

# Clinical Risk Factors Affecting Procedure-Related Major Neurological Complications in Unruptured Intracranial Aneurysms

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**Purpose:** The operative risk and natural history rupture risk for the treatment of unruptured intracranial aneurysms (UIAs) should be evaluated. The purpose of this study was to report our experience with treating UIAs and to outline clinical risk factors associated with procedure-related major neurological complications. **Materials and Methods:** We treated 1158 UIAs in 998 patients over the last 14 years. All patients underwent operation performed by a single microvascular surgeon and two interventionists at a single institution. Patient factors, aneurysm factors, and clinical outcomes were analyzed in relation to procedure-related complications. **Results:** The total complication rate was 22 (2.2%) out of 998 patients. Among them, complications developed in 14 (2.3%) out of 612 patients who underwent microsurgery and in 8 (2.1%) out of 386 patients who underwent endovascular procedures. One patient died due to intraoperative rupture during an endovascular procedure. The procedure-related complication was highly correlated with age ( $p=0.004$ ), hypertension ( $p=0.002$ ), and history of ischemic stroke ( $p<0.001$ ) in univariate analysis. The multivariate analysis revealed previous history of ischemic stroke ( $p=0.001$ ) to be strongly correlated with procedure-related complications. **Conclusion:** A history of ischemic stroke was strongly correlated with procedure-related major neurological complications when treating UIAs. Accordingly, patients with UIAs who have a previous history of ischemic stroke might be at risk of procedure-related major neurological complications.

**Key Words:** Unruptured intracranial aneurysm, procedure, complication, ischemic stroke

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## INTRODUCTION

The number of unruptured intracranial aneurysms (UIAs) diagnosed is steadily increasing due to increasing numbers of geriatric patients with UIAs and increasing use of non-invasive imaging techniques. However, the process of selecting patients for treatment has not yet been well established, thus the risks of future ruptures and

complications of preventive treatments not yet being sufficiently evaluated.<sup>1</sup> The International Study of Unruptured Intracranial Aneurysms and the Unruptured Cerebral Aneurysm Study of Japan<sup>2</sup> showed an overall rupture rate with the range of 0.5% to 0.95% per year. Any treatment aiming to prevent rupture of aneurysms might reduce the rates of morbidity and mortality to below this range. Nevertheless, while many studies have analyzed the risk factors of rupture of UIAs, studies on procedure-related complications in UIA treatment are very few, due to their small incidence.

This study was conducted as a review of our experience to treat UIAs, as well as to assess clinical risk factors associated with procedure-related major neurological complications.

## MATERIALS AND METHODS

### Patients and methods

This retrospective study was approved by our Institutional Review Board and the patients informed consent were waived. We treated and retrospectively reviewed 1158 aneurysms in 998 patients during 14-year period (Table 1). All patients were treated by a single microvascular surgeon and two interventionists at a single cerebrovascular unit. Treatment de-

isions were made through interdisciplinary approaches by a neurovascular team. Age, gender, hypertension, diabetes mellitus, size, location, and functional outcome assessed by the modified Rankin Score (mRS) were evaluated. Other factors such as smoking, alcohol intake, or a family history of subarachnoid hemorrhage (SAH) were excluded because of omission of data in medical records in some patients.

Complication was defined as a new disability resulting in a mRS of greater than 1<sup>3</sup> at one day after surgery. The evaluation of post-treatment was done by an independent observer. After one year, functional outcomes of patients were evaluated, except for patients with diseases caused by other medical complications. All patients were followed up by digital subtraction angiography in the first year and magnetic resonance angiography in subsequent years.

Treatment criteria for UIAs were 1) patients with symptoms, 2) patients below 50 years of age, 3) with aneurysms larger than 5 mm, 4) with a daughter sac, 5) with prior SAH or family history, and 6) change of shape during the follow-up period.

Treatment modality was selected based on characteristics of individual patients and UIAs through interdisciplinary decision making, offering microsurgery as a primary treatment. The patients' preferences for treatment were also considered.

**Table 1. Baseline Characteristics of 998 Patients with 1158 Unruptured Aneurysms**

Characteristics	Clipping (n=612)	Coiling (n=386)	p value
Mean age, yrs±SD	54.9±11.9	67.2±7.2	<0.001
Sex, female/male	404/208	249/137	0.633
History of hypertension (%)	196 (32)	147 (38)	0.055
Diabetes mellitus (%)	67 (11)	50 (13)	0.364
Ischemic stroke history (%)	37 (6)	27 (7)	0.596
Patients with no comorbidity (%)	325 (53)	195 (51)	0.436
Symptoms (%)			
Headache	281 (46)	131 (34)	
Vertigo	55 (9)	46 (12)	
Ischemia/TIA	12 (2)	23 (6)	
Visual disturbance	18 (3)	0 (0)	
Cranial nerve palsy	12 (2)	0 (0)	
Seizure	1 (0.2)	4 (1)	
None	233 (38)	182 (47)	0.006
Number of aneurysms	728	430	
Mean size of aneurysms, mm±SD	6.1±2.3	7.3±3.8	<0.001
Location of aneurysms (%)			<0.001
ICA	211 (29)	293 (68)	
MCA	286 (39)	25 (6)	
ACA	214 (30)	47 (11)	
VB, PCA	17 (2)	65 (15)	

ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; VB, vertebrobasilar artery; PCA, posterior cerebral artery; TIA, transient ischemic attack; SD, standard deviation.

### Microsurgical techniques

During operation, efforts were made to preserve veins. Gradual dissection along the veins was made to avoid stretching. Veins were protected with cotton gauze to avoid heating injury during coagulation of adjacent structures. Large aneurysms were treated with multiple clippings to avoid kinking and stenosis of parent artery and perforators. Fenestrated clips were used for aneurysms with atheromatous necks to avoid squeezing and migration of atheroma. We tried to reduce the temporary clipping time for elderly patients with previous ischemic stroke since the duration of temporary clipping has been shown to be related to an increased occurrence of ischemic events.<sup>4,5</sup>

### Endovascular techniques

All endovascular coiling was performed under general anesthesia. Systemic heparinization (50 U/kg) was administered when a guiding catheter was placed. A single microcatheter was deployed if the morphology of the aneurysm was saccular with a narrow neck. Aneurysms with unfavorable angio-architecture were required adjunctive techniques (double catheter, balloon-assisted, and stent-assisted), at the discretion of the interventionists. Dual-antiplatelet agents were administered orally for 3 months, usually with stent-assisted coiling. Aspirin was maintained for at least more than 12 months. Cerebral angiographs were acquired to assess the degree of aneurysm occlusion and confirm detectable thromboembolic events.

### Statistical analysis

Statistical analysis was performed using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Variables are expressed as mean±SD, number of patients (%), as appropriate. For univariate analysis, Student t-test for continuous variables, and  $\chi^2$  test for categorical variables were used. Binary logistic regression analysis to calculate odds ratios and 95% confidence interval were used. In the univariate analysis, age, gender, hypertension, diabetes mellitus, size, location, and functional outcomes assessed by mRS were included. Multivariate logistic regression was carried out using variables with *p*-value less than 0.05 on univariate analysis. All *p*-values < 0.05 were considered statistically significant.

## RESULTS

In total, 1057 procedures for 1158 aneurysms were performed

including staged operations for multiple aneurysms. There were 612 female and 386 male patients. The mean age of the patients was 56±8 years. The patients in the clipping group (54.9±11.9 years) were younger than those in the coiling group (67.2±7.2 years, *p*<0.001). For treatment, 616 microsurgical operations and 441 endovascular procedures were performed. Multiple aneurysms represented 16% of cases. UIAs were most often found in patients with headaches. A greater number of asymptomatic patients were treated by coiling (47%) than clipping (38%, *p*=0.006). The most common location for aneurysms was the internal carotid artery (ICA; 43.5%), followed by the middle cerebral artery (26.9%). Aneurysms in the ICA or posterior circulation were treated by endovascular treatments (30.9%, microsurgery: 19.7%, *p*<0.001). Mean aneurysm size was 6.7±1.3 mm. The mean aneurysm size of the clipping group (6.1±2.3 mm) was smaller than that of the coiling group (7.3±3.8 mm, *p*<0.01) (Table 1).

On average, patients were followed for 26±10.7 months after discharge. Additional retreatment was performed in 4 patients (0.5%) of the microsurgical group and in 55 (12.8%) of the endovascular surgery group. Procedure-related complications occurred in 22 cases, including one death. Overall morbidity and mortality rates were 2.2% (22 out of 998 patients) and 0.1% (1 out of 998 patients), respectively (Table 2). Complication occurred in 14 patients (2.3%) of clipping group. The number of procedure-related complications in the coiling group was eight (2.1%). After clipping, the most common injury was vessel injury, followed by ischemic attack and post-op hematoma. In the coiling group, thromboembolism and rupture during the procedure were most common.

The factors affecting procedure-related complications were age (mean age in patients without complications: 59.7±10.6 years, mean age in patients with complications; 63.7±16.9 years, *p*=0.004), hypertension (*p*=0.001), and history of ischemic stroke (*p*<0.001) in univariate analysis. Past history of ischemic stroke (*p*=0.001) was strongly associated with functional outcomes in multivariate analysis (Table 3).

## DISCUSSION

We experienced 22 complications (2.2%; 2.3% in clipping group and 2.1% in coiling group) among a total of 998 patients with UIAs. Previous studies showed the rate of morbidity and mortality to range from 1.06% to 15.7%.<sup>6-10</sup> Com-

**Table 2. Patients Who Experienced Procedure-Related Major Neurological Complications**

No.	Sex	Age	Location	Size	Shape	Modality	Procedure-related complications	Risk factor	mRS (1 yr later)
1	F	72	A2-3, Lt.	9	Saccular	Clipping	Venous infarction, Confusion	Hypertension	1 (-)
2	F	61	ICPCOM, Lt.	5	Bilobular	Clipping	Infarction of Lt. internal capsule, Hemiparesis, Rt. G IV	Occipital infarction, Hypertension	2 (2)
3	F	56	ANCOM	6	Saccular	Clipping	Infarction of fornix, Impaired cognitive function	Rt. medullar infarction, Hypertension	1 (-)
4	F	68	MCBIF, Rt.	8	Saccular	Clipping	Infarction of Rt. basal ganglia, Weakness of Lt. arm, G II	Hypertension, Diabetes mellitus	4 (3)
5	F	77	ICPCOM, Rt.	11	Saccular	Clipping	Infarction of Rt. basal ganglia, Hemiparesis, Lt. G III	None	3 (4)
6	F	72	ICCHO, Rt.	7	Saccular	Clipping	Infarction of Rt. basal ganglia, Hemiparesis, Lt. G III	Lacunar infarction in peri-ventricles, Hypertension	3 (3)
7	F	59	MCBIF, Rt.	5	Saccular	Clipping	ICH around clipping site, Hemiparesis, Lt. G IV	Hypertension, Diabetes mellitus	1 (-)
8	F	66	MCBIF, Rt.	5	Saccular	Clipping	Infarction of Rt. basal ganglia, Hemiparesis, Lt. G IV	Lt. basal ganglia infarction, Hypertension	2 (2)
9	M	51	MCBIF, Rt.	9	Saccular	Clipping	Infarction of Rt. temporal lobe, Motor aphasia	Hypertension	2 (1)
10	F	52	ICoph, Lt.	5	Broad	Clipping	Lt. visual loss	None	1 (1)
11	F	65	M1, Lt.	5	Saccular	Clipping	Infarction of Lt. basal ganglia, Rt. facial palsy, Rt. leg weakness G III	Hypertension	3 (1)
12	F	65	MCBIF, Lt.	7	Broad	Clipping	Infarction of Lt. basal ganglia, Rt. facial palsy, Rt. hemiparesis G I dysarthria	Hypertension	4 (4)
13	M	64	VA, Lt.	18	Saccular	Clipping	Injury of AICA, Dysphagia, Rt. hemiparesis G III	Hypertension	5 (4)
14	F	64	IC-Oph, Lt.	6	Saccular	Clipping	Lt. visual loss	None	1 (1)
15	F	68	BABIF	5	Saccular	Coiling	Intraoperative rupture, Coma	Infarction of Rt. frontal, Hypertension	5 (5)
16	F	71	ICPCOM, Rt.	14	Saccular	Coiling	Infarction of Rt. MCA territory due to Thromboembolism, Lt. hemiplegia	None	4 (4)
17	M	77	ANCOM	5	Saccular	Coiling	Infarction of distal ACA territory, Both lower extremities weakness G III	Infarction of Lt. frontal, Hypertension	4 (4)
18	F	64	BABIF	6	Saccular	Coiling	Intraoperative rupture, Death	Infarction of Lt. basal ganglia	6 (6)
19	F	64	ANCOM	6	Saccular	Coiling	A2 occlusion due to coil migration, Stupor, Rt. hemiparesis G II	Lacunar infarction in peri-ventricles, Hypertension	5 (4)
20	F	56	ICA, Lt.	7	Saccular	Coiling	Intraoperative rupture, Drowsy mental status	None	1 (-)
21	F	62	ICPCOM, Lt.	9	Saccular	Coiling	Infarction of Lt. MCA territory, Thromboembolism, aphasia	None	1 (1)
22	M	48	VA, Lt.	7	Fusiform	Coiling	Infarction of Lt. cerebellum, Thromboembolism, Lt. deafness	Infarction of Rt. cerebellum with Rt. deafness	2 (2)

A2-3, distal anterior cerebral artery; ANCOM, anterior communicating artery; ICA, distal internal carotid artery; ICCHO, anterior choroidal artery; ICPCOM, posterior communicating artery; MCBIF, middle cerebral bifurcation artery; M1, proximal middle cerebral artery; MCA, middle cerebral artery; BABIF, basilar bifurcation artery; VA, vertebral artery; AICA, anterior inferior cerebellar artery.

**Table 3. Univariate Analysis and Multivariate Analysis of Various Factors Related Complications**

	Univariate analysis			Multivariate analysis		
	<i>p</i> value	OR for Cx	95% CI for OR	<i>p</i> value	OR for Cx	95% CI for OR
Age	0.004	1.059	1.018–1.102	0.327	1.028	0.972–1.088
HTN	0.002	4.233	1.709–10.485	0.339	1.798	0.54–5.981
Stroke Hx	<0.001	9.388	3.78–23.313	0.001	5.63	2.093–15.145
Size	0.073	1.115	0.99–1.257			
DM	0.699	0.749	0.173–3.245			
Location	0.097	2.558	0.845–7.746			

HTN, hypertension; Stroke Hx, past ischemic stroke history; DM, diabetes mellitus; Cx, complications; OR, odds ratio; CI, confidence interval.

pared to recent studies, the rates in the present study are similar: our results as well as those of previous reports showed slightly higher morbidity and mortality compared to the risk of rupture of UIAs.<sup>2,11</sup>

Our study revealed that procedural adverse events in the patients with treated UIAs were highly correlated to past history of ischemic stroke. In our study, patients who experienced thromboembolic complications in the coiling group tended to have a past history of ischemic stroke (62.5%). There is currently no report describing the direct relationship between procedure-related complications in the endovascular treatment of UIAs and history of ischemic stroke. According to several studies,<sup>12,13</sup> general anesthesia for endovascular treatment might be related to cerebrovascular injuries. Additionally, a history of ischemic stroke may be correlated with injuries to vessels in the surgical field. Furthermore, previous studies showed that the incidence of stroke events in patients with a history of stroke was higher than that in the general population after clipping.<sup>14,15</sup> Wiebers, et al.<sup>10</sup> suggested previous ischemic cerebral vascular disease as a predictive variable of poor surgical outcomes. In the present study, we found that age and hypertension were associated with procedure-related complications. However, in the previous studies, only the rupture risk of small UIAs was shown in patients with old age or hypertension.<sup>10,11</sup> Thus, age and hypertension may increase cerebrovascular events as atherosclerotic burdens.

Previous studies have suggested size,<sup>16</sup> location, multiplicity,<sup>17</sup> temporary clipping,<sup>18</sup> and calcification of the aneurysm<sup>19</sup> as predictors of outcomes for treatment of UIAs. In the present study, however, size did not show any statistical significance in our study. The reason is probably that, in regards to aneurysm size, our indications for treating UIAs were smaller than those in other studies; we treated UIAs with a size of 5 mm. As a result of genetic differences, aneurysms of Eastern Asian patients tend to rupture more easily at sizes smaller than 7 mm.<sup>2,11,20</sup> In addition to aneurysm

size, aneurysm location also did not affect the outcomes of treatment in this study. This might be because we preferred to treat anterior circulation aneurysms predominantly by clipping rather than coiling. Previous studies showed that posterior circulation is related to poor outcomes in the treatment of aneurysms.<sup>16,19,21,22</sup>

The recovery rate for neurologic deficits was higher in the clipping group [7 (50%) out of 14] than the coiling group [2 (25%) out of 8]. At one-year clinical follow-up, there were some cases in which complications were improved, and complications fully recovered in a few patients who exhibited neurologic deficits at discharge. According to subgroup analysis, the mean mRS of the clipping group with complications was 2.36 at one day after surgery and improved to 1.86 after one year. Meanwhile, the mean mRS of the coiling group with complications was 3.5 at one day after surgery, and nearly recovered to 3.13 after one year. Nevertheless, this difference between the two groups did not have statistical significance ( $p=0.357$ ).

The reason, that neurologic deficits tended to recover more frequently in the clipping group than the coiling group, might be relatively younger age ( $p<0.001$ ) of patients treated by microsurgery. Therefore, the chances that the procedure-related complications in the clipping group recovered over time might be higher than those for the coiling group. The another reason for this result could also be that thromboembolic complications in the coiling group might be more permanent than a vessel injury or a post-operative hematoma in the clipping group.

There were some limitations to this study. First, this study was retrospective and cannot exclude possible selection bias. A neurosurgeon and two interventionists made decisions on a case-by case basis, following our own management protocols without randomization. As a result, more elderly patients and more patients with ICA or posterior circulation aneurysms were treated with endovascular treatment. Notwithstanding, the patients were collected via pro-

spectively designed hospital database and assessed by an independent observer. Second, smoking, alcohol intake, cholesterol levels, obesity, and cardiovascular disease could not be analyzed. These factors are known to be associated with the occurrence of the ischemic stroke,<sup>23-25</sup> and could be related to procedure-related complications.

A few latest western society studies demonstrated factors predicting inpatient complications from cerebral aneurysm clipping in patients.<sup>15,26</sup> However, our study is the first to report that previous ischemic stroke could be a risk factor in patients with surgically or endovascularly treated UIAs in Korean. A history of ischemic stroke was strongly correlated with procedure-related major neurological complications when treating UIAs. Accordingly, patients with UIAs who have a previous history of ischemic stroke might be at risk of procedure-related major neurological complications.

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