Neurol Med Chir (Tokyo) 54, 98–106, 2014

doi: 10.2176/nmc.oa.2013-0184
Online December 27, 2013

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

Endovascular Treatment for Ruptured Vertebral Artery Dissecting Aneurysms: Results from Japanese Registry of Neuroendovascular Therapy (JR-NET) 1 and 2

Tetsu SATOW,[1] Daizo ISHII,[1] Koji IIHARA,[1,2] and Nobuyuki SAKAI,[3]
on behalf of JR-NET study group

[1]Department of Neurosurgery, National Cerebral and Cardiovascular Center, Suita, Osaka;
[2]Department of Neurosurgery, Graduate School of Medical Sciences,
Kyushu University, Fukuoka, Fukuoka;
[3]Department of Neurosurgery, Kobe City Medical Center General Hospital, Kobe, Hyogo

Abstract

In treating ruptured vertebral artery dissecting aneurysms (VADAs), neuroendovascular therapy (NET) represented by coil obliteration is considered to be a reliable intervention. However, there has been no multi-center based study in this setting so far. In this article, results of NET for ruptured VADA obtained from Japanese Registry of Neuroendovascular Therapy (JR-NET) 1 and 2 were assessed to elucidate the factors associated with favorable outcome. A total of 213 in JR-NET1 and 381 patients in JR-NET2 with ruptured VADA were included, and they were separately analyzed because several important datasets such as vasospasm and site of dissecting aneurysms in relation to the posterior inferior cerebellar artery (PICA) were collected only in JR-NET1. The ratio of poor World Federation of Neurosurgical Societies (WFNS) grade (4 and 5) was 48.8% and 53.9%, and the ratio of favorable outcome (modified Rankin scale, mRS 0 to 2) at 30 days after onset was 61.1 % and 49.1% in JR-NET1 and 2, respectively. In both studies, poor WFNS grade and procedural complication were independently correlated as negative factors for favorable outcome. In JR-NET1, PICA-involved lesion was also designated as a negative factor while elderly age and absence of postprocedural antithrombotic therapy was detected as other negative factors in JR-NET2. The ratios of favorable outcome in poor grade patients were 25.4% in JR-NET1 and 31.3% in JR-NET2, which seemed compatible with the previous studies. These results may provide a baseline data for the NET in this disease and could be useful for validating the benefits of novel devices.

Key words: vertebral artery, dissecting aneurysm, subarachnoid hemorrhage, neuroendovascular therapy, nationwide survey

Introduction

Vertebral artery dissecting aneurysm (VADA) is nowadays increasingly recognized as a cause of subarachnoid hemorrhage and ischemic stroke.[1] In patients with ruptured VADAs, a high incidence of rebleeding and a high mortality rate at the time of rebleeding was reported.[2,3] Recently, catheter-based neuroendovascular approach has emerged as first-line therapy for ruptured VADA along with the development of new techniques and devices and their results are favorable so far.[4–10]

There was no report, however, as to the detailed data of the relationship between NET and patient's outcome in a large multi-center based study.

This study was aimed to clarify the current status and results of NET for ruptured VADA in Japan from the

Received May 27, 2013; Accepted November 11, 2013

data of Japanese Registry of Neuroendovascular Therapy (JR-NET) 1 and 2, thereby extracting a clue for elucidating the appropriate therapy for this harmful disease.

Materials and Methods

The data in this study were collected from JR-NET1 and 2. Briefly, JR-NET1 was the registration of therapeutic procedures and outcomes from the certified board members of Japanese Society for Neuroendovascular Therapy (JSNET) between 2005 and 2006 while JR-NET2 was that of JSNET board members between 2007 and 2009. The Institutional Review Board at each center approved the use of retrospective data from the patients.

The total numbers of registration were 11,213 cases in JR-NET1 and 20,751 cases in JR-NET2. Among all the datasets, the incidence of ruptured VADA was 213 (1.9%) and 381 (1.8%) in JR-NET1 and JR-NET2, respectively.

The following factors were collected in both studies: age, sex, and World Federation of Neurosurgical Societies (WFNS) grade on admission as patient-derived factors while the timing of neuroendovascular therapy (NET), mode of anesthesia, technical success which was defined as the absence of blood flow to the ruptured lesion, participation of board members as in charge of the procedure, intraprocedural use of heparin, postprocedural antithrombotic therapy, and ischemic/hemorrhagic complications as periprocedural factors. No detailed information about used devices for the lesion such as coils (bare platinum or surface modified), stents, and balloons were collected in both studies. A modified Rankin scale (mRS) score at 30 days after the onset was used for evaluation of patients' outcome and defined as the primary endpoint. The point of 0 to 2 in mRS, which means independence of the patients, was considered as a favorable outcome.

The relationship between factors listed above and mRS scores at 30 days were analyzed to clarify the influencing factors for favorable outcome.

As the datasets collected only in JR-NET1 noted above were expected to influence on the outcome, we analyzed the data of each study separately.

Statistical analysis

Analyses were performed using JMP version 9.0 (SAS Institute, Cary, North Carolina, USA). Statistical significance for intergroup differences was assessed using the z test for categorical variables and the Mann-Whitney U test for continuous variables. A logistic regression analysis was carried out using the factors with statistically significant differences by univariate analyses to determine any factors that were significantly related to the favorable outcome. P values < 0.05 were considered to indicate a significant difference.

Results

I. Patient characteristics

The patients' demographics are shown in Table 1. The mean age was 52.5 and 54.6 years in JR-NET1 and JR-NET2, respectively. Male preponderance was noted in both studies. As to WFNS grade on admission, the incidence of poor grade (Grades 4 and 5) was 48.9% and 52.0% in JR-NET1 and JR-NET2, respectively.

Table 2 summarized the timing of intervention. 49.2% of the cases in JR-NET1 while 74.3% in JR-NET2 were treated within 24 hours after onset,

Table 1 Patients' baseline characteristics in JR-NET1 and 2

	JR-NET1 (n = 213)	JR-NET2 (n = 381)	p value
Age (SD)	52.5 (± 10.4)	54.6 (± 11.7)	0.17
Male (%)	143 (67.1)	232 (60.9)	0.13
WFNS grade (%)			
1	20 (9.4)	33 (8.7)	
2	52 (24.4)	72 (18.9)	
3	37 (17.4)	71 (18.6)	
4	47 (22.1)	89 (23.4)	
5	57 (26.8)	109 (28.6)	
Poor (4 and 5, %)	104 (48.9)	198 (52.0)	0.46
Unknown (%)	0 (0.0)	7 (1.8)	

JR-NET: Japanese Registry of Neuroendovascular Therapy, WFNS: World Federation of Neurosurgical Societies.

Table 2 Interval from admission to treatment in JR-NET1 and 2

	JR-NET1 n = 213	JR-NET2 n = 381	p value
< 24 h	105 (49.2)	283 (74.3)	< 0.0001
24 h to 72 h	68 (32.0)	57 (15.0)	
< 72 h	*173 (81.2)*	*340 (89.3)*	*0.006*
Days 3 to 7	14 (6.6)	13 (3.4)	
Days 8 to 14	8 (3.8)	8 (2.1)	
After day 14	16 (7.6)	20 (5.2)	

Figures in the parentheses indicate column percentages. h: hours, JR-NET: Japanese Registry of Neuroendovascular Therapy.

which had a significant difference ($p < 0.0001$) between the two studies.

Approximately three-fourth of the cases were under general anesthesia (74.6% and 80.1% in JR-NET1 and JR-NET2, respectively).

II. Therapeutic demographics

Technical success was noted in 98.6% and 98.7% in JR-NET1 and JR-NET2, respectively.

As shown in Table 3, intraprocedural use of heparin was noted in 88.3% and 78.8% of the cases in JR-NET1 and JR-NET2, respectively. In more than half of the cases with heparin use, the administration of heparin was performed after the placement of sheath introducers. Postprocedural antithrombotic therapy was performed in approximately two-third of the cases (63.4% in JR-NET1 and 63.5% in JR-NET2). The ratios of anticoagulant use were 53.3% and 43.4% in JR-NET1 and JR-NET2, respectively. Antiplatelet agents were used approximately in 80% of all the cases in both studies, and concomitant use were observed approximately in one-third of the cases throughout two studies.

Procedural complication was observed in 9.9% and 10.8% in JR-NET1 and JR-NET2, respectively. The clinical outcome at 30 days after the onset was favorable in 61.0% and 49.1% whereas fatal in 15.5% and 14.4% in JR-NET1 and JR-NET2, respectively (Table 4).

Table 3 Periprocedural antithrombotic therapy in JR-NET1 and 2

	JR-NET1 n = 213	JR-NET2 n = 381	p value
Intraprocedural use of heparin, yes	188 (88.3)	300 (78.8)	0.004
Timing	n = 188	n = 300	
After introduction of sheath	97 (51.6)	194 (64.7)	0.004
After navigation of a microcatheter	22 (11.7)	29 (9.7)	0.47
After placement of first coil	64 (34.0)	68 (22.7)	0.005
Others	5 (2.7)	9 (3.0)	
Postprocedural antithrombotic therapy, yes	135 (63.4)	242 (63.5)	0.97
Mode	n = 135	n = 242	
Anticoagulant only	27 (20.0)	21 (8.7)	0.001
Antiplatelet only	61 (45.2)	102 (42.1)	0.57
Anticoagulant and antiplatelet	45 (33.3)	84 (34.7)	0.79
Unknown	2 (1.5)	35 (14.5)	

Figures in the parentheses indicate column percentages. JR-NET: Japanese Registry of Neuroendovascular Therapy.

III. Relationship between patient characteristics, procedural factors and clinical outcome

In JR-NET1, univariate analysis showed that age, poor WFNS grade, posterior inferior cerebellar artery (PICA)-involved lesion, use of heparin, and procedural complication were significantly related to the favorable outcome. Among them, poor WFNS grade, PICA-involved lesion, and procedural complication were identified as independent factors by multivariate analysis (Table 5).

Similarly, univariate analysis showed that age, poor WFNS grade, postprocedural antithrombotic therapy, and absence of procedural complication were significantly related to the favorable outcome in JR-NET2. Multivariate analysis in this registry revealed that age, poor WFNS grade, postprocedural antithrombotic therapy, and procedural complication were independently correlated with the favorable outcome (Table 6).

In addition, factors associated with favorable outcome in poor grade patients were also analyzed. However, there were no significant factors detected as positive or negative factors for favorable outcome, except for the ischemic complication in JR-NET1 (Table 7).

IV. Relationship between location of the lesion and NET in JR-NET1

Information as to the locations of VADA and site of intervention in relation to the dissecting aneurysms which were only available in JR-NET1 study is shown in Table 8. Locations of VADA were classified into four groups: proximal to PICA (pP), distal to PICA (dP), PICA involved (Pi), and no PICA (nP). Coil placement in the aneurysmal dilatation (AD) were performed in 78.7% (37/47) of group pP, 95.2%

Table 4 Clinical outcome at 30 days in JR-NET1 and 2

	JR-NET1 n = 213	JR-NET2 n = 381	p value
mRS 0	80 (37.6)	101 (26.5)	
1	38 (17.8)	49 (12.9)	
2	12 (5.6)	37 (9.7)	
0–2	*130 (61.0)*	*187 (49.1)*	*0.005*
3	16 (7.5)	30 (7.9)	
4	23 (10.8)	42 (11.0)	
5	11 (5.2)	36 (9.4)	
6	33 (15.5)	55 (14.4)	
Unknown	0 (0)	31 (8.1)	

JR-NET: Japanese Registry of Neuroendovascular Therapy, mRS: modified Rankin scale.

Table 5 Results of univariate and multivariate analyses for favorable outcome in JR-NET1

Variable	Number	Favorable outcome	Univariate	Multivariate	
			p value	OR (95% CI)	p value
Age	54.2 (± 10.5)	50.6 (± 10.1)	0.034	0.99 (0.95–1.02)	0.46
Male	143/213 (67.1)	85/130 (65.4)	0.49		
Poor WFNS grade (4 and 5)	104/213 (48.8)	33/130 (25.4)	< 0.0001	0.066 (0.026–0.16)	< 0.0001
OTT					
> 24 h	103/192 (53.6)	62/124 (50.0)	0.23	1.61 (0.66–4.04)	0.29
24 h to 72 h	67/192 (34.9)	45/124 (36.3)	0.098	0.62 (0.24–2.98)	0.81
> 72 h	22/192 (11.5)	17/124 (13.7)	0.23	1.16 (0.38–4.98)	0.62
Board members in charge of procedure	180/210 (85.7)	110/129 (85.2)	1.00		
PICA involved lesion	50/213 (23.5)	22/130 (16.9)	0.02	0.41 (0.15–1.05)	0.05
Use of heparin	188/210 (89.5)	121/129 (93.8)	0.01	2.41 (0.17–9.31)	0.17
Postprocedural antithrombotic therapy	135/207 (65.2)	89/128 (69.5)	0.09	1.26 (0.33–1.98)	0.67
Procedural complications	21/210 (10.0)	8/130 (6.2)	0.0007		
Ischemic	13/210 (6.2)	4/130 (3.1)	0.001	0.11 (1.59–59.9)	0.012
Hemorrhagic	5/210 (2.4)	0/130 (0.0)	< 0.0001	< 0.0001 (0–0.04)	0.039
Vasospasm	24/195 (12.3)	11/130 (9.5)	0.06	0.24 (0.04–1.08)	0.08

Standard deviation or percentages are in parentheses otherwise indicated. CI: confidence interval, h: hours, OR: odds ratio, OTT: Onset-to-treat time, PICA: posterior inferior cerebellar artery, WFNS: World Federation of Neurosurgical Societies.

Table 6 Results of univariate and multivariate analyses for favorable outcome in JR-NET2

Variable	Number	Favorable outcome (n = 187)	Univariate	Multivariate	
			p value	OR (95% CI)	p value
Age	54.6 (± 11.7)	50.8 (± 10.1)	< 0.0001	1.06 (1.04–1.09)	< 0.0001
Male	232 (60.9)	108 (57.5)	0.21		
Poor WFNS grade (4 and 5)	198 (52.0)	62 (31.3)	< 0.0001	0.13 (0.08–0.21)	< 0.0001
OTT					
> 24 h	283 (74.3)	141 (75.4)	0.21	0.74 (0.36–1.50)	0.4
24 h to 72 h	57 (15.0)	27 (14.4)	0.17	0.87 (0.33–2.33)	0.78
> 72 h	41 (10.7)	19 (10.2)	0.20	1.55 (0.71–3.46)	0.28
Board members in charge of procedure	341 (89.5)	167 (89.3)	1.00		
Use of heparin	300 (78.3)	150 (80.2)	0.13	0.97 (0.53–1.77)	0.91
Postprocedural antithrombotic therapy	211 (55.4)	122 (65.2)	0.0002	2.15 (1.32–3.54)	0.002
Procedural complications	41 (10.8)	15 (8.0)	0.09		
Ischemic	33 (8.7)	15 (8.0)	0.71	0.39 (0.16–0.92)	0.03
Hemorrhagic	8 (2.1)	0 (0.0)	0.007	< 0.0001 (0–0.19)	0.0005

Standard deviation or percentages are in parentheses otherwise indicated. CI: confidence interval, h: hours, OR: odds ratio, OTT: onset-to-treat time, WFNS: World Federation of Neurosurgical Societies.

Table 7 Results of univariate and multivariate analyses for favorable outcome in patients with poor WFNS grade on admission

Variable	JR-NET1 (n = 104)			JR-NET2 (n = 198)		
	Univariate	Multivariate		Univariate	Multivariate	
	p value	OR (95% CI)	p value	p value	OR (95% CI)	p value
Age	0.59	0.96 (0.92–1.02)	0.25	0.02	1.05 (0.98–1.09)	0.06
Male	0.82			0.53		
OTT						
> 24 h	0.49	0.55 (0.18–1.63)	0.28	0.29	0.85 (0.32–2.44)	0.75
24 h to 72 h	0.64	0.84 (0.15–5.18)	0.84	0.61	1.87 (0.60–7.15)	0.28
> 72 h	0.48	1.52 (0.29–9.19)	0.62	0.45	2.20 (0.51–10.7)	0.29
BM in charge of procedure	0.77	1.46 (0.35–6.06)	0.59	0.81	1.16 (0.42–3.53)	0.78
PICA involved lesion	0.64	0.68 (0.19–2.22)	0.54	n/a		
Use of heparin	0.78	2.11 (0.56–9.37)	0.28	0.35	1.28 (0.58–3.03)	0.55
Postprocedural AT	0.78	1.12 (0.39–3.29)	0.82	0.36	1.46 (0.78–2.79)	0.23
Procedural complications	0.01			0.23		
Ischemic	0.05	0.13 (0–0.008)	0.008	0.51	0.41 (0.05–1.93)	0.28
Hemorrhagic	< 0.0001	0.01 (0–11.7)	0.41	0.56	0.19 (0.02–2.35)	0.16
Vasospasm	0.08	0.25 (0.03–1.56)	0.14	n/a		

AT: antithrombotic therapy, BM: board members, CI: confidence interval, h: hours, JR-NET: Japanese Registry of Neuroendovascular Therapy, n/a: not applicable, OR: odds ratio, OTT: onset-to-treat time, WFNS: World Federation of Neurosurgical Societies.

Table 8 Obliterated sites and location of aneurysmal dilatation in JR-NET1

	Proximal to PICA	Distal to PICA	PICA involved	No PICA	Unknown	p value
Number (%)	47 (22.1)	83 (39.0)	50 (23.5)	29 (13.6)	4 (1.9)	
Favorable outcome	30/47 (63.8)	56/83 (67.5)	22 (44.0)*	20 (69.0)	2 (50.0)	0.01
Obliterated site (%)	n = 47	n = 83	n = 50	n = 29	n = 4	
Proximal only	8 (16.8)	1 (1.2)	10 (20.0)	0 (0.0)	3 (75.0)	
AD only	14 (29.8)	54 (65.1)	24 (24.0)	13 (44.8)	1 (25.0)	
Distal only	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Proximal and AD	19 (40.4)	16 (19.3)	11 (22.0)	10 (34.5)	0 (0.0)	
Distal and AD	1 (2.1)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	
Proximal, distal, and AD	2 (4.2)	6 (7.2)	4 (8.0)	6 (20.7)	0 (0.0)	
AD and stenting	1 (2.1)	1 (1.2)	1 (2.0)	0 (0.0)	0 (0.0)	
Stenting only	1 (2.1)	3 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	
Use of balloon GC (%)	13 (27.7)	13 (15.7)	16 (34.0)	12 (41.4)	1 (25.0)	
Postprocedural status of PICA						
Preserved	46	83	23	10	1	
Occluded	1	0	23	0	0	
With bypass surgery	0	0	4	0	0	
Unknown	0	0	0	19	3	

*Statistically significant. AD: aneurysmal dilatation, GC: guiding catheter, PICA: posterior inferior cerebellar artery.

(79/83) of group dP, 80% (40/50) of group Pi, and 100% (29/29) of group nP. Balloon guiding catheter was used in 27.7%, 15.7%, 34.0%, and 41.4% in cases of group pP, dP, Pi, and nP, respectively.

In group Pi, the ratio of favorable outcome was smaller than other groups (44%, p = 0.01). The proportion of using a balloon guiding catheter was rather small, and PICA was sacrificed in approximately half of the cases. Ischemic complication was noted in 21.7% cases with sacrifice of PICA, resulting in smaller proportion of favorable outcome comparing with cases in which PICA was preserved (34.8% versus 52.2%) although there was no statistic difference in favorable outcome (p = 0.11, Table 9).

Discussion

It is well known that the prognosis of ruptured VADA is very poor. Two major reasons are poor grade on admission and high incidence of rerupture at ultra-early stage.[2,3] With the invent of NET, the first-line therapy for ruptured VADA has been shifted to NET in this decade because of its less invasiveness and time consciousness: direct access to the lesion without damaging the cerebellum and cranial nerves is possible and the therapeutic procedures can be performed in conjunction with the diagnostic angiography.[11]

This is the first nationwide survey of NET for ruptured VADA and provides important information about current status of NET and its relationship with clinical outcomes. Although the protocols were almost the same in JR-NET1 and 2, several datasets including the location of the lesion and vasospasm which were collected only in JR-NET1 seemed to be associated with favorable outcomes (Table 5). Thus, JR-NET1 and 2 were analyzed separately instead of analyzing these two studies as a composite to provide the accurate information.

Approximately 50% of all the cases in both studies were categorized as poor WFNS grade, which was compatible with previous reports.[4,12] There was a significant difference in terms of onset-to-treatment time (OTT) between two studies and approximately three-fourth of the patients were treated within 24 hours after onset in JR-NET2 (Table 2). This result may be due to widespread recognition as to the importance of preventing ultra-early rebleeding and nationwide prevalence of NET itself.

In both studies, poor WFNS grade and procedural complication were independently detected as negative factors for favorable outcome. This finding was compatible with previous studies on the outcome of subarachnoid hemorrhage including a recent study from our country,[13,14] and also with a single-center study regarding ruptured VADA[12] (Tables 5 and 6). The ratios of favorable outcome of patients with poor WFNS grade at onset were 25.4% and 31.3% in JR-NET1 and JR-NET2, respectively. These results were compatible with the previous studies as shown in Table 10, and were better than the result of PRESAT study, which dealt only with saccular aneurysms, whose ratio of favorable outcome in the patients with poor grade was 20.0%.[14] The clinical course of poor grade SAH caused by ruptured VADA might be more promising than SAH with ruptured, saccular aneurysms.

We also analyzed the relationship between collected datasets and favorable outcome in poor grade patients, only to find that the ischemic complication in JR-NET1 was negatively associated with favorable outcome. A possible explanation is that the determinants other than poor grade itself as detected in Tables 5 and 6 were less correlated with favorable outcome in this subgroup mainly due to sample size.

In JR-NET2, age and postprocedural antithrombotic therapy were demonstrated as independent factors for favorable outcome. As to age, the odds

Table 9 Procedural complication, favorable outcome, and postprocedural status of PICA in JR-NET1

	Procedural complication n = 9	Hemorrhagic complication n = 3	Ischemic complication n = 5	Favorable outcome	p value
PICA preserved	1/23 (4.3)	1/23 (4.3)	0/23 (0.0)	12/23 (52.2)	0.11
PICA occluded	8/23 (34.8)	2/23 (8.6)	5/23 (21.7)	8/23 (34.8)	
OA-PICA bypass	0/4 (0.0)	0/4 (0.0)	0/4 (0.0)	2/4 (50.0)	

Percentages are in parentheses, OA: occipital artery, PICA: posterior inferior cerebellar artery.

Table 10 Comparison of profiles and outcomes between previous studies on ruptured VADA and JR-NET studies

Series	Number	Age (mean)	Poor WFNS grade n (%)	Techniques used (n)	Used scale for outcome	Favorable outcome n (%)		Death n (%)
						All	Poor WFNS grade	
Kurata et al.[6]	18	52	9 (50.0)	IT (18)	GOS	14 (77.7)	3 (33.3)	3 (16.7)
Ravinov et al.[8]	21	52	6 (28.6)	IT (11), PO (7)	mRS	11 (52.4)	1 (16.7)	0 (0.0)
Yuki et al.[10]	27	45	8 (29.6)	IT (26), PO (1)	mRS	14 (51.8)	1 (12.5)	5 (9.3)
Sugiu et al.[9]	20	56	8 (40.0)	IT (19), SAC (1)	GOS	15 (75.0)	3 (37.5)	4 (20.0)
Endo et al.[11]	38	53	19 (50.0)	IT (38)	mRS	23 (60.5)	9 (47.4)	6 (15.8)
JR-NET1	213	54	104 (48.8)	IT (183), PO (23), SAC (3), SM (4)	mRS	130 (61.0)	33 (25.4)	33 (15.5)
JR-NET2	381	55	198 (52.0)	n/a	mRS	187 (49.1)	62 (31.3)	55 (14.4)

A favorable outcome is considered for patients with an mRS score of 0–2, or with GR or MD by GOS. GOS: Glasgow outcome scale, GR: good recovery, IT: internal trapping, JR-NET: Japanese Registry of Neuroendovascular Therapy, MD: moderate disability, mRS: modified Rankin scale, n/a: not available, PO: proximal occlusion, SAC: stent-assisted coiling, SM: stent monotherapy, VADA: vertebral artery dissecting aneurysm, WFNS: World Federation of Neurosurgical Societies.

ratio was only 1.06 although elderly age is considered as an indicator for poor outcome in previous studies listed above.[13,14] This might be explained by the fact that the age at onset in this disease was relatively young as compared with studies dealing with saccular aneurysms[6,7,12] (Table 6).

The efficacy and safety of antithrombotic therapy during and after the NET for ruptured aneurysms remains an unsolved issue. One systematic review suggested that the antiplatelet drugs reduced the risk of delayed cerebral ischemia in patients with subarachnoid hemorrhage.[15] On the contrary, a subanalysis of International Subarachnoid Aneurysm Trial (ISAT) revealed that antiplatelet therapy during or after endovascular coiling improved outcome in patients with SAH.[16] The majority of the procedures in our studies were parent artery occlusion, thus use of antiplatelets or anticoagulants might favor in avoiding thromboembolic complications especially with small branches originating from affected VA, and unfavorable outcomes such as re-rupture due to recanalization in acute stage might have occurred less frequently than coiling of saccular aneurysms.

However, this factor was not independently correlated with favorable outcome in JR-NET1 which had more variables; it seems to be premature to recommend postprocedural antithrombotic therapy. The detailed information of antithrombotic therapy especially such as dose, mode, and duration of the used drugs is needed to validate the efficacy of periprocedural antithrombic therapy for NET in ruptured VADA.

Comparing two studies, the proportion of patients with favorable outcome at 30 days decreased from 61.0% in JR-NET1 to 49.1% in JR-NET2 (Table 4). The reason for this decline is difficult to describe as there were no differences between two studies in the proportion of poor grade patients, technical success, and incidence of procedural complication. Although the OTT was shorter in JR-NET2, no correlation between OTT and favorable outcome was observed by either univariate or multivariate analysis. The participation of board members as in charge of the procedure also did not correlate with the outcome in each study. No major change was found in the used devices or techniques between two periods. According to the results shown in Table 10, it may be more reasonable to understand that the ratio of favorable outcome in patients with ruptured VADA who underwent NET lies between these numbers noted above.

Regarding the location of the lesion and the mode of the procedure in JR-NET1, the result in group Pi demonstrated that the occlusion of PICA did not affect the ratio of favorable outcome despite the increased incidence of ischemic complication (Table 9). This result should be dealt with special care as there was no information about the perfusion territory of the affected PICA in this series. Complete obliteration of the lesion might be preferred in group Pi in this study as the most important role of NET for ruptured VADAs was the prevention of rerupture. A recent report from Japan, however, demonstrated that the postoperative medullary infarction was associated with unfavorable outcomes after internal coil trapping for ruptured VADAs.[11] Furthermore, the fact that the hemorrhagic complication occurred only in one case (4.3%) in which PICA were preserved in this group may imply that the proximal occlusion may be enough for the prevention of rerupture in acute phase as proposed by authors.[5]

Regarding use of a balloon-guiding catheter, its necessity remains an enigma[17] although the merits of this method were considered as prevention of distal embolism and reduction of subarachnoid bleeding at the time of intraprocedural rupture.[18] In group Pi, however, the territory of PICA was forced to be fed by retrograde blood flow via contralateral VA, which should run through coil mass when proximal flow control was performed.[19] The anxiety for thromboembolism in PICA territory might be the major reason for the smallest number of cases with this method in group Pi.

Stent-assisted coiling and stent monotherapy including the use of flow diverters are becoming an alternative method of NET for this disease and the initial results seem feasible.[20–22] Stent was used only in seven cases in JR-NET1, and unfortunately the use of stent was not in the collected datasets in JR-NET2. The number of stents use in ruptured VADA was considered to be small as stents designed for intracranial use were not available in Japan during the study period. A prospective, multi-centered study on the efficacy and safety of stenting along with antithrombotic therapy is strongly awaited.

This study has several limitations. This study was retrospective, and data were missing in some patients. The clinical evaluation during the study period and angiographic examinations were not evaluated by physicians who were blinded to the therapy. Furthermore, lack in unity in the datasets among two studies may have dimmed the influence of procedural/medical factors for favorable outcome. If all the datasets in JR-NET1 were collected in JR-NET2, influence of age, PICA-involved lesion, postprocedural antithrombotic therapy upon favorable outcome could be clarified for the better guidelines for NET and periprocedural management in ruptured VADA. Also, the determinants of favorable outcome after NET in poor grade patients might be presented.

Nevertheless, this study provides important information as to the current status of NET in Japan, especially the correlations among patients' status at onset, procedural results, and clinical outcomes.

Conclusion

Ruptured VADA treated by NET, mainly by proximal occlusion and internal trapping, resulted in high technical success rate up to 98.7%, and approximately 50% to 60% of the patients had a favorable outcome at 30 days after onset. Poor WFNS grade and intraprocedural complication were detected as negative factors for favorable outcomes. The results of this study may be used as baseline data for validation of future NET including the novel devices in Japan.

Acknowledgments

This study was supported by research grants for cardiovascular diseases (17C-1, 20C-2) from the Ministry of Health, Labor, and Welfare of Japan.

The authors would like to express their heartfelt thanks to all the doctors who devoted their time to this investigation.

The JR-NET Study Group: Principle investigator; Nobuyuki Sakai, Kobe City Medical Center General Hospital, Kobe, Japan: Investigators; Akio Hyodo, Dokkyo Medical University Koshigaya Hospital, Koshigaya, Japan (17C-1, 20C-2), Shigeru Miyachi, Nagoya University, Nagoya, Japan (17C-1, 20C-2), Yoji Nagai, Translational Research Informatics Center, Kobe, Japan (17C-1, 20C-2), Chiaki Sakai, Institute of Biomedical Research and Innovation, Kobe, Japan (17C-1, 20C-2) Waro Taki, Mie University, Tsu, Japan (17C-1, 20C-2), Tomoaki Terada, Wakayama Rosai Hospital, Wakayama, Japan (17C-1, 20C-2), Masayuki Ezura, Sendai Medical Center, Sendai, Japan (17C-1), Toshio Hyogo, Nakamura Memorial Hospital, Sapporo, Japan (17C-1), Shunji Matsubara, Tokushima University, Tokushima, Japan (17C-1), Kentaro Hayashi, Nagasaki University, Nagasaki Japan (20C-2); Co-investigators; Toshiyuki Fujinaka, Osaka University, Suita, Japan, Yasushi Ito, Niigata University, Niigata, Japan, Shigeki Kobayashi, Chiba Emergency Medical Center, Chiba, Japan, Masaki Komiyama, Osaka City General Hospital, Osaka, Japan, Naoya Kuwayama, Toyama University, Toyama, Japan, Yuji Matsumaru, Toranomon Hospital, Japan, Yasushi Matsumoto, Konan Hospital, Sendai, Japan, Yuichi Murayama, Jikei Medical University, Tokyo, Japan, Ichiro Nokahara, Kokura Memorial Hospital, Kokura, Japan, Shigeru Nemoto, Jichi Medical University, Shimotsuke, Japan, Koichi Sato, Tokushima Red Cross Hospital, Tokushima, Japan, Kenji Sugiu, Okayama University, Okayama, Japan, Shinichi Yoshimura, Gifu University, Gifu, Japan, and certified specialist of Japanese Society of Neuroendovascular Therapy.

Conflicts of Interest Disclosure

The authors declare that there are no conflicts of interest.

References

1) Arnold M, Bousser MG, Fahrni G, Fischer U, Georgiadis D, Gandjour J, Benninger D, Sturzenegger M, Mattle HP, Baumgartner RW: Vertebral artery dissection:

presenting findings and predictors of outcome. *Stroke* 37: 2499–2503, 2006
2) Aoki N, Sakai T: Rebleeding from intracranial dissecting aneurysm in the vertebral artery. *Stroke* 21: 1628–1631, 1990
3) Mizutani T, Aruga T, Kirino T, Miki Y, Saito I, Tsuchida T: Recurrent subarachnoid hemorrhage from untreated ruptured vertebrobasilar dissecting aneurysms. *Neurosurgery* 36: 905–911; discussion 912–913, 1995
4) Albuquerque FC, Fiorella DJ, Han PP, Deshmukh VR, Kim LJ, McDougall CG: Endovascular management of intracranial vertebral artery dissecting aneurysms. *Neurosurg Focus* 18: E3, 2005
5) Iihara K, Sakai N, Murao K, Sakai H, Higashi T, Kogure S, Takahashi JC, Nagata I: Dissecting aneurysms of the vertebral artery: a management strategy. *J Neurosurg* 97: 259–267, 2002
6) Kurata A, Ohmomo T, Miyasaka Y, Fujii K, Kan S, Kitahara T: Coil embolization for the treatment of ruptured dissecting vertebral aneurysms. *AJNR Am J Neuroradiol* 22: 11–18, 2001
7) Peluso JP, van Rooij WJ, Sluzewski M, Beute GN, Majoie CB: Endovascular treatment of symptomatic intradural vertebral dissecting aneurysms. *AJNR Am J Neuroradiol* 29: 102–106, 2008
8) Rabinov JD, Hellinger FR, Morris PP, Ogilvy CS, Putman CM: Endovascular management of vertebrobasilar dissecting aneurysms. *AJNR Am J Neuroradiol* 24: 1421–1428, 2003
9) Sugiu K, Tokunaga K, Watanabe K, Sasahara W, Ono S, Tamiya T, Date I: Emergent endovascular treatment of ruptured vertebral artery dissecting aneurysms. *Neuroradiology* 47: 158–164, 2005
10) Yuki I, Murayama Y, Viñuela F: Endovascular management of dissecting vertebrobasilar artery aneurysms in patients presenting with acute subarachnoid hemorrhage. *J Neurosurg* 103: 649–655, 2005
11) Endo H, Matsumoto Y, Kondo R, Sato K, Fujimura M, Inoue T, Shimizu H, Takahashi A, Tominaga T: Medullary infarction as a poor prognostic factor after internal coil trapping of a ruptured vertebral artery dissection. *J Neurosurg* 118: 131–139, 2013
12) Lee JM, Kim TS, Joo SP, Yoon W, Choi HY: Endovascular treatment of ruptured dissecting vertebral artery aneurysms—long-term follow-up results, benefits of early embolization, and predictors of outcome. *Acta Neurochir (Wien)* 152: 1455–1465, 2010
13) Rosengart AJ, Schultheiss KE, Tolentino J, Macdonald RL: Prognostic factors for outcome in patients with aneurysmal subarachnoid hemorrhage. *Stroke* 38: 2315–2321, 2007
14) Taki W, Sakai N, Suzuki H; PRESAT Group: Determinants of poor outcome after aneurysmal subarachnoid hemorrhage when both clipping and coiling are available: Prospective Registry of Subarachnoid Aneurysms Treatment (PRESAT) in Japan. *World Neurosurg* 76: 437–445, 2011
15) Dorhout Mees SM, Rinkel GJ, Hop JW, Algra A, van Gijn J: Antiplatelet therapy in aneurysmal subarachnoid hemorrhage: a systematic review. *Stroke* 34: 2285–2289, 2003
16) van den Bergh WM, Kerr RS, Algra A, Rinkel GJ, Molyneux AJ; International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group: Effect of antiplatelet therapy for endovascular coiling in aneurysmal subarachnoid hemorrhage. *Stroke* 40: 1969–1972, 2009
17) Barr JD, Lemley TJ: Endovascular arterial occlusion accomplished using microcoils deployed with and without proximal flow arrest: results in 19 patients. *AJNR Am J Neuroradiol* 20: 1452–1456, 1999
18) Graves VB, Perl J, Strother CM, Wallace RC, Kesava PP, Masaryk TJ: Endovascular occlusion of the carotid or vertebral artery with temporary proximal flow arrest and microcoils: clinical results. *AJNR Am J Neuroradiol* 18: 1201–1206, 1997
19) Kudo T, Iihara K, Satow T, Murao K, Miyamoto S: Incidence of ischemic complications after endovascular treatment for ruptured dissecting vertebral artery aneurysms. Comparison between those arising proximal to and distal to the origin of the posterior inferior cerebellar artery. *Interv Neuroradiol* 13(Suppl 1): 157–162, 2007
20) Narata AP, Yilmaz H, Schaller K, Lovblad KO, Pereira VM: Flow-diverting stent for ruptured intracranial dissecting aneurysm of vertebral artery. *Neurosurgery* 70: 982–988; discussion 988–989, 2012
21) Park SI, Kim BM, Kim DI, Shin YS, Suh SH, Chung EC, Kim SY, Kim SH, Won YS: Clinical and angiographic follow-up of stent-only therapy for acute intracranial vertebrobasilar dissecting aneurysms. *AJNR Am J Neuroradiol* 30: 1351–1356, 2009
22) Suzuki S, Kurata A, Iwamoto K, Sato K, Niki J, Miyazaki T, Yamada M, Oka H, Fujii K, Kan S: Endovascular surgery using stents for vertebral artery dissecting aneurysms and a review of the literature. *Minim Invasive Neurosurg* 51: 193–198, 2008

Address reprint requests to: Tetsu Satow, MD, PhD, Department of Neurosuergery, National Cerebral and Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan.
e-mail: tetsus@ncvc.go.jp