



Clinical Outcomes of Endovascular Coil Embolization for Ruptured Middle Cerebral Artery Aneurysms

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Objective: Middle cerebral artery (MCA) aneurysms are difficult to treat with coil embolization (CE) due to their location and shape, but the number of CE-treated MCA has gradually increased as treatment techniques have improved. However, the outcomes of CE for ruptured MCA aneurysms are poorly understood. This study aimed to evaluate the outcomes of CE for ruptured MCA aneurysms.

Methods: We retrospectively analyzed the medical records of patients with aneurysmal subarachnoid hemorrhages (aSAH) that were treated with CE between 2013 and 2020, and compared the differences in outcomes depending on aneurysm location.

Results: A total of 468 patients with aSAH were included: 39 patients had ruptured MCA aneurysms (group M), and 429 had ruptured aneurysms at other sites (group O). There were no significant differences between the background characteristics of the 2 groups. Also, there were no significant intergroup differences in occlusion status, the frequency of complications such as ischemia, hemorrhaging, rebleeding, retreatment, or the modified Rankin Scale score at discharge. However, intracerebral hemorrhage (ICH) removal was required significantly more frequently in group M than in group O (10.3% vs. 0.5%, $p = 0.0006$). By case-matching analysis, there were no significant differences in these outcomes. All MCA cases that needed removal had more than 36 ml of hematoma volume. Logistic regression analysis showed that the existence of ICH at onset was a poor prognostic factor for ruptured MCA aneurysms.

Conclusion: CE for ruptured MCA aneurysms produced acceptable outcomes in selected cases. However, the indications for CE in patients with ICH should be carefully considered.

Keywords ▶ middle cerebral artery aneurysm, subarachnoid hemorrhage, coil embolization, intracerebral hematoma

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Introduction

Endovascular treatment for cerebral aneurysms has become more common. However, in many institutions, clipping is still the first-line treatment for middle cerebral artery (MCA) aneurysms.^{1,2} MCA bifurcation aneurysms are often wide-necked, which makes endovascular treatment difficult.^{3–5} On the other hand, the difficulty of clipping increases for short M1 segments, the superior wall type of M1 segment, or larger size. It was reported that symptomatic complications occurred after clipping for M1 segment aneurysms in 8.7%–33.3% of patients, and such complications were even more common in cases involving ruptured aneurysms.^{6–9} Recently, the number of reports in which coil embolization (CE) was performed for unruptured MCA aneurysms has gradually been increasing as treatment techniques and devices have improved.^{10–12} For unruptured MCA aneurysms, good outcomes may be achieved using adjunctive techniques such as stent-assist

coiling.^{12–14)} However, stents have not been approved for ruptured aneurysms in Japan. Furthermore, stents are difficult to use for ruptured aneurysms because of the use of antithrombotics in the perioperative period. Compared to unruptured MCA aneurysms, the outcomes of endovascular CE for ruptured MCA aneurysms are unclear. This study aimed to evaluate the clinical outcomes of CE for ruptured MCA aneurysms.

Materials and Methods

Patient population

This was a retrospective multicenter cohort study conducted by 6 institutions in Japan. This was approved by the institutional ethics committee (H30-137) and complied with the conditions laid out by the Declaration of Helsinki. Opt-out consent was employed, and the requirement to obtain informed consent was waived by Institutional Review Board. The data set consisted of the medical records of consecutive subarachnoid hemorrhage (SAH) patients who were treated with endovascular management (EM) during the period from January 2013 through April 2020.

Surgical clipping and endovascular treatment were performed at all institutions. At each institution, the treatment modality was determined after considering both surgery and endovascular treatment on a case-by-case basis. All endovascular procedures were performed under general anesthesia. During the procedure, the activated clotting time was controlled above 200 seconds by heparin. The following data were collected from medical records: age, sex, World Federation of Neurosurgical Societies (WFNS) grades,¹⁵⁾ modified Rankin Scale (mRS) scores before onset,¹⁶⁾ aneurysm maximum size, dome/neck ratio,¹⁷⁾ aspect ratio,¹⁷⁾ the presence of intracerebral hemorrhage (ICH), the presence of intra-aneurysmal thrombosis, and the percentage of adjunctive technique.

The degree of aneurysm occlusion after the initial CE was classified as follows: total exclusion of the aneurysm from the circulation was defined as complete occlusion (CO), limited residual filling at the junction with the parent vessel was defined as a neck remnant (NR), and residual filling within the coil interstices or at the aneurysm's perimeter was defined as body filling (BF).

The primary endpoint was a favorable outcome, defined as mRS 0–2 at discharge. The secondary endpoints were the degree of aneurysm occlusion, periprocedural hemorrhagic events, periprocedural ischemic events, rebleeding after the procedure, retreatment for aneurysm, and removal

of ICH after CE. Periprocedural hemorrhagic events included intraprocedural aneurysmal perforation, blood vessel perforation, and enlargement of the ICH after the procedure. All ischemic strokes, whether symptomatic or not, related to the procedure or delayed cerebral ischemia (DCI) were counted as ischemic events. DCI was defined as cerebral infarction due to vasospasm detected by magnetic resonance imaging within 14 days after the procedure. “Retreatment” included endovascular treatment or clipping for treated aneurysms. All radiological and clinical outcomes were determined by 2 or more neurosurgeons at each institution who did not know the object of this study.

Statistical analysis

To clarify the characteristics of CE for ruptured MCA aneurysms, we compared the clinical factors and outcomes of patients who underwent this procedure with those of patients who underwent CE for ruptured aneurysms located at other sites. To identify the clinical factors that influenced the clinical outcomes of patients who underwent CE for ruptured MCA aneurysms, univariate and multivariate logistic regression analyses were performed. The variables that exhibited significance in the univariate analyses were included in the multivariate analysis.

For baseline variables, summary statistics are presented (frequencies and percentages for categorical data and medians and interquartile ranges [IQR] for continuous data). Fisher's exact test was used to analyze categorical data, and the Wilcoxon rank-sum test was used to analyze continuous data.

A case-matched study was conducted to reduce bias due to differences in patient background between the 2 groups. Patient selection was performed employing the propensity score matching method for clinical factors (age, sex, WFNS grade, mRS score before onset, the existence of ICH, and the existence of intra-aneurysmal thrombosis).

All comparisons were planned, and all tests were 2-sided. *p*-Values of less than 0.05 were considered to indicate a significant difference. All statistical analyses were performed using JMP (Japanese version 12 for Windows; SAS Institute Inc., Cary, NC, USA).

Results

After excluding 86 patients whose SAH was caused by dissection or fusiform aneurysms, 13 patients who were treated >14 days after onset, a patient with an arteriovenous malformation-related aneurysm, and 37 patients for

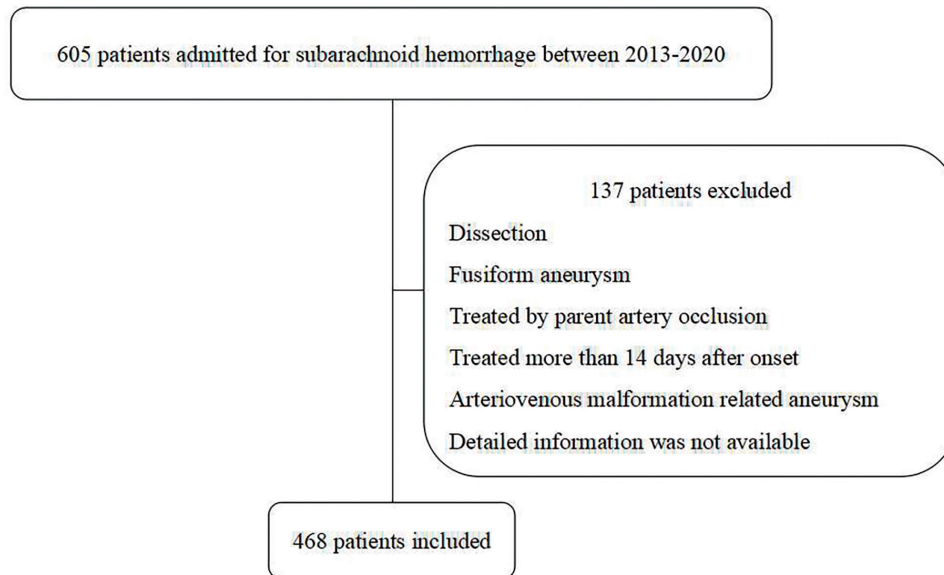


Fig. 1 Schematic drawing of the patient selection method.

whom detailed information was not obtained, 468 patients were identified (**Fig. 1**). There were 170 cases of MCA aneurysms that underwent clipping during the same period. Neuroimaging follow-up was performed in 258 patients (55.1%) after discharge.

Table 1 summarizes the clinical characteristics of all patients and the 2 groups; patients with ruptured MCA aneurysms were placed in group M (39 patients), while those whose ruptured aneurysms were located at other sites were included in group O (429 patients). Thirty-five (89.7%) of the 39 cases in group M were bifurcation aneurysms. There were no significant intergroup differences in clinical characteristics, including age, sex, the proportion of patients with WFNS grades 1–3, the proportion of patients with mRS scores of 0–2 before onset, the maximum aneurysm diameter, dome/neck ratio, aspect ratio, the frequency of ICH, and the presence/absence of intra-aneurysmal thromboses. Adjunctive techniques were used less frequently in group M than in group O (43.6% vs. 60.6%, $p = 0.04$).

The patients' outcomes are summarized in **Table 2**. The proportion of patients with mRS scores of 0–2 at discharge was 61.5% in MCA cases, and this result was not significantly different from those of aneurysms at other sites ($p = 0.51$). The proportion of BF cases did not differ significantly between the 2 groups ($p = 0.11$). There were no significant differences in the frequencies of periprocedural hemorrhagic events ($p = 0.07$) or ischemic events

($p = 0.45$) between the 2 groups. One of the 2 M1 aneurysms resulted in procedure-related cerebral ischemia. One of the 2 distal MCA aneurysms required the removal of ICH after CE. In addition, the frequencies of rebleeding and retreatment after the first procedure did not differ significantly (both $p = 1.00$). On the other hand, the percentage of patients requiring post-treatment ICH removal was significantly higher in group M than in group O (10.3% vs. 0.5%, $p = 0.0006$). Three of 8 (37.5%) cases of ruptured MCA aneurysms with ICH had hematoma enlargement. These 3 cases required ICH removal after CE. A remaining patient who required hematoma removal had a hematoma with midline shift before CE, but CE was preceded by hematoma removal and the patient died. On the other hand, 9 (18.8%) of 48 cases with ruptured aneurysms with ICH at other sites had enlarged hematomas, and 2 (4.2%) of these cases required hematoma removal. The percentage of patients with ICH that required hematoma removal due to enlargement after CE was significantly higher for MCA aneurysm than for other sites ($p = 0.01$). The mortality rates did not differ significantly between the 2 groups ($p = 0.56$).

After case matching, each of the 39 patients was selected. There were no significant differences in patient characteristics (**Table 3**) and outcomes of CE (**Table 4**) between the 2 groups.

In the multivariate analysis of patients with ruptured MCA aneurysms (**Table 5**), only the presence of ICH

Table 1 Summary of the clinical characteristics of 468 patients in which aneurysmal SAH were treated with interventional radiology

	Total	Group M	Group O	p-Value
No. of patients	468	39 (8.3%)	429 (91.7%)	
Age, years				
Median	67.0	63.0	67.0	0.17
IQR	54.0–77.0	59.0–70.0	53.0–78.0	
Sex, female	336 (71.8%)	26 (66.7%)	310 (72.3%)	0.46
WFNS grade, 1–3	333 (71.1%)	28 (71.8%)	305 (71.1%)	1.00
mRS score before onset, 0–2	453 (97.0%)	69 (94.5%)	385 (97.5%)	0.25
Location				
MCA	39 (8.3%)			
M1 superior wall	2 (0.4%)			
Bifurcation	2 (0.4%)			
Distal MCA	35 (7.5%)			
ICA	176 (37.6%)			
Acom	63 (26.1%)			
A1	2 (0.8%)			
dACA	7 (2.9%)			
BA	65 (13.9%)			
VA	28 (6.0%)			
AN maximum size, mm				
Median	5.7	5.9	5.7	0.86
IQR	4.0–7.8	3.6–7.8	4.0–7.9	
Dome/neck ratio				
Median	1.54	1.63	1.54	0.92
IQR	1.23–2.06	1.20–2.12	1.24–2.05	
Aspect ratio				
Median	1.50	1.41	1.50	0.59
IQR	1.13–1.95	1.11–2.00	1.13–1.94	
ICH, yes	56 (12.0%)	8 (18.0%)	48 (11.2%)	0.12
Intra-aneurysmal thrombosis	10 (2.1%)	1 (2.6%)	9 (2.1%)	0.58
Adjunctive technique, yes	277 (59.2%)	17 (43.6%)	260 (60.6%)	0.04
Balloon	245 (52.4%)	14 (35.9%)	231 (53.8%)	
Double catheter	44 (9.4%)	6 (15.4%)	38 (8.9%)	
Stent	23 (4.9%)	1 (2.6%)	23 (5.4%)	
Follow-up period, median days (IQR)	61.0 (26.0–548.0)	491 (88.0–1416.0)	55 (25.0–439.8)	0.0002

Acom, anterior communicating artery; AN, aneurysm; BA, basilar artery; dACA, distal anterior cerebral artery; ICA, internal carotid artery; ICH, intracerebral hemorrhage; IQR, interquartile range; MCA, middle cerebral artery; mRS, modified Rankin Scale; SAH, subarachnoid hemorrhage; VA, vertebral artery; WFNS, World Federation of Neurosurgical Societies

was found to be associated with poor outcomes (odds ratio [OR]: 9.43, $p = 0.03$). There was a total of 8 patients with ICH in the MCA aneurysm group. Of these, 4 patients did not require hematoma removal after interventional radiology (IVR), with hematoma volumes of 5.3, 14.9, 24.1, and 32.7 ml, respectively. The remaining 4 patients required hematoma removal, with hematoma volumes of 36.7, 37.0, 67.4, and 124.7 ml, respectively. All patients with ruptured MCA aneurysm who needed removal had more than 36 ml of hematoma volume. The median hematoma volume was 19.5 and 52.5 ml, showing a significant difference ($p = 0.03$).

Discussion

In this study, we examined the treatment outcome of CE for ruptured MCA aneurysms, mainly composed of bifurcation aneurysms. We also compared the clinical characteristics and outcomes of such procedures with those of CE for ruptured aneurysms at other locations. The favorable outcome at discharge after CE was 61.5% for MCA aneurysms, which was not significantly different from the 55.9% of those for aneurysms at other sites. The rate of periprocedural complications, rebleeding rate, and retreatment rate did not differ significantly between the groups.

Table 2 Outcomes of 468 patients in which aneurysmal SAH was treated with interventional radiology

	Total	Group M	Group O	p-Value
Degree of occlusion				
BF	150 (32.1%)	17 (43.6%)	133 (31.0%)	0.11
NR	174 (37.2%)	12 (30.8%)	162 (37.8%)	
CO	144 (30.7%)	10 (25.6%)	134 (31.2%)	
Periprocedural hemorrhagic events	28 (6.0%)	5 (12.8%)	23 (5.4%)	0.07
Enlargement of ICH	12 (2.6%)	3 (7.7%)	9 (2.1%)	
Perforation	16 (3.4%)	2 (5.1%)	14 (3.3%)	
Periprocedural ischemic events	57 (12.2%)	6 (15.4%)	51 (11.9%)	0.45
Rebleeding after procedure	13 (2.8%)	1 (2.6%)	12 (2.8%)	1.00
Retreatment for aneurysm	29 (6.2%)	2 (5.1%)	27 (6.3%)	1.00
Removal of ICH	6 (1.3%)	4 (10.3%)	2 (0.5%)	0.0006
mRS score @ discharge				
0–2	264 (56.4%)	24 (61.5%)	240 (55.9%)	0.51
3–5	163 (34.6%)	13 (33.3%)	150 (35.0%)	
6	41 (8.7%)	2 (5.1%)	39 (9.1%)	0.56

BF, body filling; CO, complete occlusion; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; NR, neck remnant; SAH, subarachnoid hemorrhage

Table 3 Results of the univariate and multivariate analyses of the risk factors associated with poor outcomes in patients with ruptured MCA AN

	Outcome at discharge		Univariate		Multivariate	
	mRS score: 0–2 (good)	mRS score: 3–6 (poor)	OR (95% CI)	p-Value	OR (95% CI)	p-Value
No. of patients	24 (61.5%)	15 (38.5%)				
Age, median (IQR)	61.0 (50.5–67.0)	67.0 (60.0–75.0)	1.06 (0.99–1.15)	0.11		
Sex, female	13 (54.2%)	13 (86.7%)	5.50 (1.01–29.85)	0.04	4.06 (0.62–43.50)	0.13
WFNS grade, 4–5	3 (12.5%)	8 (53.3%)	8.00 (1.64–38.79)	0.01	4.55 (0.77–30.82)	0.05
AN maximum size (IQR)	5.8 (3.7–7.2)	5.9 (3.3–13.0)	1.13 (0.95–1.36)	0.46		
Aspect ratio (IQR)	1.4 (1.1–1.6)	1.6 (1.1–2.5)	2.84 (0.82–18.61)	0.33		
Dome/neck ratio (IQR)	1.8 (1.2–2.2)	1.4 (1.2–1.9)	0.59 (0.19–1.57)	0.44		
ICH	1 (4.2%)	6 (40.0%)	15.33 (1.61–145.90)	0.008	9.43 (1.18–201.30)	0.03
Result of occlusion, BF	10 (41.7%)	7 (46.7%)	1.23 (0.33–4.49)	1.00		

AN, aneurysm; BF, body filling; CI, confidence interval; ICH, intracerebral hemorrhage; IQR, interquartile range; MCA, middle cerebral artery; mRS, modified Rankin Scale; OR, odds ratio; WFNS, World Federation of Neurosurgical Societies

Based on these results, CE for ruptured MCA aneurysms was acceptable. On the other hand, the presence of ICH was found to be a prognostic factor of CE for MCA aneurysm. Post-treatment hematoma removal was required more often in cases of MCA aneurysm cases than in cases of other sites.

There were a few studies that reported the outcomes of CE for ruptured MCA aneurysms. In a case series of ruptured MCA aneurysms, 58.5% of CE patients had a good prognosis, which was not so different from the findings of the present study.¹⁸⁾ On the other hand, to our knowledge, there were no reports of CE for ruptured MCA aneurysm with ICH. A retrospective cohort study reported that the ICH rate was higher in cases with MCA aneurysm than in cases of aneurysm at other sites ($p < 0.001$, adjusted OR: 7.04).¹⁹⁾ They also revealed that the ICH volume was

greater in cases with MCA aneurysm (median; 32 ml vs. 5 ml, $p < 0.0001$).¹⁹⁾ In addition, a previous study reported that IVR was associated with a higher incidence of enlargement of ICH than clipping.²⁰⁾ Antithrombotic drugs are usually used during IVR, and this increases the risk of enlargement of ICH. As expected, a prospective cohort study reported that the hematoma enlargement was associated with poor prognosis.²¹⁾ Furthermore, a correlation between delayed hematoma removal and poor prognosis has been reported.²²⁾ In this study, ICH due to MCA aneurysm often enlarged after CE and needed to be removed. In the case of MCA aneurysm with ICH, treatment options should be considered, such as hematoma removal before CE.

Procedure-related complications were prognostic factors, and because the MCA aneurysm was located distally, the risk of complications was expected to be high. In a

Table 4 Summary of the clinical characteristics of 78 case-matched patients in which aneurysmal SAH were treated with interventional radiology

	Total	Group M	Group O	p-Value
No. of patients	78	39	39	
Age, years				
Median	64.0	63.0	65.0	0.70
IQR	58.0–70.0	59.0–70.0	55.0–71.0	
Sex, female	52 (66.7%)	26 (66.7%)	26 (66.7%)	1.00
WFNS grade, 1–3	61 (78.2%)	28 (71.8%)	33 (84.6%)	0.27
mRS score before onset, 0–2	78 (100%)	39 (100%)	39 (100%)	–
AN maximum size, mm				
Median	5.8	5.9	5.6	0.70
IQR	3.9–8.2	3.6–7.8	4.2–8.6	
Dome/neck ratio				
Median	1.59	1.63	1.55	0.56
IQR	1.19–2.01	1.20–2.12	1.13–2.00	
Aspect ratio				
Median	1.43	1.41	1.45	0.82
IQR	1.09–1.79	1.11–2.00	1.04–1.77	
ICH, yes	15 (19.2%)	8 (18.0%)	7 (18.0%)	1.00
Intra-aneurysmal thrombosis	2 (2.6%)	1 (2.6%)	1 (2.6%)	1.00
Adjunctive technique, yes	46 (59.0%)	17 (43.6%)	29 (74.4%)	0.01
Balloon	40 (51.3%)	14 (35.9%)	26 (66.7%)	
Double catheter	10 (12.8%)	6 (15.4%)	4 (10.3%)	
Stent	4 (5.1%)	1 (2.6%)	3 (7.7%)	

AN, aneurysm; ICH, intracerebral hemorrhage; IQR, interquartile range; mRS, modified Rankin Scale; SAH, subarachnoid hemorrhage; WFNS, World Federation of Neurosurgical Societies

Table 5 Outcomes of 78 case-matched patients in which aneurysmal SAH were treated with interventional radiology

	Total	Group M	Group O	p-Value
Degree of occlusion				
BF	150 (32.1%)	17 (43.6%)	8 (20.5%)	0.05
NR	174 (37.2%)	12 (30.8%)	16 (41.0%)	
CO	144 (30.7%)	10 (25.6%)	15 (38.5%)	
Periprocedural hemorrhagic events	28 (6.0%)	5 (12.8%)	2 (5.1%)	0.43
Enlargement of ICH	12 (2.6%)	3 (7.7%)	0	
Perforation	16 (3.4%)	2 (5.1%)	2 (5.1%)	
Periprocedural ischemic events	57 (12.2%)	6 (15.4%)	9 (23.1%)	0.57
Rebleeding after procedure	13 (2.8%)	1 (2.6%)	0	1.00
Retreatment for aneurysm	29 (6.2%)	2 (5.1%)	3 (7.7%)	1.00
Removal of ICH	6 (1.3%)	4 (10.3%)	0	0.12
mRS score @ discharge				
0–2	264 (56.4%)	24 (61.5%)	27 (69.2%)	0.63
3–5	163 (34.6%)	13 (33.3%)	11 (35.0%)	
6	41 (8.7%)	2 (5.1%)	1 (2.6%)	1.00

BF, body filling; CO, complete occlusion; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; NR, neck remnant; SAH, subarachnoid hemorrhage

multicenter retrospective study of ruptured MCA aneurysm, CE-related symptomatic ischemia was 5.3%.²³⁾ This result was less than the post-clipping ischemia (19.8%) in the same study ($p = 0.01$).²³⁾ Another previous study of CE for ruptured MCA aneurysms reported a procedure-related complications rate of 5.1% and a disease-related complications rate of 8.5%.¹⁸⁾ In the current study, perioperative hemorrhagic and ischemic complications occurred after

CE for a ruptured MCA aneurysm in 10.3% and 15.4% of cases, respectively. These results were more common than in previous reports but were thought to be due to differences in patient backgrounds and assessment methods. In addition, postoperative ischemia was often difficult to determine whether they were associated with the procedure or with SAH itself. Furthermore, it was often difficult to assess the presence or absence of symptoms due to

complications in patients with SAH. In this study, all cases with infarction on postoperative MRI were counted as ischemic complications. To reduce bias as much as possible, this study used case-matching analysis, and there was no difference in complication rates. This result suggested that CE for MCA aneurysms can be treated as safely as CE for other sites.

Rerupture would also affect the prognosis. Incomplete occlusion was reported to be one of the risk factors for rerupture.²⁴⁾ The CO rate at 1 year after CE for ruptured MCA aneurysms was reported to be 41.7%.²⁵⁾ In the current study, the CO rate was 25.6%, and this was lower than those found in previous studies. This was attributed to the fact that the differences in evaluators and the timing of evaluations had an impact. In our study, the CO rate for ruptured aneurysms at other sites was not significantly different from that for the ruptured MCA aneurysms. In a prospective study of CE for 72 MCA aneurysms, including both ruptured and unruptured aneurysms, the retreatment rate after 1 year was 9.7%.²⁶⁾ In addition, a few retrospective observational studies have reported that the retreatment rate after CE was 4.9%–10.4%.^{15,27–29)} The rebleeding rate after CE for ruptured MCA aneurysms was similarly low, at 6.1%.²⁵⁾ In this study, the rebleeding and retreatment rates were 2.6% and 5.1%, respectively, for ruptured MCA aneurysms, and these were not different from past reports. Furthermore, the MCA aneurysms had a longer follow-up period than the aneurysms at other sites; nevertheless, the rebleeding and retreatment rates for the MCA aneurysms were comparable to those of the aneurysms at other sites. This suggested that the recurrence-preventing effects of CE for ruptured MCA aneurysms were at least as good as those of CE for ruptured aneurysms at other sites.

It was expected that the outcome of IVR for MCA ruptured aneurysms would be inferior to that of other sites, but contrary to expectations, the outcome in this study was not different. Clipping may have been chosen in cases where the surgeon deemed it difficult to treat by CE, but the results suggested that good outcomes could be achieved for those cases deemed CE-eligible. On the other hand, many cases of MCA aneurysm with ICH had additional hematoma removal after CE, indicating the need for caution in treatment selection.

Limitations

This was a retrospective multicenter study, and there were differences in the treatment strategy, the timing of imaging studies, and the assessment of complications among the

facilities. A case-matching study was conducted to reduce any bias due to differences in patient background, and there was no statistical difference in treatment outcomes between MCA aneurysms and other sites. However, no comparison with clipping was performed because the data on clipping cases were not available. Hence, our results may not apply to all ruptured MCA aneurysms. In addition, the post-treatment complications, retreatment, and rebleeding rates may have been underestimated because some patients were in poor condition and could not be evaluated with post-treatment imaging. In fact, 55% of cases did not have image follow-up.

Conclusion

The outcomes of CE for ruptured MCA aneurysms did not differ significantly from those of CE for ruptured aneurysms at other sites, suggesting outcomes of CE for ruptured MCA aneurysms were acceptable. On the other hand, for MCA aneurysm with ICH, the risk of hematoma enlargement after CE was high, and treatment selection should be done carefully.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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