, and innominate artery stenosis) revealed a significant effect of the lesion location in several survey items. Aortitis as a cause of steno-occlusive lesion was seen more frequently in innominate artery (0.2% in VA stenosis, 2.1% in subclavian artery stenosis, and 13.2% in innomi-

nate artery stenosis, $p < 0.001$). In the group of VA stenosis, more patients have minor or major stroke than in the group of subclavian or innominate stenosis ($p < 0.001$, Fig. 5A). Revascularization for chronic total occlusion was performed more frequently in the group of subclavian artery stenosis (0.5% in VA stenosis, 15.9% in subclavian artery stenosis, and 5.3% in innominate artery stenosis, $p < 0.001$). Protection against distal embolism was performed more frequently in the group of innominate artery stenosis ($p < 0.001$, Fig. 5B). The mRS deteriorated more frequently after the revascularization for VA stenosis ($p < 0.001$). There was no apparent effect of lesion location in other survey items.

IV. Comparison between JR-NET and JR-NET2

The number of registered cases of extracranial PTA or stenting was markedly higher in JR-NET2 (622 cases) than in JR-NET (337 cases). The distribution of lesion sites treated in JR-NET and JR-NET2 was not significantly different ($p = 0.151$). For procedures, the number of patients who received preoperative antiplatelets did not differ significantly ($p = 0.275$). The type and combination of antiplatelet agents used was significantly different when comparing the two
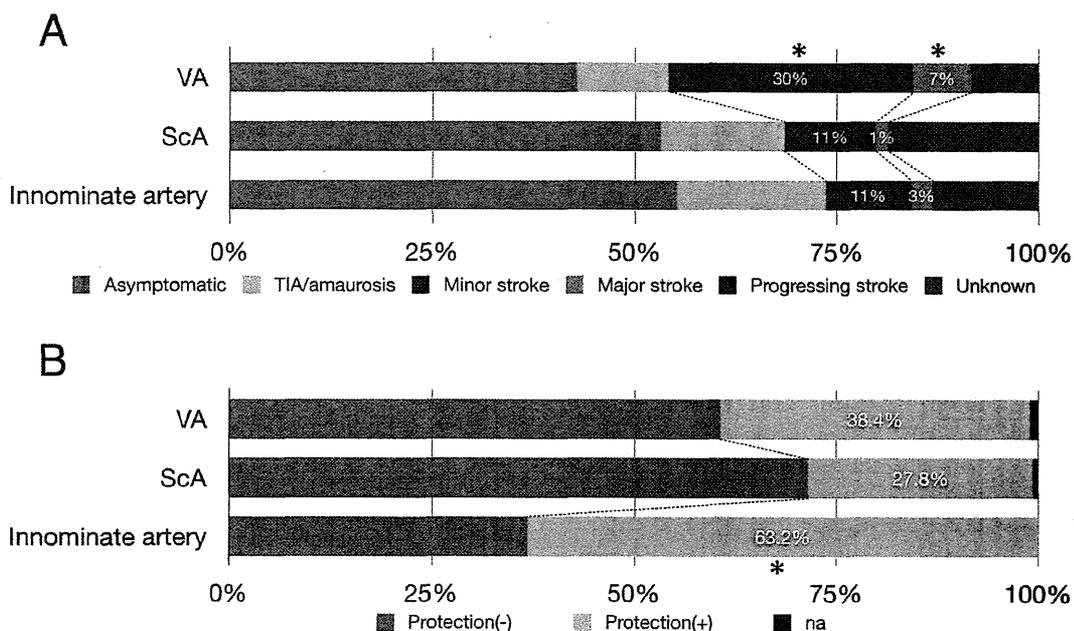
A

B

Fig. 5   Effects of lesion location. A: Symptom. B: Protection against distal embolism. *Asterisks* indicate the items demonstrating significant effect of lesion location. VA: vertebral artery, ScA: subclavian artery, TIA: transient ischemic attack, na: not available.

registries (p < 0.001). For example, a single use of cilostazol was significantly lower in JR-NET2 (5 of 601 patients, 0.8%) than in JR-NET (12 of 320 patients, 3.8%) (p = 0.004), while triple antiplatelet therapy (5 of 320 patients [1.6%] in JR-NET and 31 of 601 patients [5.2%] in JR-NET2, p = 0.012) was significantly higher in JR-NET2 than in JR-NET (Fig. 3). The rate of utilization of protection against distal embolism was similar when comparing the two registries (113 of 337 patients [33.5%] in JR-NET and 221 of 622 patients [35.5%] in JR-NET2, p = 0.502). The distal balloon protection was the most popular method in both JR-NET (83.2%) and JR-NET2 (87.3%). The rate of the favorable outcome was significantly higher in JR-NET2 than in JR-NET (271 of 337 patients [80.4%] in JR-NET and 548 of 622 patients [88.1%] in JR-NET2, p < 0.001, Fig. 4B) but the rate of patients whose mRS deteriorated by more than two points was similar when comparing the two registries (8 patients [2.3%] in JR-NET1 vs. 14 patients [2.3%] in JR-NET2, p = 0.867).

The complication rate (5.9% in JR-NET vs. 3.2% in JR-NET2, p = 0.066) and the variation of complications were not significantly different when comparing JR-NET and JR-NET2. Embolic complications, the most frequent complication both in JR-NET and JR-NET2, occurred in 4 out of 20 patients and in

8 out of 20 patients (p = 0.493).

Discussion

The results of JR-NET and JR-NET2 suggest that stenting and PTA of extracranial steno-occlusive lesions are relatively safe. Postprocedural morbidity and mortality were low (2.0% and 0.3%, respectively) and the rate of periprocedural complications was within the acceptable limits (5.0%). These results are consistent with the previous reports concerning extracranial VA[6,7] and subclavian stenoses.[8,9]

Although the ability of PTA or stenting to prevent vertebrobasilar ischemic events is an important goal, the follow-up period in JR-NET and JR-NET2 (30 days after procedures) was too short to investigate this issue. In patients with VA stenosis, the CAVATAS study suggested that there was a very low rate of recurrent vertebrobasilar ischemic event irrespective of whether the patient received medical treatment alone or endovascular treatment in combination with medical treatment.[6] According to the analysis of lesion location effect in our study, a patient having VA stenosis is likely to have higher rate of mRS deterioration after the procedure than a patient having subclavian artery stenosis or innominate artery stenosis. There is a possibility that the event risk

concerning these lesions might even be lower than the morbidity risk reported in our study. Further studies are needed to clarify the natural course of these lesions and to lower the morbidity and mortality of this procedure.

The rate of the favorable outcome was higher in JR-NET2 when compared to JR-NET but the rate of complications and the rate of worsening mRS after the procedure was similar when comparing the two groups. The improved outcomes in JR-NET2 likely reflect the changes in treatment strategies based on advances in devices and antiplatelet therapy, while the rate of complications and deteriorating mRS after procedure did not significantly changed. These results indicate the indication of endovascular treatment as a preventive measure increased, while recent development of endovascular treatment did not necessarily connect with the improvement of safety of this treatment. Clinicians should keep in mind that patients with extracranial stenotic lesion might have a favorable outcome, even in the absence of the treatment, and that the endovascular treatment for such lesions is still associated with a risk of complications (albeit low). Continuous efforts should be made to reduce the complication rate, and further trials are needed to validate the beneficial effect of this procedure.

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Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices in this article. All authors who are members of the Japan Neurosurgical Society (JNS) have registered online self-reported COI Disclosure Statement Forms through the website for JNS members.

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

Angioplasty and Stenting for Intracranial Stenosis

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Abstract

Of the patients enrolled in the Japanese Registry of Neuroendovascular Therapy (JR-NET), a surveillance study in Japanese, 1133 patients who underwent intracranial percutaneous transluminal angioplasty (PTA)/stenting for intracranial stenosis during the period from 2005 to 2009 were investigated. A technical success was achieved in 98.3% of the patients, and 70.5% and 7.5% had a residual stenosis of < 30% and ≥ 50%, respectively. The incidence of ischemic complications and hemorrhagic complications was as low as 7.7% and 2.5%, respectively, but tended to increase in patients who underwent stenting. While a significant correlation with ischemic complications was observed in previously untreated patients and patients who underwent stenting followed by post-dilatation, a significant correlation with hemorrhagic complications was observed in patients who received emergency treatment and those treated between 24 hours and 14 days of the onset. Flexible intracranial stents are expected to contribute to improvement in the treatment outcome.

Key words: intracranial stenosis, angioplasty, stenting

Introduction

Angioplasty has traditionally been used for the treatment of intracranial stenosis, primarily for intracranial stenosis refractory to medical therapy. However, since no stent is specifically designed for intracranial arteries, treatment is usually completed with balloon angioplasty alone, and stenting using a coronary stent is applied only in unavoidable circumstances. While more flexible intracranial stents that are compatible with the characteristics of more tortuous intracranial arteries have been awaited for a long time, the Wingspan (Stryker, Kalamazoo, Michigan, USA) was approved in the United States in 2005, and an investigator-initiated clinical trial is under way in Japan with the aim of gaining coverage by the Japanese National Health Insurance system. In advance of introduction of intracranial stents in Japan, review of previous treatment results in Japan may be essential for the

development of endovascular therapy for intracranial stenosis. The Japanese Registry of Neuroendovascular Therapy (JR-NET) was a retrospective registration survey on all neuroendovascular procedures performed in Japan. Procedures performed from 2005 to 2006 were included in JR-NET1, and those from 2007 to 2009 were included in JR-NET2. We report the results of the JR-NET, including analysis and discussion.

Materials

All patients enrolled in JR-NET1 or JR-NET2 who were treated with intracranial percutaneous transluminal angioplasty (PTA)/stenting for intracranial stenosis were included in the present study. Data from a total of 1133 patients who underwent angioplasty/stenting for intracranial stenosis were analyzed: 438 patients in JR-NET1 (2005 to 2006) and 695 patients in JR-NET2 (2007 to 2009).

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Methods

Data files from JR-NET were used to determine correlations between differences in the baseline characteristics of patients, procedures, or perioperative management, and the occurrence of hemorrhagic or ischemic complications in a retrospective manner. Data were analyzed for each factor, except for "unknown" data and missing data. For the factors asked about in JR-NET2 but not in JR-NET1 (presence or absence of pre-dilatation and post-dilatation, type of stent, timing of treatment, and presence or absence ofgeneral anesthesia), only data from JR-NET2 were used. Statistical analysis was performed by chi-square test using excel statistics.

Results

The baseline characteristics of patients, lesion profile, treatment situation, treatment, treatment outcome, and complications are shown in Table 1. The mean age was 66.7 (19 to 94) years, and the proportion of male subjects was as high as 76.5%. At baseline, the mean modified Rankin scale (mRS) was 0.86, and patients with an mRS of 0 to 2 accounted for 89.1%. Of all patients, 25.0% received treatment under general anesthesia, and 17.0% received emergency treatment. Stenting was performed in 60.6% patients. The most common preoperative antiplatelet treatment was treatment with two agents in 71.6%, followed by treatment with one agent in 14.1%. While the most common postoperative antithrombotic agents

Table 1 Characteristics of 1,133 patients

Patient characteristics		
Baseline characteristics of patients	Age	Mean 66.8 (19–94) years
	Sex	Male 76.5%
	mRS at baseline	Mean 0.86
	mRS 0 to 2	89.1%
	Previously untreated	92.7%
Lesion profile	Region	IC (intracranial epidural): 36.0%, IC (intradural): 84.7%, MCA: 22.2%, VA: 16.6%, BA: 14.4%, other: 2.4%
	Symptom at diagnosis	Asymptomatic: 19.9%, amaurosis: 1.4%, TIA (cerebrum): 22.1%, minor stroke: 36.5%, major stroke: 8.7%, progressing: 11.3%
	Timing of treatment (JR-NET2)	Within 24 hr: 13.5%, within 14 days: 20%, after at least 15 days: 66.5%
	Percent diameter stenosis	< 50%: 2.4%, 50% to 60%: 4.5%, 60% to 70%: 9.9%, 70% to 80%: 32.0%, 80% to 90%: 26.7%, 90% to 100%: 22.2%, 100%: 2.3%
	Lesion length	< 5 mm: 25.0%, 5–10 mm: 53.2%, 10–15 mm: 16.3%, ≥ 15 mm: 5.5%
	Normal vascular diameter	< 2 mm: 1.9%, 2–2.5 mm: 16.0%, 2.5–3 mm: 24.1%, 3–3.5 mm: 25.1%, 3.5–4 mm: 19.7%, ≥ 4 mm: 13.2%
	Pathology	Arteriosclerosis: 93%, traumatic dissection 0.3%, iatrogenic dissection 0.7%, idiopathic dissection 1.1%, others 4.7%
	Refractory to medical therapy	44.9%
Treatment situation	Diagnostic cerebral angiography	39.6%
	Emergency treatment	17.0%
	Treatment at another hospital	10.6%
	Investigator	Supervisory physician: 55.0%, specialist: 37.4%, nonspecialist: 7.5%
	Scrub-in of supervisory physician	62.5%
	No. of scrub-in supervisory physicians and specialists	1: 58.0%, 2: 33.0%, ≥ 3: 9.0%
	General anesthesia (JR-NET2)	25.0%

(Continued)

Table 1 (Continued)

Treatment	Stenting	Yes: 60.6%
	Presence or absence of pre-dilatation (JR-NET2)	Yes: 72.0%
	Use of coronary stent (JR-NET2)	97.9%
	Presence or absence of post-dilatation (JR-NET2)	28.8%
	Preoperative antiplatelet treatment	No: 5.4%, 1 agent: 14.1%, 2 agents: 71.6%, 3 agents: 8.9%
	Postoperative antiplatelet treatment	No: 6.0%, 1 agent: 12.7%, 2 agents: 71.7%, 3 agents: 9.6%
	Postoperative antithrombotic treatment	No: 26.4%, heparin: 25.9%, argatroban: 38.9%, ozagrel: 3.1%, combination: 5.6%
	Other concurrent treatment	12.8%
Treatment outcome	Technical success	98.3%
	Residual stenosis immediately after treatment	< 30%: 70.5%, 30% to 50%: 22.1%, ≥ 50%: 7.5%
	Hemorrhagic complication	2.5%
	Ischemic complication	7.7%
	mRS at 30 days postoperatively	Mean 1.02
	Postoperative increase in mRS ≥ 2 points	8.6%
	Mortality	1.9%

BA: basilar artery, IC: internal cerebral artery, JR-NET: Japanese Registry of Neuroendovascular Therapy, MCA: middle cerebral artery, mRS: modified Rankin scale, TIA: transient ischemic attack, VA: vertebral artery.

Table 2 Details of ischemic complications and hemorrhagic complications

	Total	Incidence(%)
Ischemic complication		
Distal embolization	39	3.4
Vascular dissection	21	1.9
Acute obstruction	15	1.3
Other	4	0.4
Unknown	8	0.8
Total	87	7.7
Hemorrhagic complication		
Vascular rupture	7	0.6
Hyperperfusion	5	0.4
Vascular dissection	3	0.3
Vessel perforation	2	0.2
Other	5	0.4
Unknown	6	0.5
Total	28	2.5

were argatroban in 38.9% and heparin in 25.9%, no postoperative antithrombotic treatment was performed in 26.4%. Technical success was achieved in 98.3%, and 70.5% and 7.5% had a residual stenosis of < 30% and ≥ 50%, respectively. The incidence of ischemic complications and hemorrhagic complications was 7.7% (87 patients) and 2.5% (28 patients), respectively, and 1 patient had both ischemic and hemorrhagic complications. As a result, the incidence of hemorrhagic and ischemic complications within 30 days postoperatively was 10.1%. At 30 days postoperatively, the mean mRS was 1.02, and the mRS increased from baseline by 2 points or more in 8.6%. The mortality was 1.9%.

Ischemic and hemorrhagic complications are listed in Table 2. The most common ischemic complication was distal embolization in 3.4%, followed by vascular dissection in 1.9%. The most common hemorrhagic complications were vascular rupture in 0.6% and hyperperfusion-related hemorrhage in 0.4% of patients.

Correlation between each factor tested and ischemic complications are shown in Table 3. The following factors were significantly correlated with ischemic complications: no previous treatment; not refractory to medical therapy; stenting followed by post-dilatation; postoperative antithrombotic treatment; and supervisory physician who served as the investigator. The incidence of ischemic complications was significantly lower in patients who received

Table 3 Correlation between each factor and ischemic complications

Baseline characteristics of patients	Age	≤ 49 years: 7.0%, 50 to 59 years: 6.9%, 60 to 69 years: 7.1%, 70 to 79 years: 6.7%, ≥ 80 years: 2.7%
	Sex	Male: 6.6%, female: 6.6%
	mRS at baseline	0 to 2: 6.9%, 3 to 5: 5.2%
	Previous treatment	Previously untreated: 8.4%, previously treated: 2.2% (p < 0.05)
Lesion profile	Region	IC (intracranial epidural): 6.2%, IC (intradural): 5.5%, MCA: 7.5%, VA: 9.6%, BA: 11.0%
	Symptom at diagnosis	Asymptomatic: 8.0%, symptomatic: 7.8%
		Nonprogressively symptomatic: 8.1%, progressively symptomatic: 5.8%
	Timing of treatment (only symptomatic patients)	Within 24 hr: 8.8%, between 24 hr and 14 days: 5.9%, after at least 15 days: 7.7%
	Percent diameter stenosis	< 50%: 8.0%, 50% to 60%: 8.7%, 60% to 70%: 8.9%, 70% to 80%: 7.3%, 80% to 90%: 7.3%, 90% to 100%: 8.4%, 100%: 8.7%
	Lesion length	< 5 mm: 8.3%, 5–10 mm: 6.4%, 10–15 mm: 12.2%, ≥ 15 mm: 5.4%
	Normal vascular diameter	< 2 mm: 0%, 2–2.5 mm: 10.4%, 2.5–3 mm: 10.2%, 3–3.5 mm: 5.9%, 3.5–4 mm: 6.5%, ≥ 4 mm: 6.7%
	Pathology	Arteriosclerosis: 7.2%, traumatic dissection 0%, iatrogenic dissection 0%, idiopathic dissection 12.5%, others 3.1%
	Refractory to medical therapy	No: 8.8%, yes: 5.0% (p < 0.05)
Treatment	Stenting	No: 6.6%, yes: 9.7%
	Presence or absence of pre-dilatation (JR-NET2)	No: 10.1%, yes: 6.0%
	Presence or absence of post-dilatation (JR-NET2)	No: 5.7%, yes: 9.8%
	Stent + presence or absence of post-dilatation (JR-NET2)	No: 5.6%, yes: 14.0% (p < 0.05)
	Preoperative antiplatelet treatment	No: 8.9%, 1 agent: 6.2%, 2 agents: 8.2%, 3 agents: 7.6%
	Postoperative antiplatelet treatment	No: 11.2%, 1 agent: 8.3%, 2 agents: 7.0%, 3 agents: 12.0%
	Postoperative antithrombotic treatment	No: 4.9%, heparin: 3.5%, argatroban: 9.7%, ozagrel: 12.9%, combination: 30.3% (p < 0.000000001*)
	Other concurrent treatment	No: 7.3%, yes: 11.0%
Treatment situation	Diagnostic cerebral angiography	No: 8.0%, yes: 7.4%
	Emergency treatment	Planned: 7.2%, emergency: 10.4%
	Treatment facility	Hospital at work: 8.2%, another hospital: 3.3%
	Investigator	Supervisory physician: 10.1%, specialist: 4.5%, nonspecialist: 5.8% (p < 0.01**)
	Scrub-in of supervisory physician	No: 2.7%, yes: 10.0% (p < 0.001)
	No. of scrub-in supervisory physicians and specialists	1: 7.1%, 2: 8.8%, ≥ 3: 3.3%
	General anesthesia	Local anesthesia: 7.7%, general anesthesia: 5.7%
Treatment outcome	Residual stenosis immediately after treatment	< 30%: 7.4%, 30% to 50%: 7.0%, ≥ 50%: 11.7%

*: Each p-value is shown in Table 4. **: Supervisory physician vs. specialist (p < 0.001). mRS: modified Rankin scale.