

[Title of Paper]

Mobile endovascular therapy for acute treatment of ruptured vertebral artery dissecting aneurysm in multiple hospitals

[Authors]

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Abstract

Background The patients with ruptured vertebral artery dissecting aneurysm (rVADA) should be treated as early as possible because VADA carries extremely high risk of rebleeding in the acute phase. We have established a mobile endovascular strategy for the patients with rVADA between our flagship center and its affiliated local hospitals. We introduced and reviewed our mobile endovascular therapy in this study.

Methods We retrospectively evaluated 98 consecutive patients who underwent endovascular surgery for rVADA from 2000 to 2018 at our institution or five affiliated hospitals. When each patient was initially transported to the local affiliated hospitals, neuroendovascular surgeons traveled directly to the affiliated hospital from the flagship center in order to treat the patient there. Clinical outcomes using modified Rankin Scale at six months after treatment, radiological results and procedure-related complications were reviewed to justify our mobile endovascular strategy.

Results All aneurysms were cured successfully by internal trapping. Favorable outcome was achieved in 61 patients (62.2%) even though 53 patients (54.1%) had presented with severe subarachnoid hemorrhage. Overall mortality rate, treatment-related mortality rate, and treatment related complication rate were 18.4% (18/98), 0%, and 16% (16/98), respectively. There were no differences in clinical and radiological outcomes between the patients treated in the flagship center and those who treated in the affiliated hospitals. Treatment in the affiliated hospital was not a predictive factor of unfavorable outcome in our multivariate analysis, and elderly age (≥ 60) was negatively associated with favorable outcome.

Conclusions Our results prove the efficacy and safety of mobile endovascular therapy for the treatment of rVADA in the ultra-acute stage. Mobile endovascular therapy may work well in the acute treatment of rVADAs in the certain circumstance.

Keywords: endovascular treatment, vertebrobasilar, dissection, subarachnoid hemorrhage, stroke units

Introduction

Ruptured vertebral artery dissecting aneurysms (rVADAs) have been recognized as an important cause of hemorrhagic stroke[22]. The efficacy and safety of endovascular treatment for VADAs are now widely recognized[3, 5, 12, 23]. Ruptured VADAs have a high rate of rebleeding (50-70%) and mortality (20-50%) in the ultra-acute stage of their onset, so early intervention is strongly recommended[10, 15, 19].

Although there are a lot of stroke hospitals in Japan, most of them, especially those in rural areas, are small to medium in size and they often have no neuroendovascular surgeons on staff. Transfer of the patients with untreated rVADA from such a local hospital to a flagship center might cause fatal re-bleeding, because transfer itself might be huge stress for the patients[9, 16]. Thus, we have supposed that the transfer of the endovascular surgeon might be better rather than transfer of the patients in such emergent situation. We have established a standardized therapeutic strategy for rVADAs between our flagship center and its local affiliated hospitals.

When a patient is initially admitted to one of our affiliated hospitals, a neuroendovascular surgeon travels from the flagship center directly to the affiliated hospital to treat the patient there. We retrospectively evaluated the clinical and imaging outcomes of patients with ruptured VADAs treated by our endovascular treatment team in multiple hospitals in this study.

Methods

Patient population

We retrospectively reviewed all patients who underwent endovascular treatment of rVADAs between 2000 and 2018 at our flagship institution or one of our five affiliated hospitals. VADAs were diagnosed by digital subtraction angiography or CT angiography when a pearl-and-string sign or a fusiform dilatation was identified at the vertebral artery. Patients with subarachnoid hemorrhage (SAH) due to ruptured VADAs were all included in this study. Less than six months' follow-up, insufficient angiographic data, intracranial stent usage for VA preservation, and previously treated cases were excluded from the study. The Institutional Review Board at each institution approved this study and information about opt-out was put up in each hospital.

Baseline characteristics

Patient data including age, sex, anatomical features of the aneurysm, severity of the SAH (Hunt and Kosnik grade), rebleeding before treatment, and treatment modalities were obtained from medical records. The time from onset to intervention and the angiographic follow-up duration were also reviewed. The laterality of the lesion and posterior inferior cerebellar artery (PICA) involvement were checked as anatomical features of the aneurysm. VADAs were classified into four types according to their location in relation to the PICA origin: pre-PICA, post-PICA, non-PICA and PICA-involved types. Rebleeding before treatment was detected when sudden neurological deteriorations with major change of vital signs were observed.

Treatment strategy

All cases of ruptured VADA were treated as early as possible even if the patient's condition was severe (H&K

grade IV or V). If the patient was initially admitted to an affiliated hospital with interventional capacity but no neurointerventionalist and diagnosed with SAH due to ruptured VADA, the primary physician consulted with an endovascular surgeon at the flagship center about the indicated treatment. If an endovascular surgeon was available, the surgeon rushed to the primary hospital (2-99 miles from the flagship center) and performed endovascular surgery at the primary hospital. If the endovascular surgeons are not available just on the time of onset, treatment was performed as soon as an endovascular surgeon was available.

All hospitals participating in this study had an intensive care unit and a capacity for providing standardized management for SAH in accordance with “Japanese Guidelines for the Management of Stroke”: the hospitals in this study had two or more neurosurgeons (but no neuroendovascular surgeon), and had a capability of providing 24/7 neurological surgery under general anesthesia (including craniotomy and ventricular drainage), neuroimaging study, and bed for neurointensive care. While waiting for the surgeon’s arrival, the patient was usually given a general anesthesia to prevent from fatal rebleeding. If the patient’s vital signs indicated that the patient was too unstable to treat, conservative therapy was selected during the acute phase and the endovascular procedure was performed in the subacute or chronic phase. The patients who underwent endovascular treatment in our flagship center included some who were transported from hospitals without sufficient interventional radiology equipment.

The endovascular management for each patient in this series was standardized. Ruptured VADAs were embolized with detachable coils sacrificing the parent artery (endovascular internal trapping), while the patients were under general anesthesia. Systematic heparinization of the patients was performed after the first coil or the first several coils were inserted. Internal trapping was performed keeping the embolized segment as short as possible. Patients who underwent internal trapping of VA received mono-antiplatelet medication only after endovascular treatment. Postoperative management of acute stage was controlled at the hospital in which each patient underwent the endovascular surgery.

Outcomes and complications

Clinical and radiological outcomes were also obtained from medical records. Clinical outcomes were evaluated according to a modified Rankin Scale (mRS) at six months after treatment. Surviving patients were scheduled for annual angiographic follow-up consisting of either magnetic resonance angiography or catheter-based angiography. Recurrence was defined as recanalization of VA or aneurysmal regrowth. All procedure-related complications were recorded. Ischemic complication was defined as symptomatic infarction confirmed by postoperative radiologic evaluation. Hemorrhagic complication was defined as intraprocedural rupture confirmed by contrast extravasation during procedure or newly developed hemorrhage confirmed by postoperative radiologic evaluation.

Statistical analysis

Variables are presented as counts (with percentage) for categorical variables and means $\pm$ standard deviations for continuous variables, except for the time from onset to treatment and the follow-up duration, which are presented as medians. Student’s t-test, the Mann-Whitney U test, Pearson’s chi-square test and Fisher’s exact

test were used to compare variables between groups as appropriate. Binary logistic regression analysis was used to measure the association between treatment in the affiliated hospitals and clinical outcome (favorable: mRS 0-2, unfavorable: mRS 3-6). For the multivariate analysis, we selected 7 variables, which consisted of 4 variables with P-value<0.05 in univariate models in the current study population (older age (≥ 60), severe H&K grade (IV or V), late treatment (time from onset to treatment >24h), and rebleeding before treatment), and 3 clinically relevant variables consistent with the previous reports (male sex, PICA involved type, and medullary infarction) [2, 12, 17]. The variable of treatment institution (“treated in the affiliated hospitals”) was also used as input. P-value <0.05 was considered to indicate significance. All statistical analyses were performed using JMP software version 10.0.2 (SAS Institute, Cary, NC, United States).

Results

A total of 100 patients with ruptured VADA were treated with an endovascular approach in our institution or one of our five affiliated hospitals between 2000 and 2018. Among them, one patient was excluded due to insufficient data, and another was excluded because of stent usage for VA preservation. Thus a total of 98 patients were enrolled in the current study. Their baseline values are shown in Table 1. The mean age of the patients was 52.9 ± 10.9 years (mean $\pm$ SD). The percentage with severe SAH (H&K grade IV or V) was 54.1%. Four patients had bilateral VADAs. In patients with bilateral lesions, the ruptured side was identified based on the morphological features of the aneurysms and distribution of the hematoma demonstrated by CT. There were 50 post-PICA VADAs, 15 PICA-involved VADAs, 12 pre-PICA VADAs, and 21 non-PICA VADAs. Sixty-seven cases (68.4%) were treated at an affiliated hospital, and 60 of these were treated within 24 hours of onset. Twenty-nine patients (29.6%) experienced sudden neurological deterioration prior to treatment, which we interpreted as indicative of rebleeding. None of the patients’ baseline characteristics was significantly different between the cases treated in the flagship hospital and in the affiliated hospitals.

Outcomes and complications

The details of our patients’ outcomes and complications are summarized in Table 2. Internal trapping was performed in all patients and no patients experienced treatment failure. Favorable clinical outcome (mRS 0-2) was achieved in 61 (62.2%) patients. As for patients with severe SAH, 45.3% (24/53 cases) obtained favorable outcomes. Seventeen other patients with severe SAH died within the first 30 days after treatment. One patient with bilateral VADAs died 10 days after intervention due to the rupture of the VADA contralateral to the treated side. Among the 80 surviving patients, 76 received postoperative radiologic evaluation and 65 received angiographic follow-up over the 46-month median follow-up duration (1-179 months). Total recurrence and retreatment rates were 6.3% (5/80) and 5.0% (4/80), respectively.

Two patients developed rupture of aneurysm during the procedure, but hemorrhage was minimal and both of them achieved good clinical outcome (mRS 1). Postoperative hemorrhage was observed in two patients; one of these, with bilateral VADAs, experienced bleeding from the VADA on the untreated side 10 days after the first treatment, and the other experienced rebleeding because of insufficient coil packing. Ischemic complications were

observed in 11 patients (11.2%), eight of whom experienced medullary infarction. The differences between the flagship hospital and the affiliated hospitals were not significant in terms of the rate of favorable outcome, complications, recurrence, and retreatment ($p=0.56, 0.57, 1.00$, and 1.00 , respectively).

Factors associated with unfavorable outcome

Among the reviewed variables, elderly age (≥ 60), severe H&K grade, and rebleeding before treatment were identified as significant factors predicting unfavorable clinical outcome in our univariate analysis (Table 3). Late treatment was significantly related to favorable outcome. The results of the multivariate logistic regression analysis showed that only one factor, elderly age, remained as an independent risk factor for unfavorable outcome (OR 4.26; 95% CI 1.02-17.8; $p=0.047$). Treatment in an affiliated hospital was not a significant predictive factor of unfavorable clinical outcome (OR 0.64; 95% CI 0.16-2.51; $p=0.52$).

Discussion

In the Japanese population, dissecting aneurysms occur most frequently at the intracranial VAs, and 53% of all cases present with SAH[22]. Previous reports have shown that ruptured VADAs should be treated as soon as possible because these lesions have an extremely high rate of rebleeding, especially within 24 hours of onset[10, 15]. Recently, endovascular treatment is preferred for VADA because of its efficacy and minimal invasiveness[18, 19]. A number of treatment modalities and strategies for VADAs exist, but the optimal therapy for each patient with VADA must be chosen empirically because no randomized controlled trials have compared the various treatment modalities[5]. To address this, additional information on long-term outcomes is desirable as it will help surgeons evaluate the different modalities and choose appropriate treatment strategies.

Although the efficacy of endovascular treatment is now widely recognized, the techniques are not yet available everywhere. To promote rapid diagnosis of and intervention in acute ischemic stroke with large vessel occlusion, mobile stroke units have been implemented in several countries. In addition, some authors have introduced new models of care for large vessel occlusion that require neurointerventionalists to travel to their patients (drip-and-drive or trip-and-treat models)[1, 21]. Although the number of certified neuroendovascular surgeons in Japan is gradually increasing year by year, it is still insufficient to meet the population's needs, especially in rural areas. Endovascular surgeons are not available in every hospital. In time-critical diseases such as SAH due to ruptured aneurysm, it is often more practical to transport the surgeon rather than the patient because such patients are generally in unstable condition that transfer is risky. For this reason, our institution has often sent expert neuroendovascular surgeons to the affiliated hospitals where patients with ruptured VADA were initially admitted. No previous reports have reviewed the clinical and radiological outcomes of ruptured VADA treated by a single expert team in multiple hospitals using mobile endovascular therapy.

Mobile endovascular therapy has a few problems. First, the timing of each intervention depends on the availability of the endovascular surgeon and the travel time, which can vary depending on the traffic situation. The time required for surgeon transfer may delay the timing of the intervention. Second, the protocol for surgeon transfer is not well established; this requires individual surgeons to make independent decisions on the spot, which can

cause in their being rushed and/or distracted, which can increase the risk of traffic collisions and stress. Finally, surgeons newly arrived from the flagship center are unfamiliar with the medical staff and the equipment in the affiliated hospital, which can lead to human errors in treatment. In our series, however, none of these potential issues caused insurmountable problems: treatment institution was not a factor influencing the clinical outcome, and 89.6% of patients treated in affiliated hospitals were operated on by a surgeon from the flagship center within 24 hours of onset. Thus, surgeon transfer was not associated with a higher risk of negative outcome or with an excessive delay in treatment intervention. We have usually asked our affiliated hospitals to introduce general anesthesia for the patient while waiting for the surgeon's arrival, in order to prevent from fatal rebleeding.

In the Japan Registry of Neuroendovascular Therapy 3 (JR-NET3), the most influential factor associated with favorable outcome in ruptured VADA cases was “the doctor responsible for treatment”[12]. The creators of this registry emphasize the importance of education and training in endovascular treatment to improve patient outcomes. Taking these findings together, we conclude that the question of who will perform the surgery is more significant than that of where the surgery will take place. Especially for unstable cases, surgeon transfer rather than patient transfer is an option in cases of ruptured VADA.

The proportion of patients with favorable clinical outcome (mRS 0-2) in the present study (61.6%) was comparable with those in previous reports[13, 14, 20]. In addition, the rate of favorable outcome in patients with severe SAH was 43.4%, which was similar to the results reported in JR-NET[12, 17]. Severe SAH with saccular aneurysm often does not warrant aggressive surgical treatment, whereas SAH due to VADA has a different pathological mechanism and clinical course. Because patients with ruptured VADAs often recover from their initial critical condition, we should consider surgical treatment for patients with ruptured VADAs even with severe SAH grades.

Rebleeding before treatment was significantly related to unfavorable outcome in our univariate analysis. Yet patients who received late treatment (more than 24 hours from onset) had better clinical outcome than patients who received early treatment (within 24 hours). These seem to be contradictory results; some possible explanations for this are as follows. The patients who received late treatment were survivors without crucial deterioration in the acute phase, that is, they were inherently mild cases. In addition, we aggressively treated all cases in the acute stage, even those with severe SAH. This practice could have ensured that the early treatment group included more cases with poor prognosis than the late treatment group did. Second, the possibility of rebleeding decreases markedly after 24 hours from onset because of aneurysmal wall remodeling[10]. This confirms that the contradictory results are a consequence of our aggressive intervention as early as possible, even in severe SAH cases. These results should not be taken to encourage late treatment, however, because, as previously shown, we achieved good clinical outcome for certain patients with severe SAH by preventing rebleeding. The detailed reasons for each instance of delayed intervention (onset to treatment > 24h) were not obtained in all cases. It is likely, however, that the most common reasons were the unavailability of surgeons and patients' severity at onset.

Sixteen patients (16.3%) had procedure-related complications, of which the most frequent type was ischemia. One of the major ischemic complications was medullary infarction (8 out of 11 ischemic complications) which

has elsewhere been reported to correlate with unfavorable outcomes[2]. Internal trapping can lead to occlusion of the perforators arising from the VA, and longer length of the trapped area is associated with a higher incidence of postoperative medullary infarction[7]. Since most of the ruptured VADA sites corresponded to the most markedly dilated segments, occlusion of the dilated segment only might be sufficient to avoid rebleeding[11]. For this reason we have attempted to occlude only the dilated segment of each VADA, keeping the coil mass as short as possible. In previous reports, the incidence of medullary infarction after internal trapping for ruptured VADA has ranged from 5.6 to 47%[2, 4, 6, 8]. Because our incidence of symptomatic medullary infarction (8 out of 76 cases with postoperative imaging) falls within this range, our internal trapping strategy for VADA appears to be effective and reasonable. In our series, unlike those in previous reports, the presence of ischemic complications including medullary infarction was not a predictive factor of clinical outcome. This is because most of the ischemic complications presented with only minor symptoms that did not affect patient outcomes. The reason why the ischemic complications in our series were not severe is uncertain, but our practice of limiting the length of the occluded segment might have contributed to this outcome. However, this short segment occlusion strategy has a potential risk of recurrence of the dissection. So close follow-up study might be needed after the treatment. Other treatment strategies, such as stent-assisted coil embolization and flow diverter stent, or other protocol of anticoagulant drugs might reduce the ischemic complications. However, for the moment, all kinds of intracranial stent are off-label for a ruptured aneurysm in our country. And there is no definitive consensus about which and how many anticoagulants should be used after an internal trapping. Further studies are needed to clarify the best strategy for rVADAs.

This retrospective study had several limitations. First, we were unable to perform postoperative radiological evaluation for all patients. Patients who had died and those with poor prognosis did not undergo sufficient radiological follow-up, so there could be a selection bias for radiological outcomes. This would lead to small ischemic complications with minimal symptoms being overlooked in some patients, which would account for the unexpectedly low rate of ischemic complications. The rates of recurrence and retreatment could be also underestimated for the same reason. Second, because the imaging equipment varied between the institutions, imaging protocol and quality were not unified throughout the study. Finally, rebleeds were identified clinically without imaging studies. This might make some false positive cases about rebleeds.

Conclusions

The current study shows the efficacy and safety of our mobile endovascular therapy in the treatment of ruptured VADA in the acute stage. Although there is room for improvement in terms of the availability of endovascular surgeons and the incidence of complications, the outcomes of our endovascular treatment for VADA were comparatively favorable even in the affiliated hospitals.

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Compliance of Ethical Standards**Conflict of Interest**

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethics Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the research committee of each institution in this study and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Author Contributions

Naoya Kidani and Kenji Sugiu contributed to the study conception and design. Material preparation, data collection and analysis were performed by Kaoru Terasaka, Hiroyuki Nakashima, Koji Tokunaga, Kazuki Kobayashi, Hirokazu Kambara.

The first draft of the manuscript was written by Naoya Kidani and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Demographic data and clinical characteristics of the patients

	Flagship center	Affiliated hospitals	
	n=	31 (%)	67 (%)
			p value
Age, mean $\pm$ SD		51.8 $\pm$ 11.4	55.2 $\pm$ 9.2
Male sex		18 (58.1)	39 (68.4)
Hunt & Kosnik grade			
I-III		13 (41.9)	32 (47.8)
IV & V		18 (58.1)	35 (52.2)
Laterality			
Right		19 (61.3)	36 (53.7)
Left		10 (32.3)	29 (43.3)
Bilateral		2 (6.5)	2 (3.0)
Location of ruptured VADA			
Post PICA		19 (61.3)	31 (46.3)
PICA involved		4 (12.9)	11 (16.4)
Pre PICA		3 (9.7)	9 (13.4)
Non PICA		5 (16.1)	16 (23.9)
Time from onset to treatment			
median (hours)		6 [2;600]	6 [3;120]
<24 hours		24 (77.4)	59 (88.1%)
>24 hours		7 (22.6)	8 (11.9)
Rebleeding before treatment		8 (25.8)	21 (31.3)

SD indicates standard deviation; VADA, vertebral artery dissecting aneurysm; PICA, posterior inferior cerebellar artery

* Student t-test, † Pearson's χ^2 test, ‡ Mann-Whitney's U test

Table 2. Outcomes and complications

	Flagship center	Affiliated hospitals	
n=	31 (%)	67 (%)	p value
mRS at 6 months			
0	10 (32.3)	17 (25.4)	
1	6 (19.4)	19 (28.4)	
2	2 (6.5)	7 (10.4)	
3	3 (9.7)	2 (3.0)	
4	2 (6.5)	3 (4.5)	
5	3 (9.7)	6 (9.0)	
6	5 (16.1)	13 (19.4)	
Favorable outcome (mRS 0-2)	18 (58.1)	43 (64.2)	0.56 [†]
Procedural complication			
Total	6 (19.4)	10 (14.9)	0.57 [§]
Ischemic	4 (12.9)	7 (10.4)	0.74 [§]
Hemorrhagic	2 (6.5)	2 (3.0)	0.58 [§]
Puncture site	0	1 (1.5)	
Angiographical follow up			
median (months)	53 [1;172]	35 [1;179]	
Recurrence	1 (3.2)	4 (6.0)	1.00 [§]
Retreatment	1 (3.2)	3 (4.5)	1.00 [§]

mRS indicates modified Rankin Scale.

[†] Pearson's χ^2 test, [§] Fisher's exact test

Table 3. Factors associated with unfavorable outcome

Variable	Total n = 98 (%)	Favorable outcome 61 (%)	Unfavorable outcome 37 (%)	Univariate analysis	Multivariate analysis	
				OR (95% CI)	OR (95% CI)	p value
Elderly age (≥ 60)	25 (25.5)	10 (16.4)	15 (40.5)	3.48 (1.35-8.93)	4.26 (1.02-17.8)	0.047
Male	57 (58.2)	37 (60.7)	20 (54.1)	0.76 (0.33-1.74)	1.28 (0.35-4.69)	0.71
Severe Hunt & Kosnik grade	53 (54.1)	24 (39.3)	29 (78.4)	5.59 (2.19-14.3)	2.74 (0.65-11.6)	0.17
PICA involved type	15 (15.3)	6 (9.8)	9 (24.3)	2.95 (0.95-9.11)	0.66 (0.061-7.04)	0.73
Late treatment (onset to treatment > 24 hours)	15 (15.3)	14 (23.0)	1 (2.7)	0.09 (0.011-0.74) ‡	0.19 (0.019-1.86)	0.15
Rebleeding before treatment	29 (29.6)	13 (21.3)	16 (43.2)	2.81 (1.15-6.88)	1.12 (0.25-5.05)	0.89
Treated in the affiliated hospital	67 (68.4)	43 (70.5)	24 (64.9)	0.77 (0.32-1.85)	0.64 (0.16-2.51)	0.52
Medullary infarction	8 (8.2)	6 (9.8)	2 (5.4)	0.85 (0.16-4.44)	1.63 (0.26-10.3)	0.61

Favorable outcome is considered for patients with modified Rankin Score of 0-2, and unfavorable outcome is considered for patients with score of 3-6.

OR indicates odds ratio; CI, confidence interval; PICA, posterior inferior cerebellar artery

‡ Late treatment was *positive* predictor of favorable outcome.