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Comparison of Symptomatic Vasospasm after Surgical Clipping and Endovascular Coiling

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Abstract

Vasospasm, initial neurological damage, rebleeding, and periprocedural complications are associated prognostic factors for clinical outcomes after aneurysmal subarachnoid hemorrhage (SAH). In this study, factors related to delayed ischemic neurological deficit (DIND) are evaluated using data from our institute for the last 18 years. Data from 2001 to 2018 of patients with aneurysmal SAH who underwent surgical clipping (SC) or endovascular coiling (EC) within 7 days of onset were retrospectively analyzed. Cases of mortality within 5 days after treatment were excluded. Multivariate analysis was used to identify the risk factors for DIND. In total, 840 cases of SAH were assessed; among these cases, 384 (45.7%) and 456 (54.3%) were treated with SC and EC, respectively. The frequency of DIND in the EC group was significantly less than that in the SC group (11.8% vs. 17.7%; p = 0.016). In the results of multivariate analysis, internal carotid artery (ICA) aneurysm and hemorrhagic complications were the risk factors for DIND. Cilostazol administration and EC were significant factors for vasospasm prevention after aneurysmal SAH (odds ratio of ICA aneurysm: 1.59, hemorrhagic complications: 1.76, SC: 1.51, and cilostazol administration: 0.51, respectively). Cilostazol administration was also a significant factor in patients who were treated with EC. ICA aneurysm, treatment strategy, hemorrhagic complications, and cilostazol administration were associated with DIND. Oral administration of cilostazol and avoiding hemorrhagic complications were effective in DIND prevention. If both treatments are available for ruptured aneurysms, clinicians should choose EC on the basis of its ability to prevent DIND.

Keywords: vasospasm, surgical clipping, endovascular coiling, cilostazol

Introduction

Recently, the annual incidence of subarachnoid hemorrhage (SAH) worldwide was 6.67 per 100 000 (range, 0.71-12.38).[1] Despite the low incidence of SAH in patients with stroke, approximately 40% of patients with SAH have poor outcomes),[2] and effective treatment in these patients is a challenge. Important prognostic factors for SAH include impaired consciousness at disease onset,[3] rebleeding,[4] therapeutic complications,[5] and symptomatic vasospasm.[6] Approximately 30%-70% cases of SAH showed symptomatic vasospasm complication that was confirmed via cerebral angiography[7]; approximately 20%-30% of cases with vasospasm were symptomatic, and approximately 15% of those contributed to poor prognosis.

Recent research has focused on the treatment approach in delayed ischemic neurological deficit (DIND),[8] but the results indicated that the effect was limited, and prevention is essential. In this study, we assessed the incidence of DIND and risk factors in patients with SAH who underwent radical intervention at our institute in the past 18 years.

Material and Methods

Patients with SAH who underwent radical treatment for

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ruptured intracranial aneurysms within 7 days after onset in our institute between April 2001 and December 2018 were enrolled, and of these patients, 840 who survived more than 5 days after radical treatment were included in the study. The evaluated factors in this study were as follows: patient characteristics (age, gender, medical history [hypertension, diabetes mellitus, dyslipidemia, and SAH], smoking history, and family history of SAH); information on aneurysm (World Federation of Neurological Surgeons (WFNS) grading, Fisher's grading, presence or absence of intracerebral hematoma and intraventricular hematoma, site of the aneurysms, size, length of the neck, and dome-to-neck ratio); treatment modality (use of cilostazol, statin and eicosapentaenoic acid (EPA), hemorrhagic and non-hemorrhagic complications, and method of radical treatment). Since we hypothesized that hemorrhagic complications would increase vasospasm, hemorrhagic complications included postoperative hemorrhage, contusional hemorrhage, or hemorrhagic infarction. Contrarily, non-hemorrhagic complications were defined as permanent symptomatic events due to cerebral infarction and brain contusion without hematoma. The site of aneurysms was as follows: the anterior cerebral artery, anterior communicating artery, distal internal carotid artery (ICA) (distal to the posterior communicating artery [PcomA]), PcomA, proximal ICA (proximal to PcomA), middle cerebral artery (MCA), basilar artery (BA), and vertebral artery (VA). Additionally, cerebral angiography or brain magnetic resonance angiography was performed to confirm symptomatic vasospasm. DIND was defined as neurological symptoms including new transient or permanent neurological deteriorations with vasospasm in the related territory, except for other causes such as symptomatic epilepsy.

Based on the 2002 report of the International Subarachnoid Aneurysm Trial (ISAT),[9] surgeons performing surgical clipping (SC) and endovascular coiling (EC) began negotiations to promote EC as a priority treatment choice in individual patients undergoing radical treatment for ruptured intracranial aneurysms. During this study period, those who were eligible for fasudil hydrochloride were administered with the drug intravenously. After 2010, almost all the patients were administered oral treatment with cilostazol, statin, and EPA. If DIND occurred, patients were administered with Triple-H therapy or hyperdynamic therapy, and in those showing no improvement of symptoms, endovascular treatments were also performed.

In this study, the incidence of DIND since 2001 was evaluated, and a comparison of each factor was done between the SC and EC groups. First, a univariate analysis of factors related to the occurrence of DIND was performed to identify significant factors ($p < 0.05$). Additionally, a multivariate analysis was performed. Patients were classified by age (≥60 and <60 years), WFNS grading (grades 1-3 and 4-5), Fisher's grading (group 3 and other groups), (>7 and ≤7 mm), and site of the aneurysms (ICA [distal ICA, PcomA, and proximal ICA] and others). The same analysis was also performed for the EC group. All statistical analyses were performed using JMP ver. 10 (SAS Institute Inc.; Cary, NC, USA). Chi-square test, Fisher's test, and t-test were used for univariate analysis. Multivariate logistic regression analysis was also performed. P-value of <0.05 was considered to be statistically significant.

Results

Choice of treatment

Of the 840 subjects included in the study, radical treatment with SC was performed in 384 patients (45.7%), and that with EC was performed in 456 patients (54.3%). Comparing the temporal changes between the SC and EC groups, the EC group comprised approximately 30% of total patients for 2001, and the incidence was gradually increased in the following years. In 2018 (the final year of the study), EC was performed in approximately 70% of the patients. In the between-group comparison of patient characteristics, a trend of selection of SC for treatment of youths, mild cases, and patients with a history of smoking was observed; many patients in the SC group were diagnosed with small aneurysms, short neck of the aneurysms, MCA aneurysms, or aneurysms with intraventricular hematoma; many patients in the EC group were diagnosed with posterior circulation aneurysms (BA and VA). Regarding factors related to treatment, the following findings were obtained: more frequent administration of cilostazol and EPA in the EC group and a trend of higher incidence of hemorrhagic complications in the EC group than in the SC group (Table 1).

Incidence of DIND

The incidence of DIND was significantly lower in the EC group than in the SC group (11.8% [54/456] vs. 17.7% [68/384]; $p = 0.016$), whereas the incidence of DIND in the SC group was without significant temporal changes, and that in the EC group decreased gradually, without significance (Fig. 1).

Related factors to DIND

In the univariate analysis of the incidence of DIND, female sex, ICA aneurysms, no use of cilostazol in the treatment, and hemorrhagic complications were significant risk factors other than those described for SC (Table 2). In a subsequent analysis of these factors and other significant factors ($p < 0.1$) such as diabetes mellitus, ICA aneurysms, hemorrhagic complications, no use of cilostazol in the treatment, and SC were significant risk factors for DIND. The odds ratios of ICA aneurysms and hemorrhagic complications were 1.59 and 1.76, respectively, and those of cilostazol and SC were 0.51 and 1.51, respectively (Table 3). No use of cilostazol was also a significant risk factor for DIND in the EC group (Table 4).

Table 1 Comparison between surgical clipping and endovascular coil embolization

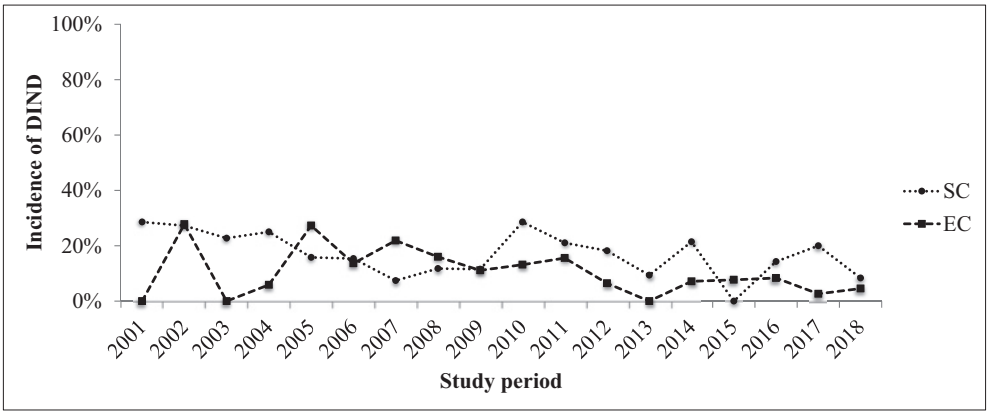
		Surgical clipping group (n = 384)	Endovascular coil embolization group (n = 456)	P-value
Age (years)		59.8 ± 13.7	63.8 ± 15.1	<0.001*
Sex (female)		257 (66.9%)	282 (61.8%)	0.126
WFNS classification	Grade 1	122 (31.8%)	99 (21.7%)	<0.001*
	Grade 2	79 (20.6%)	101 (22.2%)	
	Grade 3	22 (5.7%)	4 (0.9%)	
	Grade 4	80 (20.8%)	82 (18.0%)	
	Grade 5	81 (21.1%)	170 (37.3%)	
Hypertension		187 (48.7%)	217 (47.6%)	0.748
Diabetes mellitus		27 (7.0%)	32 (7.0%)	0.994
Dyslipidemia		63 (16.4%)	70 (15.4%)	0.676
Smoking history		165 (61.6%)	166 (52.2%)	0.023*
Family history		29 (19.1%)	34 (17.8%)	0.761
History of SAH		11 (2.9%)	24 (5.3%)	0.083
Fisher's classification	Group 1	4 (1.0%)	4 (0.9%)	0.660
	Group 2	35 (9.1%)	37 (8.1%)	
	Group 3	335 (87.2%)	408 (89.5%)	
	Group 4	10 (2.6%)	7 (1.5%)	
Intracerebral hematoma		138 (35.9%)	96 (21.1%)	<0.001*
Intraventricular hematoma		187 (48.7%)	303 (66.5%)	<0.001*
Site	ACA	39 (10.2%)	25 (5.5%)	<0.001*
	AcomA	79 (20.6%)	121 (26.5%)	
	Distal ICA	17 (4.4%)	28 (6.1%)	
	PcomA	63 (16.4%)	108 (23.7%)	
	Proximal ICA	15 (3.9%)	20 (4.4%)	
	MCA	161 (41.9%)	17 (3.7%)	
	BA	6 (1.6%)	56 (12.3%)	
	VA	4 (1.0%)	81 (17.8%)	
Size		6.43 ± 3.88	7.63 ± 4.24	<0.001*
Length of the neck		3.08 ± 1.63	3.66 ± 1.93	<0.001*
Dome-to-neck ratio		2.16 ± 0.86	2.15 ± 0.83	0.881
Cilostazol		67 (17.5%)	132 (29.0%)	<0.001*
Statin drugs		166 (43.2%)	202 (44.3%)	0.756
EPA formulations		166 (43.2%)	218 (47.8%)	0.185
Hemorrhagic complications		46 (12.0%)	79 (17.3%)	0.030*
Nonhemorrhagic complications		53 (13.8%)	56 (12.3%)	0.513
DIND		68 (17.7%)	54 (11.8%)	0.016*

*Significant groupwise difference.
WFNS, World Federation of Neurosurgical Societies; SAH, subarachnoid hemorrhage; ACA, anterior communicating artery; AcomA, anterior communicating artery; ICA, internal carotid artery; PcomA, posterior communicating artery; MCA, middle cerebral artery; BA, basilar artery; VA, vertebral artery; EPA, eicosapentaenoic acid; DIND, delayed ischemic neurological deficit.

Discussion

DIND prevention

DIND is usually considered to be a risk factor for complications in patients with the onset of SAH undergoing radical treatment. Nevertheless, no standard guidelines for the prevention and treatment of the disease have been established. The Japanese Guidelines for the Management of Stroke[10] and the American Heart Association (AHA)/the American Stroke Association (ASA) guidelines[11] recommend hypertensive therapy as a treatment approach based on the evidence.[12] Previous studies recommended Triple-H



SC, surgical clipping; EC, endovascular coil embolization.

Fig. 1 Temporal changes in the incidence of delayed ischemic neurological deficit via radical treatment.

Table 2 Factors related significantly to delayed ischemic neurological deficit based on univariate analysis

	With SV (n = 122)	Without SV (n = 718)	P-value
Age (≥60 years)	73 (59.8%)	391 (54.5%)	0.269
Female sex	89 (73.0%)	450 (62.7%)	0.029*
WFNS classification grades 1-3	65 (53.3%)	362 (50.4%)	0.559
Hypertension	543 (43.4%)	351 (48.9%)	0.266
Diabetes mellitus	4 (3.3%)	55 (7.7%)	0.080
Dyslipidemia	16 (13.1%)	117 (16.3%)	0.374
Smoking history	42 (51.9%)	289 (57.2%)	0.365
Family history	9 (20.0%)	54 (18.1%)	0.762
History of SAH	3 (2.5%)	32 (4.5%)	0.226
Fisher's classification group 3	108 (88.5%)	635 (88.4%)	0.979
Intracerebral hematoma	31 (25.4%)	203 (28.3%)	0.514
Intraventricular hematoma	66 (54.1%)	424 (59.1%)	0.305
Aneurysm site at the ICA	48 (39.3%)	203 (28.3%)	0.014*
Size	6.50 ± 2.76	7.13 ± 4.30	0.145
Length of the neck	3.26 ± 1.48	3.39 ± 1.86	0.489
Dome-to-neck ratio	2.11 ± 0.76	2.16 ± 0.86	0.577
Cilostazol	17 (13.9%)	182 (25.4%)	0.006*
Statin drugs	54 (44.3%)	314 (43.7%)	0.913
EPA formulations	54 (44.3%)	330 (46.0%)	0.728
Hemorrhagic complications	26 (21.3%)	99 (13.8%)	0.031*
Nonhemorrhagic complications	11 (9.0%)	98 (13.7%)	0.159
Radical operation type of surgical clipping	68 (55.7%)	316 (44.0%)	0.016*

*Significant groupwise difference.
SV, symptomatic vasospasm; WFNS, World Federation of Neurosurgical Societies; SAH, subarachnoid hemorrhage; ICA, internal carotid artery; EPA, eicosapentaenoic acid.

therapy[13] and hyperdynamic therapy[14] but did not confirm their efficacy. Recently, investigators have focused on the selective arterial infusion of a vasodilator such as fasudil hydrochloride and direct percutaneous transluminal angioplasty[15] and reported that the effect was limited.[16] Thus, clinicians should target DIND prevention to achieve improved outcomes of SAH. In this study, we examined factors related to DIND in approximately 850 patients with SAH who underwent surgery at our institute in the past 18 years.

Table 3 Factors related significantly to delayed ischemic neurological deficit based on multivariate analysis

	Odds ratio	95% confidence interval	P-value
Female sex	1.39	0.90-2.19	0.137
Diabetes mellitus	0.43	0.13-1.09	0.080
Aneurysm site at the ICA	1.59	1.04-2.40	0.031*
Cilostazol	0.52	0.29-0.87	0.013*
Hemorrhagic complications	1.76	1.06-8.85	0.031*
Radical operation type of surgical clipping	1.63	1.09-2.44	0.017*

*Significant groupwise difference.
ICA, internal carotid artery.

Table 4 Factors related significantly to delayed ischemic neurological deficit in the IVR group

	Univariate analysis P-value	Multivariate analysis		
		Odds ratio	95% confidence interval	P-value
Female sex	0.023	1.94	0.95-4.29	0.070
Size (>7 mm)	0.057	0.58	0.29-1.11	0.101
Cilostazol	0.034	0.46	0.19-0.98	0.044*
Hemorrhagic complications	0.031	1.80	0.86-3.59	0.114

*Significant groupwise difference.
IVR, endovascular coil embolization.

Comparison between EC and SC

Although based on the results of ISAT[9] and Barrow Ruptured Aneurysm Trial,[17] EC is increasingly considered as the first-line radical treatment for ruptured intracranial aneurysms, studies have reported conflicting results regarding the superiority of SC or EC in terms of the complication rate of DIND.[18-26] SC is effective in the removal of the hematoma in the arachnoid space, which may be correlated with the incidence of DIND, whereas EC with minimal invasiveness to the cerebral blood vessels is considered to be effective in DIND prevention. In this study, we observed a significantly lower incidence of DIND in the EC group than in the SC group. Although the incidence of DIND in the SC group showed no temporal changes, the recent incidence of DIND in the EC group tended to decrease, without significance. Advancements in several devices such as intermediate catheters and balloon catheters[27-29] have led to significant improvement in treatment outcomes of EC, which may consequently reduce the incidence of DIND.

Risk factors for DIND

Our analysis results revealed specific risk factors for DIND other than the method of radical treatment: ICA aneurysm, hemorrhagic complications, and no oral administration of cilostazol. To our best knowledge, there were no reports of a high rate of DIND complications in the rupture of ICA aneurysms, although studies have reported a correlation between the thickness of intracerebral and intraventricular hematomas and DIND incidences.[30,31] Although a recent[32] study reported that the aneurysm location did not affect the incidence of delayed cerebral infarction, female sex was reported to be an independent predictor of symptomatic vasospasm.[33] The present study had a significantly higher frequency of female patients with ICA aneurysms (ICA: 79.3% vs. others: 57.7%), and the high rate of DIND in ICA aneurysms may have been affected by these factors. In this study, we divided all the complications into two groups, namely, hemorrhagic and nonhemorrhagic complications, because we hypothesized that the increase of hematoma could induce vasospasm after radical treatment. Although our results supported this hypothesis, they were inconsistent with the result that Fisher grading did not significantly correlate with DIND. In this study, approximately 90% of the cases were classified as Fisher's group 3. Additionally, 21% were WFNS grade 4, and 33% were grade 5 in Fisher's group 3, and the ratio was significantly higher than that in other groups with 6.2% of grade 4 and 7.2% of grade 5. Since DIND was defined as the new neurological deficit, its incidence in extremely severe cases might not accurately evaluate the relationship between hematoma volume and DIND, as reported in some studies,[31,34] even after excluding the data of patients with mortality at more than 5 days after onset.

The results of several meta-analysis studies[35-37] have highlighted the potential effectiveness of cilostazol for DIND prevention. Cilostazol is a selective inhibitor of phosphodiesterase-3 and has an effect on microcirculatory vasodilatation, mediated by both cyclic adenosine monophosphate and upregulation of endothelial NO synthesis.[38] Although this effect remained controversial, the recent meta-analysis demonstrated the possibility to prevent severe angiographic and symptomatic vasospasm, new cerebral infarction, and poor outcomes.[39] The results are consistent with those of our study to reduce the incidence of DIND by approximately 50% in patients administered with cilostazol. Based on the Japanese Guidelines for the Management of Stroke 2015 (compatible with the 2017 revision), future large-scale comparative studies are needed to provide evidence-based support for cilostazol as an acceptable method to prevent DIND. This result was similar in patients who were treated with EC.

Drug administration

The AHA/ASA guidelines strongly recommend oral administration of nimodipine,[40] which has not been approved in Japan. Moreover, although the Japanese Guidelines for the Management of Stroke strongly recommends intravenous administration of fasudil hydrochloride and ozagrel sodium,[41,42] large-scale controlled trials of these drugs are needed. We could not evaluate drug efficacy due to insufficient numbers of patients meeting inclusion criteria. At our institute, besides statin, cilostazol and EPA have routinely been used since 2010, despite no clear evidence of statin[43] and EPA[44] and other drugs; nevertheless, the present study failed to show preventive effects of those against DIND.

Limitations

Our study has some limitations. First, this was a single-center retrospective study, and the comparisons were biased. The selection of various treatments was according to the physician's discretion, which may have influenced the outcome of this analysis. Aneurysm location, age, and severity of SAH may also be confounding factors, as they greatly affect the treatment strategy; larger studies are needed to remove these effects. Additionally, in our series, WFNS grades 4 and 5 were 19.3% and 29.9%, respectively, and approximately 90% of the cases were classified into Fisher's group 3, which may indicate that we were analyzing more severe cases than those in the general population. Future multicenter comparative studies to elucidate the efficacy of drugs with potential preventive action against DIND are needed.

Conclusions

ICA aneurysm was a risk factor for DIND after radical treatment for SAH in patients with intracranial aneurysms who underwent treatment at our institute. EC and oral cilostazol were factors for DIND prevention. This result was similar in patients who were treated with EC. Oral cilostazol showed potential in DIND prevention, and aggressive administration of cilostazol was the preferred treatment approach. In terms of DIND, surgeons should consider EC to be an appropriate modality.

Ethical Approval

All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study has received approval from the Institutional Review Boards of our institute, and the patient provided consent for publication.

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Conflicts of Interest Disclosure

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