

Endovascular Management of Vertebral Artery Dissecting Aneurysms: Review of 25 Patients

Disekan Vertebral Arter Anevrizmalarının Endovasküler Yönetimi: Yirmi Beş Hastanın Tedavisinin İncelenmesi

ABSTRACT

AIM:Management of Vertebral Artery (VA) dissections remains controversial. The clinical and angiographic variables of VA dissections were evaluated to demonstrate the safety and efficacy of endovascular intervention in treatment of VA dissecting aneurysms.

MATERIAL and METHODS: 25 patients with 27 VA dissecting aneurysms were treated with endovascular intervention during the last 10 years. 17 patients were admitted with subarachnoid hemorrhage. 23 aneurysms treated using destructive endovascular trapping, while reconstructive techniques were used in 3 aneurysms treated with stent-assisted coiling and one aneurysm treated with false lumen embolization.

RESULTS: The right VA was involved in 14 patients, the left VA in 9 patients, while 2 patients had bilateral VA dissection. The pearl and string sign was the commonest angiographic sign in 12 aneurysms. Perioperative complications included; rebleeding in one patient, symptomatic brain stem infarction in two patients and silent cerebellar ischemic lesion in one patient. A favorable outcome was evident more in patients with unruptured VA dissection (100%) versus (76.5%) in patients presented with SAH.

CONCLUSION: The endovascular technique should be individualized according to the clinical status of the patient, angiographic variables, condition of the posterior circulation and the available supplies.

KEYWORDS: Vertebral artery, Dissecting aneurysm, Coiling, Stent, Rebleeding, Endovascular management

ÖZ

AMAÇ: Vertebral arter diseksiyonunun yönetimi halen tartışmalıdır. Vertebral arter diseksiyonunun klinik ve anjiyografik farklılıkları ile vertebral arterin disekan anevrizmalarının endovasküler yol ile tedavisinin etkinliği ve güvenilirliği bu çalışmada değerlendirilmiştir.

YÖNTEM ve GEREÇ: Son on yılda saptanan toplam 25 vertebral arter disekan anevrizması olan hasta çalışmaya dahil edildi. Yirmibeş hastada 27 vertebral arter disekan anevrizması saptandı. Hastaların tamamı endovasküler yol ile tedavi edildi. Onyediyedi hasta subaraknoid kanama tanısı ile hastaneye kabul edildi. Toplam 27 vakanın tedavi şekli bu şekilde yapıldı: Yirmiüç anevrizma destrüktif endovasküler tuzaklama (trapping), üç vakaya stent yardımcı koilleme, son bir vaka ise ters lümen embolizasyonu (false lumen embolization) yolu ile tedavi edildi

BULGULAR: Hastaların ikisinde bilateral vertebral arter diseksiyonu, 9 hastada sol vertebral arter, 14 hastada ise sağ vertebral arter diseksiyonu saptandı. En sık görülen anjiyografik bulgu 12 hastada görülen tesbihleşme (pearl and string) işaretiydi. Perioperatif olarak, Bir hasta ikincil kanama geçirdi (Rebleeding), bir hastada beyin sapı nekrozu gelişti ve iki hastada ise sessiz serebellar iskemik lezyon gelişti. Patlamamış vertebral arter diseksiyonlarında hastalar % 100 oranında tedaviye olumlu sonuç verirken, bu oran subaraknoid kanama ile gelen hastalarda %76.5 olarak bulundu. anevrizmalarda

SONUÇ: Endovasküler tedavi hastanın kliniğine, posterior sistem vasküler varyasyonları ve posterior sistemin besleyici sistemlerine göre özelleştirilmelidir.

ANAHTAR SÖZCÜKLER: Disekan anevrizma, Koilleme, Stent, Vertebral arter, Yeniden kanama, Endovasküler yönetim

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INTRODUCTION

Vertebral artery dissection has two major types of presentation; the hemorrhagic type which presents with subarachnoid hemorrhage (SAH) caused by rupture of an intradural VA dissecting aneurysm, and ischemic type which presents with vertebrobasilar insufficiency or posterior circulation infarction attributable to arterial narrowing and thromboembolism (18). This different presentation depends on the plane of dissection. In the first group of patients, the plane of dissection is mainly subadventitial and the dissection is confined to the VA, there for dissection presents with SAH, while in the ischemic group, the plane of dissection is mainly subintimal and extends to the basilar artery (20). Strategies of vertebral artery dissection management remain unestablished and are individualized for each patient on the basis of clinical aspects and angiographic finding (18). As the majority of VA dissecting aneurysms arises distal to the Posterior inferior cerebellar artery (PICA) with a midline location, conventional surgical repair is a technically demanding with high morbidity and mortality (25, 26). The continuous advances in endovascular surgery which initially introduced to treat neurovascular pathologies inaccessible to open surgery were applied for treatment of VA dissections in several studies and case reports. However, the small numbers of patients in majority of the previously published series call for accumulated different centers experience in management of VA dissections to establish the safety and feasibility of endovascular intervention. This retrospective study was undertaken to present our experience with 25 patients and 27 VA dissecting aneurysms treated at our institution with different endovascular techniques during the last 10 years.

MATERIAL and METHODS

Between 1997 and 2006, 25 patients with 27 angiographically confirmed VA dissecting aneurysms were treated with endovascular intervention at our institution. Patients were divided into two groups; group A, 17 patients presented with confirmed SAH; group B, 8 patients with unruptured VA dissecting aneurysms presented with cerebral infarction, mass effect, or discovered incidentally after imaging for unrelated pathology. SAH was diagnosed on the basis of findings from computed tomography of the brain or the finding of

xanthochromia in the cerebrospinal fluid for one patient presenting with sudden severe agonizing headache with his CT brain was not conclusive. The clinical status of the patients was according to Hunt and Hess grading system (8). Three patients were H & H grade I, eight patients grade II, two patients grade III and four patients were grade V. The amount of blood in their initial computed tomography of the brain was according to Fisher grading system (5). All patients receive 3 H therapy (after embolization), selective calcium channel blockers (nicardipine), while dehydrating measures were restricted to the five patients with high grade SAH. External ventricular drainage was used for cisternal irrigation and management of acute hydrocephalus with gradual multi- day weaning in four patients. The aneurismal origin of SAH was confirmed as VA dissection by 3 D-CTA, or DSA, while unruptured VA dissecting aneurysms was diagnosed using MRA, 3 D-CTA or conventional DSA. VA dissection was considered proven if the investigated artery showed pearl and string sign, pearl sign only, intimal flap, double lumen at angiography as well as intramural thrombus at the brain MRI. Endovascular technique used was dependent on the clinical presentation of the patient, angiographic characteristics of the dissecting aneurysm as regard the relation to PICA, the antegrade and retrograde blood flow from the contralateral VA. As regard the location of the aneurysm to PICA; aneurysms were grouped as being, proximal, involving or distal types. In patients with unruptured dissecting lesions, endovascular therapy was limited to cases with progressive enlargement of aneurismal dilatation or recurrent ischemic symptoms despite the prolonged courses of antiplatelet and antithrombotic conservative therapy. The endovascular treatment included internal trapping in 23 aneurysms and reconstructive intervention in the remaining 4 aneurysms as shown in Table (IV). Stent assisted coiling for reconstruction of the parent artery and embolization of the fusiform dilatation was employed in 3 aneurysms in two different patients as shown in Figure 3A,B,C,D, while false lumen embolization was used in one aneurysm as shown in Figure 1A,B,C,D. The stent assisted coiling was performed using the commercially available coronary stents in Japan. Two aneurysms were treated using self expanding Radius stent, 4X20 mm (Boston scientific, Fremont, Calif), while the

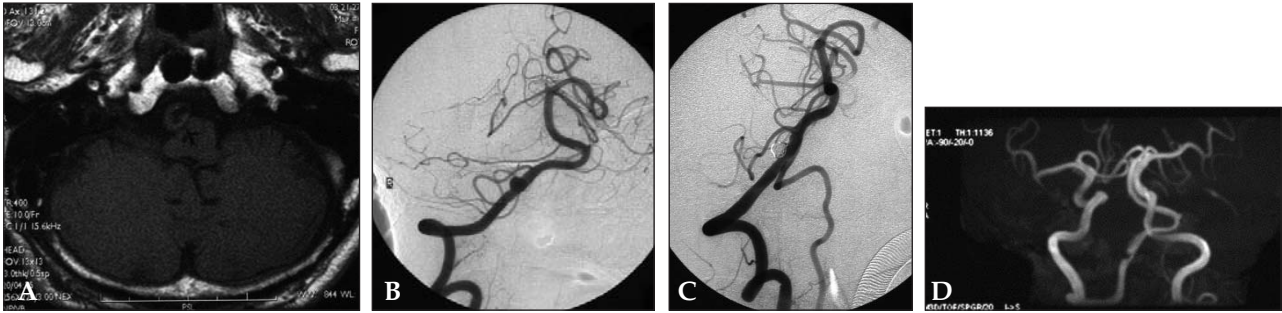


Figure 1: Right vertebral artery dissecting aneurysm treated with false lumen embolization.
 A- Axial MRI (T1-weighted image) showed the intramural thrombus of right VA dissecting aneurysm
 B- Right vertebral angiogram (AB view with slight obliquity) showed the double lumen of vertebral artery dissection
 C- Final right vertebral angiogram (AB view with slight obliquity) showed false lumen embolization
 D- Follow-up MRI, six months after embolization showed stable embolization of the false lumen with patent right vertebral artery

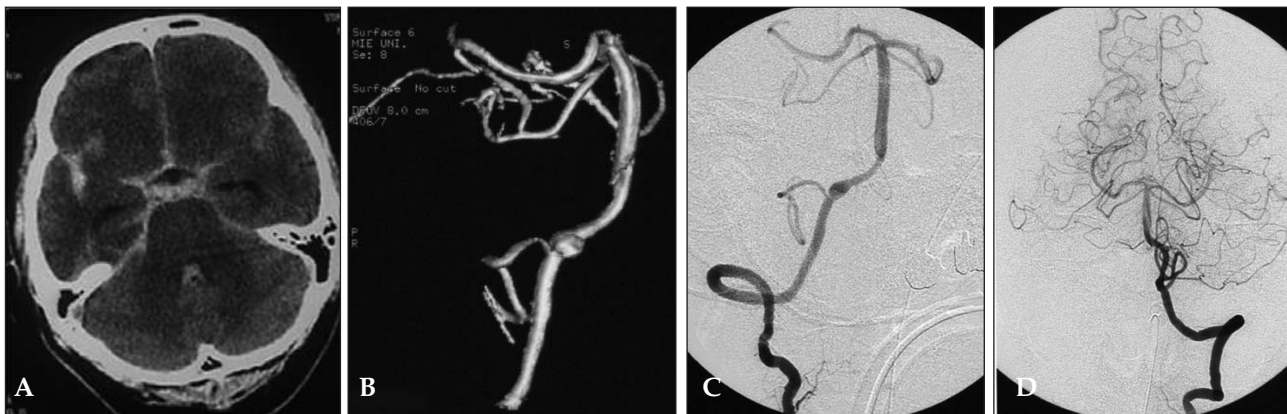


Figure 2: Right vertebral artery dissecting aneurysm treated with endovascular trapping.
 A- Initial CT brain of the patient presented with subarachnoid hemorrhage
 B- 3DCTA showed the pearl and string sign of VA dissection
 C- Right Vertebral angiogram (AB view with slight obliquity) confirm the diagnosis with PICA origin proximal to dissection
 D- Left vertebral angiogram (AB view) showed nourishment of posterior circulation from left vertebral artery
 E- Right vertebral angiogram (AB view) showed embolization of the dissected segment with preservation of PICA take off
 F- Left vertebral angiogram (AB view) showed patent nourishment of the posterior circulation with stable right vertebral artery occlusion

remaining aneurysm was treated using balloon expanding stent, S670, 3X24 mm (Medtronic, AVE, Santa Rosa, Calif). Embolization was performed with three types of coils; GDC (Target Therapeutic, Boston Scientific, Fremont, Calif), TruFill Detachable Coil System (Cordis Neurovascular, Miami Lakes, Fla) and ED coil (Kaneka Medics, Japan). Balloon occlusion test with investigation of the cerebral blood flow during and before the test using single photon emission tomography was performed for the patients with unruptured VA dissecting aneurysms

selected for internal trapping. Patients with ruptured VA dissecting aneurysms and PICA involved type; our technique included flow reduction by proximal VA occlusion and sparing of aneurysmal dilatation to preserve PICA take off. Strict angiographic follow up is essential, if more aneurysmal dilatation is confirmed, additional coiling of the dilated segment is initiated using the contralateral VA. All patients received 4000 to 5000 units of heparin at early embolization with an additional 1000 units/hour to prevent embolic

events. At the end of the procedure heparin was not reversed and left for natural tapering. Postprocedural, all patients underwent close neurological monitoring at our neurointensive care unit. Antiplatelet therapy with ticlopidine and aspirin was maintained for at least 3 months after treatment. Serial follow-up angiographic examinations were performed to ensure complete angiographic healing with occlusion of the dissected segment with conventional DSA or MRA. The patient outcome was according to Glasgow Outcome Scale (10). The duration of clinical and angiographic follow up range from 13 months to 10 years, mean 61.8 months.

Parametric data were expressed as means \pm SD. Univariate analysis was done on each variable using the chi-square test, Fisher's exact test or Student's test, as appropriate. A P value <0.05 was considered significant.

RESULTS

The clinical characteristics in the 25 patients are presented in Table (I,II). There was a predominance of male patients (84%). The ages of these patients ranged from 38 to 66 years (mean age was 50.29 \pm 7.76- years). Hypertension (20%) was the most commonly encountered risk factor, while 18 (72%) patients had no associated medical morbidity. Right VA was the site of aneurysm in 14 patients, left VA in 9 patients, while 2 patients had bilateral VA dissection. Pearl and string sign was the commonest angiographic sign in 12 (44.4%) aneurysms as shown in Table (III), while pearl sign only was reported in 11 (40.7%) aneurysms. PICA-distal type of VA dissection was reported in 14 (51.9%) lesions. All the patients with ruptured VA dissecting aneurysms were treated between days 0 to day 5 postictal including those with grade V with pressure from their families. All the planned endovascular procedures were completed successfully. Perioperative technical complications were encountered in 4 (16%) patients as shown in Table (V). The incidence of rebleeding after treatment in our patients whom presented with SAH was 5.9% (1/17). Periprocedural brain stem infarction due to distal thromboembolism occurred in two patients, while the remaining patient demonstrated silent cerebellar ischemia after embolization. Rebleeding after successful initial embolization and symptomatic cerebral ischemia precipitated

additional morbidity or death in the three patients. Retreatment with additional coiling of the dilated segment was performed in two patients with PICA involved type, while no additional treatment was performed for the only patient who suffered rebleeding after internal endovascular trapping due to poor clinical status. This retreatment did not precipitate additional morbidity or mortality apart from the small silent cerebellar ischemic lesion in the postoperative diffusion-weighted MR imaging in one patient after PICA sacrifice. 19 (76%) patients showed favorable outcome (good recovery and moderate disability), while three patients died from rebleeding, or initial brain stem injury after SAH. Good recovery was significantly evident in patients with unruptured VA dissection (75%) versus (47%) in patients presented with SAH as shown in Table (VI.) None of the 21 survivors had experienced hemorrhagic or ischemic complications during the mean follow up period 61.8 months.

DISCUSSION

VA dissecting aneurysms usually occurred in young men (9). The mean age of patients in our study is 50.29-years. This coincides with that reported in the series of Ahn and others; the mean age in their study was 51- years (1), while, Kurata and his colleagues (13), and Nakagawa et al (18) reported patients of older age than our study. The mean age was (54 and 55.2-years) respectively. We demonstrated marked male predominance in our study, Nakagawa and coworkers (18), reported 76.5% of their patients were male, Naito and others (17), Kurata and others showed male dominance in their study as 79.2% of the treated patients were male (13). Similar gender difference was also evident in extracranial carotid dissection (4), and is unlikely due to a sex based selection bias as in our study. This may partially attributable to higher frequency of minor trauma in men during their routine daily activities. Another possible contributing factor might be the difference in strength of neck muscles and dynamic stabilization during head acceleration between both sexes (22). Dissecting aneurysms showed some degree of sidedness in our study; right vertebral artery was involved in 60.9% of the patients treated excluding two patients with bilateral VA dissection. The right side predominance was noted in the recently published series by Rabinov and others (19). 21/35 (60%) patients were treated for dissecting aneurysms of their right VA. Mizutani and

Table I: Demographic Characteristics of the 25 Patients

Case	Age	Sex	Risk factors	Clinical presentation	H&H grade	Fisher grade	Outcome GOS
1-	46	M	Hypertension	Headache, Vomiting Disturbed consciousness	III	III	GR
2-	39	M	No	Wallenberg syndrome	-	-	MD
3-	46	M	No	Disturbed consciousness	II	III	Death
4-	42	M	No	Wallenberg syndrome	-	-	GR
5-	55	F	No	Headache, Disturbed consciousness	II	III	MD
6-	41	M	No	Headache	I	I	GR
7-	43	M	No	Vertigo	-	-	MD
8-	48	M	Hypertension	incidental	-	-	GR
9-	48	M	No	Headache, Disturbed consciousness	II	III	GR
10-	61	M	CHD	Headache, Disturbed consciousness	II	III	MD
11-	52	M	MD, CHD	Headache, Disturbed consciousness	II	I	MD
12-	41	M	No	right-facial numbness	-	-	GR
13-	38	M	No	Headache, Disturbed consciousness	III	III	GR
14-	52	M	Hypertension	Vertigo	-	-	GR
15-	50	M	No	Headache, Disturbed consciousness	II	III	GR
16-	59	M	Hypertension	Headache	I	II	GR
17-	59	M	No	Disturbed consciousness	V	III	Death
18-	56	F	No	Disturbed consciousness	V	IV	PVS
19-	47	F	No	Headche, vomiting	II	III	MD
20-	51	M	No	Vertigo	-	-	GR
21-	50	M	No	Headache	I	II	GR
22-	60	F	No	Disturbed consciousness	V	III	Death
23-	66	M	No	Headache	-	-	GR
24-	50	M	CHD,	Disturbed consciousness Hypertension	V	III	MD
25-	62	M	No	Disturbed consciousness	II	III	GR

Table II: Summary of Patients' Characteristics.

parameters	(n=25)	%
Age (years): Mean±SD (range)	50.49±7.73 (38–66)	
Sex (M/F):	21/4	84/16
Risk Factor:		
No	18	72
Hypertension	5	20
CHD	3	12
CHD+DM	1	4
Hypertension+CHD	1	4
Clinical presentation:		
Headache	12	48
Vomiting	2	8
Disturbed consciousness	13	42
Wallenberg syndrome	2	8
Vertigo	3	12
incidental	1	4
right facial numbness	1	4
H&H grade:		
	Median II (Range I-V)	
None	8	32
I	3	12
II	8	32
III	2	8
IV	0	0
V	4	16
Fisher grade:		
	Median III (Range I-IV)	
None	8	32
I	2	8
II	2	8
III	12	48
IV	1	4
Outcome GOS:		
GR	14	56
MD	7	28
SD	0	0
PVS	1	4
Death	3	12

GR; good recovery, MD; moderate disability, SD; severe disability, PVS; persistent vegetative state, CHD; coronary heart disease, DM; diabetes mellitus



Figure 3: Bilateral vertebral artery dissecting aneurysms treated with stent-assisted coiling.

A- Right vertebral angiogram (AB view) showed bilateral vertebral artery dissecting aneurysms

B- Right vertebral angiogram (AB view) after stent-assisted coiling of left VA dissecting aneurysm

C- Right vertebral angiogram after treatment of the right vertebral artery dissecting aneurysm six months after initial embolization showed stable aneurysmal occlusion with patent vertebral arteries

D- Follow up vertebral angiograms (AB and Lateral views) after one year showed stable embolization and patent parent arteries

Table III: Angiographic Characteristics of 27 VA Dissecting Aneurysms

Characteristics	No (27) & %
Sidedness	
Right	14 (51.8%)
Left	9 (33.3%)
Bilateral	4 (14.7%)
Location of PICA	
Distal	14 (51.9%)
Proximal	8 (29.6%)
Involved	2 (7.4%)
Double PICA pattern	1 (3.7%)
AICA-PICA pattern	2 (7.4%)
Angiographic feature of the aneurysm	
Pearl & String	12 (44.4%)
Pearl only	11 (40.7%)
Constriction and distal Tapering	3 (11.1%)
Double lumen	1 (3.7%)

Table IV: Endovascular Techniques Applied for Treatment of VA Dissecting Aneurysms

Technique	No of aneurysms
Internal trapping	23
Stent-assisted coiling	3
False lumen embolization	1

Table V: Perioperative Technical Complications

Complication	No of patients (25)	management
Angiographic recanalization	2 (8%)	Retreatment
Rebleeding	1 (8%)	No treatment
Distal Ischemia (Wallenberg Syndrome)	2 (8%)	Anticoagulant

coworkers (15) demonstrated the right side predominancy (24:13) representing (64.9%) of their patients. The authors excluded four patients with bilateral VA dissecting aneurysms and one patient with a basilar artery dissecting aneurysm.

Preoperative angiogram in our study showed that pearl and string sign is the most common

pathognomonic angiographic signs of VA dissection. Kitanaka and his colleagues reported pearl and string sign in 14 of the 16 patients with SAH (11). Hosoya et al (7) in their series of 31 patients with vertebrobasilar artery dissection, 20 patients had pearl and string sign, this represented 68.3% of the arteries treated. Naito and others (17) in their series demonstrated pearl and string as the most commonly encountered angiographic signs in their 21 patients who initially presenting without SAH; further the two patients who developed early SAH in their study had typical pearl and string signs. The authors recommend early endovascular interventions in the acute stage for patients with unruptured VA dissections who had this aneurismal dilatation. This was also our protocol in treatment of unruptured VADA. All patients received initial prolonged periods of conservative therapy using antiplatelet and antithrombotic medications. The decision to operate was after failure of spontaneous healing of aneurismal dilatation as shown in their follow up angiographic examinations. High perioperative technical complications with poor outcome can not be appreciated in those patients based on the natural history of unruptured VA dissection which is usually benign (18). Spontaneous healing of the dissected segment has been noted with low rate of recurrent ischemic attacks and favorable outcome with conservative treatment using antiplatelet and antithrombotic therapy (27). Yoshimoto et al demonstrated that 90% of their patients with unruptured VA dissecting aneurysms made a good recovery and returned to their previous lifestyle, although recurrent ischemic attacks was observed in two patients (27). Naito et al, reported good recoveries in 85.7% of their patients. The authors showed that no patient experienced further ischemic attacks, although three patients developed early or late SAH which is higher than previously considered (17). These results highlight the need for safe active treatment modality when dealing with such pathology. Our results with endoluminal repair compared favorably with the previous studies of conservative treatment.

Reconstructive and destructive strategies can be achieved with conventional surgical repair or the newly emerging endovascular interventions (1, 2). Reconstructive techniques which maintain the blood flow through the parent artery are more reasonable and specially indicated if important branches take

off the diseased segment or with insufficient collateral blood flow to the remainder of the posterior circulation (1). However; destructive endovascular procedures with proximal occlusion of the parent artery and occlusion of the dissected segment with detachable coils and/or balloons as shown in Figure 2A,B,C,D,E,F can be sufficient with favorable outcome in the majority of patients (9). The main concern with endovascular occlusion of the parent artery is the possibility of thrombus propagation to the PICA even if not included in the dissected segment and the perforators originating from the vertebral artery. Special attention is more required when dissection is near to the union of both vertebral arteries. Perforators can arise from the vertebrobasilar arteries between approximately 14 mm proximal and 16 mm distal to the union (14).

Recanalization of the VA after complete initial parent artery occlusion may be encountered with subsequent rebleeding as occurred in one of our patients. Sawada and associates reported two cases in which an occluded VA recanalized in an antegrade fashion, despite the fact that angiographic examination demonstrated complete occlusion of the affected site including the aneurysm and the parent artery (21). However; recanalization and subsequent rebleeding is not rare event after proximal clipping. Aoki and Sakai reported massive rebleeding from the dissecting aneurysm of the left vertebral artery that occurred intraoperatively following proximal clipping (3), in the series of Friedman and Drake (6), rebleeding occurred after proximal clipping of right vertebral artery dissecting aneurysm, Kitanaka and others reported rerupture of right vertebral dissecting aneurysm 18 days after proximal clipping (11). In the aforementioned studies, second operation was performed and

surgical trapping was done for all of the patients. However; a deeper operative field is required than when proximal clipping alone is attempted with subsequent injury to the surrounding structures, further, the distal clip may interrupt the blood flow to the vital perforating branches from the vertebral artery (11). In a series of 24 patients with intracranial vertebral artery dissection, 16 patients were admitted with SAH and 8 did not have SAH, Kitanaka et al, reported the perioperative surgical complications as follows; 68.4% of their patients had mild to severe cranial nerve palsy, 26.3% had new long tract signs which were considered representative of new brain stem ischemia, 21% had dangerous or troublesome respiratory complications (12). In a nationwide study (24), the complication rate in the surgically treated Japanese patients with hemorrhagic intracranial aneurysms was 27%, although the series revealed significantly better mortality rate (17%) in the patients who underwent surgery than the (44%) mortality rate of conservatively treated patients with similar clinical status on admission. The aforementioned series of conventional repair reported higher periprocedural complications than reported with endoluminal repair. Kurata et al, reported thromboembolic events in one of their 18 patients with ruptured VA dissection with infarction of PICA territory occurred (13), Ahn and others demonstrated no perioperative complications in 14 patients treated with stent placement(10 patients) or stent assisted coiling(4 patients). Their results may be limited with the lower incidence of complete aneurysmal occlusion, 6 patients out of 12 with follow up angiograms at 6-12 months demonstrated incomplete occlusion (1). Iihara and his colleagues reported that the treatment related morbidity was 16.7% in 18 patients; 12 cases

Table VI: Correlation Between Outcome and Clinical Presentation

Outcome	Ruptured VA Dissecting aneurysms No (17 pat)	Unruptured VA dissecting aneurysms No (8 pat)	P
GR	8(47%)	6 (75%)	<0.05
MD	5 (29.4%)	2 (25%)	>0.05
SD	-	-	
PVS	1 (5.9%)	-	
Death	3 (17.6%)	-	

P<0.05 is significant

without involvement of PICA and 6 cases with PICA involved type (9).

The over all prognosis of VA dissecting aneurysms in our study coincides with the previously published series, Rabinov et al, reported favorable outcome in 68% of 25 treated patients with 20% mortality rate at 3.5 years mean clinical follow up (19). Iihara et al reported good recovery in 64% of their patients whom presented with SAH and 100% in their patients with unruptured VADA with only 5.5% mortality rate in all patients treated (9).

Our study is limited with the heterogeneous endovascular techniques used for treatment of our patients. However; in absence of firm conclusions from large population studies, lack of long-term cumulative experience with endovascular therapy, unsimilar interventional supplies approved for humanarian use among different centers. We believe that the endovascular techniques for management of VA dissecting aneurysms should be individualized as regard the clinical presentation of the patient, the angiographic characteristics of dissection as well as the condition of the posterior circulation. Despite the aforementioned limitation, the lower incidence of periprocedural morbidity in our study as compared with previously published surgical complications adds to the safety and feasibility of endovascular intervention as minimally invasive standard modality for treatment of VA dissecting aneurysms.

CONCLUSIONS

The authors' experience demonstrates that the endovascular treatment is a minimally invasive safe and feasible treatment that should be considered standard and first choice in management of ruptured and unruptured dynamic vertebral artery dissecting aneurysms. The endovascular technique should be individualized according to the clinical presentation of the patient, angiographic variables of dissection, condition of the collateral and posterior circulation as well as the available supplies and expertise.

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