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Efficacy and safety of endovascular coil embolization for unruptured middle cerebral artery aneurysms: middle-term clinical and imaging outcomes with 3 years mean follow-up periods, a 16-year experience

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ABSTRACT

The anatomical characteristics of middle cerebral artery aneurysms make endovascular treatment difficult. This study evaluated the efficacy and safety of endovascular treatment of unruptured middle cerebral artery aneurysm in preventing rupture. A retrospective review of patients who underwent coil embolization for unruptured middle cerebral artery aneurysm between 2006 and 2022 at Nagoya University Hospital with at least 12 months followed up was conducted. Imaging and clinical outcomes were described using the Raymond classification and the modified Rankin Scale, respectively. Good imaging outcome was defined as complete occlusion or neck remnant and clinical outcome as modified Rankin Scale score of 0–2. Patients were divided into initial and recurrent group based on the number of treatments, pre- and post-stent groups based on when stents became available in Japan. A total of 77 patients (80 with aneurysms) were included in the final analysis. Their average age was 60.3 years, and their average follow-up period was 38 months. Favorable clinical outcomes were achieved for 96.2% among 66 (97.0%) initial and 11 (91.7%) recurrent aneurysms. Furthermore, good imaging outcomes were obtained in 90.0 %, and 5% had permanent symptomatic ischemic complications. The pre-stent group had a significantly higher proportion of patients with narrow-neck aneurysms than the post-stent group. There were no significant differences in terms of imaging and clinical outcomes or complication rates. The present study demonstrated that endovascular treatment of unruptured middle cerebral artery aneurysm was safe and effective in preventing rupture. The wide-neck aneurysm was also well embolized by using adjunctive technique.

Keywords: endovascular, coil embolization, stent, middle cerebral artery, cerebral aneurysm

Abbreviations:
AR: aneurysm remnant
CO: complete occlusion
DAPT: dual-antiplatelet therapy
MCA: middle cerebral artery

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MRI: magnetic resonance imaging
NR: neck remnant

INTRODUCTION

Endovascular treatment is reportedly effective in managing both ruptured and unruptured aneurysms.[1,2] However, controversies exist regarding the indication and efficacy of this treatment for middle cerebral artery (MCA) aneurysms due to challenges posed by their anatomic features,[3-6] such as a wide neck or a branch artery origin.[7-9] Previous studies have reported that fewer endovascular treatments have been performed on MCA aneurysms than on aneurysms in other locations and that these treatments had poor results, including modified Rankin Scale (mRS) score of 3–6 (18%–22%) and the occurrence of complications (9%–18%) and recurrences (10%–24%).[10-12] With the advances in endovascular treatment techniques, new devices have been developed for MCA aneurysms, including stents, flow diverters, and intra-saccular flow disruptors.[13-15] In Japan, coil embolization using stents has been increasingly adopted for the endovascular treatment of MCA aneurysms; contrarily, the use of intrasaccular flow disruptors is still limited, whereas flow diverters have not been approved for use. Recent advances in treatment techniques and the development of new devices have enabled operators to manage difficult-to-treat MCA aneurysms.[16-18]

Our hospital is a teaching and training facility for endovascular treatment. Based on more than 16 years of experience in endovascular treatment of aneurysms, proficiency in techniques, our institution's policy is to treat aneurysms first with TAE, including MCA aneurysms. The present study aimed to investigate the safety and efficacy of endovascular treatment of unruptured MCA aneurysm in preventing rupture by describing our team strategy and outcomes for unruptured MCA aneurysms.

MATERIALS AND METHODS

This was a retrospective single-center study involving consecutive patients who underwent endovascular coil embolization for MCA aneurysms between 2006 and 2022 at Nagoya University Hospital. The patients' medical records were reviewed. The study inclusion criteria were patients with unruptured aneurysms and who underwent coil embolization with a follow-up period of at least 12 months. The study was approved by the local ethics committees of Nagoya University Hospital (2020-0404). All patients provided informed consent prior to study participation.

Treatment indication

The treatment indications for endovascular coil embolization for MCA aneurysms in our institution at the time of the study were categorized depending on stent usage. Between 2006 and 2013, coil embolization for MCA aneurysms was performed only under the following conditions: a narrow neck (dome-to-neck ratio greater than or equal to 1.5) and patency of normal arterial branches adjacent to the aneurysm. Since 2014, the aforementioned indications were broadened to cover both wide-neck and dome-branching cases after the approval of stent usage with coil embolization in Japan. The 77 patients were divided into the initial and recurrent groups and into the pre- and post-stent groups based on the stent usage. The pre-stent group was defined as patients who treated between 2006 and 2013, whereas the post-stent group was defined as

patients who treated between 2014 and 2022.

Preoperative assessments for aneurysm and endovascular procedures

Preoperative magnetic resonance imaging (MRI) and computed tomographic angiography (CTA) were employed to evaluate the morphological features of the aneurysms and an optimal access route. When the location of the aneurysm and branching vessels such as perforating branches were not clear on MRI and CTA, digital subtraction angiography (DSA) was added preoperatively to provide a more detailed understanding of the anatomy around the aneurysm. The choice of treatment procedures, such as the use of single or double catheter, balloon-assisted technique, or stent placement, was left to the operators' discretion. The stents used were Neuroform EZ (Stryker, Kalamazoo, MI, USA), Neuroform Atlas (Stryker, Kalamazoo, MI, USA), Enterprise (Codman & Shurtleff Inc Raynham, MA, USA), Lvis (MicroVention/Terumo, CA, USA), LvisJr (MicroVention/Terumo, CA, USA), and PulseRider (Codman & Shurtleff Inc Raynham, MA, USA).

Perioperative antithrombotic therapy

Before 2010, a preoperative antithrombotic protocol had not yet been established in our institution. Between 2006 and 2010, 6 of the 77 patients received a single antithrombotic agent that was either aspirin (100 mg) or clopidogrel (75 mg). After 2010 when a preoperative antithrombotic protocol had been established, the remaining 71 patients received both agents preoperatively daily for 2 weeks. Before the endovascular procedure, heparin was administered according to the patient's weight and controlled to maintain an activated clotting time (ACT) above 250 (range, 250–350) seconds. Heparinization was reversed if the ACT was above 300 seconds at the end of the treatment. An intraoperative anticoagulation regimen was administered throughout the surgery. After the endovascular procedure, patients in whom a stent was not used continued single-antiplatelet therapy (SAPT) for 1 month, whereas those in whom stents were used, excluding PulseRider, received dual-antiplatelet therapy (DAPT) for 6 months, followed by SAPT for 18 months. Patients in whom a PulseRider stent was used received DAPT for 3 months, followed by SAPT for 3 months.

Postoperative imaging and clinical evaluation

Postoperative therapeutic results were assessed based on the findings of MRI performed 2–3 days (immediately), 6 months, and 12 months postoperatively and at the last follow-up visit. Cerebral angiography was only performed when aneurysmal recurrence was suspected after reviewing the MRI findings. The results of coil embolization were classified into four according to the Raymond classification: complete occlusion (CO), neck remnant (NR), aneurysm remnant (AR), or failure (F). We recategorized both CO and NR as "good imaging outcome," AR and F as "poor imaging outcome," changes from AR to NR or CO during the clinical course as "image improvement," and changes from CO or NR to AR as "image deterioration."

Postoperative clinical outcomes were based on the mRS. Favorable and unfavorable clinical outcomes were defined as mRS scores of 0–2 and 3–6, respectively. Complications related to endovascular coil embolization were evaluated immediately, 6 months, and 12 months after surgery and at the last follow-up visit. Complications were classified into none, mild (transient ischemic attack and asymptomatic cerebral infarction on MRI), and severe (symptomatic cerebral infarction or intracranial hemorrhage).

Statistical analyses

The patient groups were compared using the $\chi 2$ test and Fisher's exact test. A p value of

<0.05 was considered to indicate statistical significance. All statistical analyses were conducted using StatMate (version 4.01 Nihon 3B Scientific, Niigata, Japan).

RESULTS

Patient characteristics

A total of 84 patients underwent coil embolization for MCA aneurysms. Five patients with a ruptured aneurysm, two with a shorter follow-up period were excluded. The final analysis included 77 patients (37 men and 40 women) with unruptured aneurysms, 2 of whom had multiple aneurysms, 1 of whom had retreatment at our hospital; thus, a total of 80 aneurysms were treated. The features of the aneurysms are summarized in Table 1. Their average age was 60.3 (SD: 10.5; range, 40–84) years. The average aneurysm size was 6.2 (SD: 2.8; range, 2.9–16.7) mm, and most aneurysms (81.2%) were located at the M1-2 bifurcation. The number of narrow- and wide-neck aneurysms were 31 (38.7%) and 49 (61.3%), respectively. A total of 68 aneurysms (85.0%) were initially managed with endovascular treatment; Of the 12 cases, 11 aneurysms recurred after treatment at other institutions and were retreated at our hospital. One aneurysm recurred after treatment at our hospital and was retreated. The average follow-up period was 38 (SD: 20.4; range, 12–90) months.

Table 1 Data of non-ruptured middle cerebral artery aneurysms

	n (%)
Number	80
Average age (SD)	60.3 ±10.5
Male sex	37 (48.0)
Average follow-up period (SD) month	38.0 ±26.0
Average (SD) size mm	6.2 ±2.8
Location	
M1	9 (11.3)
M1-2 bifurcation	65 (81.2)
M2	6 (7.5)
Neck type	
Narrow	31 (38.7)
Wide	49 (61.3)
Number of treatment	
Initial	68 (85.0)
Recurrent	12 (15.0)

M: middle cerebral artery
SD: standard deviation

Imaging outcomes

The imaging outcomes are summarized in Table 2. In the immediate phase, 67 (83.8%) of the 80 aneurysms had good outcomes. On the other hand, 12 (15.0%) had AR and 1 (1.2%) had F. In the latest phase, the number of aneurysms with good imaging outcomes increased from 67 (83.8%) to 72 (90.0%); nine patients showed image improvement after transitioning from AR to NR (5) and from AR to CO (4), whereas four patients showed image deterioration after transitioning from NR to AR (4). At the immediate and latest phases, among the patients with good clinical outcomes, 28 showed image improvement after transitioning from NR to CO, whereas four patients had image deterioration after transitioning from CO to NR. In all phases, the proportion of patients with good outcomes exceeded 80%; however, the difference was not significant between initial and recurrent groups.

Table 2 Comparison of imaging outcomes between the initial and recurrent groups according to the follow-up periods

	CO+NR n (%)	AR+F n (%)	*p* value
Immediate			
Initial (n = 68)	57 (83.8)	11 (16.2)	
Recurrent (n = 12)	10 (83.3)	2 (16.7)	
Total (n = 80)	67 (83.8)	13 (16.2)	$p = 0.96$
6 months			
Initial (n = 68)	60 (88.2)	8 (11.8)	
Recurrent (n = 12)	10 (83.3)	2 (16.7)	
Total (n = 80)	70 (87.5)	10 (12.5)	$p = 0.63$
12 months			
Initial (n = 68)	62 (91.1)	6 (8.9)	
Recurrent (n = 12)	10 (83.3)	2 (16.7)	
Total (n = 80)	72 (90.0)	8 (10.0)	$p = 0.40$
Latest			
Initial (n = 68)	62 (91.1)	6 (8.9)	
Recurrent (n = 12)	10 (83.3)	2 (16.7)	
Total (n = 80)	72 (90.0)	8 (10.0)	$p = 0.40$

AR: aneurysm remnant
CO: complete occlusion
F: failure
NR: neck remnant

Clinical outcomes and complications

The clinical outcomes are summarized in Table 3. Favorable clinical outcomes were achieved in 77 (96.2%) out of 80 aneurysms, including 66 (97.0%) initial and 11 (91.7%) recurrent aneurysms, whereas unfavorable clinical outcomes were obtained in 3 (3.8%) patients. Three had worsening neurological findings due to acute cerebral infarction related to embolization procedures and perioperative management. Table 4 is a list of complications. Four patients had severe complications, all of which were symptomatic cerebral infarctions. During the follow-up period, there were no cases of death or intracranial hemorrhage due to the treatment. There was a higher rate of severe complications in the recurrent group (8.3%), but no significant difference between initial and recurrent group.

Table 3 Comparison of clinical outcomes between the initial and recurrent groups based on the modified Rankin Scale (mRS)

Clinical outcome	mRS: 0–2 n (%)	mRS: 3–6 n (%)	*p* value
Initial (n = 68)	66 (97.0)	2 (3.0)	
Recurrent (n = 12)	11 (91.7)	1 (8.3)	
Total (n = 80)	77 (96.2)	3 (3.8)	$p = 0.36$

Table 4 Rate and breakdown of complications between the initial and recurrent groups

Complication	Initial (n = 68) (%)	Recurrent (n = 12) (%)	Total (n = 80)
None	48 (70.6)	8 (66.7)	56 (70.0)
Mild	17 (25.0)	3 (25.0)	20 (25.0)
TIA	2	0	
Asym Inf	15	3	
Severe	3 (4.4)	1 (8.3)	4 (5.0)
ICH	0	0	
Sym Inf	3	1	

Asym Inf: asymptomatic infarction
ICH: intracranial hemorrhage
Sym Inf: symptomatic infarction
TIA: transient ischemic attack

Comparison between the pre- and post-stent periods

Comparison of pre- and post-stent period is summarized in Table 5. The pre-stent group consisted of 26 (33%) patients who underwent coil embolization without a stent, whereas the post-stent group consisted of 54 (67%) patients who underwent coil embolization either with or without a stent. Transition of procedures, aneurysmal neck type, imaging and clinical outcomes, and complication were compared between pre- and post-stent group. In majority of the patients (41%; 22/54 patients) in the post-stent group, a stent was used during coil embolization. This group had significantly higher rates of adjunctive technique (double catheter, balloon-assisted or

stent-assisted technique) than the pre-stent group (72.2% vs 38.5%, respectively; $p = 0.00369$). Rate of wide neck of post-stent group was 74.1% (40/54), which was significantly higher than that of the pre-stent group ($p = 0.00069$). The percentages of favorable clinical outcomes in the pre- and post-stent groups were 96.1% and 96.2%, respectively. There were no significant differences in imaging and clinical outcomes or postoperative complications between the two groups.

Table 5 Comparison of pre- and post-stent periods

	Total (n = 80) n (%)	Pre-stent group (n = 26; 33%) n (%)	Post-stent group (n = 54; 67%) n (%)	*p* value
Transition of procedures				
Simple tech	31 (38.7)	16 (61.5)	15 (27.8)	$p = 0.004$
Adjunctive tech	49 (61.3)	10 (38.5)	39 (72.2)	
Neck types				
Narrow	31 (38.7)	17 (65.4)	14 (25.9)	$p = 0.001$
Wide	49 (61.3)	9 (34.6)	40 (74.1)	
Imaging outcomes				
Good (CO+NR)	72 (90)	22 (84.6)	50 (92.5)	$p = 0.27$
Poor (AR+F)	8 (10)	4 (15.4)	4 (7.5)	
Clinical outcomes				
Favorable (mRS: 0–2)	77 (96.2)	25 (96.1)	52 (96.2)	$p = 0.89$
Unfavorable (mRS: 3–6)	3 (3.8)	1 (3.9)	2 (3.8)	
Complications				
None	56 (70)	19 (73.1)	37 (68.5)	$p = 0.67$
Mild	20 (25)	6 (23.1)	14 (25.9)	
Severe	4 (5)	1 (3.8)	3 (5.6)	

mRS: modified Rankin Scale
AR: aneurysm remnant
CO: complete occlusion
F: failure
NR: neck remnant
tech: technique

DISCUSSION

In this study, endovascular treatment of unruptured MCA aneurysms achieved adequate embolization (CO + NR) and favorable clinical outcomes (mRS score: 0–2) over an average follow-up duration of 38 months in more than 90% patients. Furthermore, none of the treated cases had intracranial hemorrhage during the follow-up. The proportion of patients with permanent symptomatic complications during the perioperative period was low.

The meta-analysis of endovascular treatment for unruptured MCA aneurysms by Smith et al reported a poor imaging outcomes of 39–57% for endovascular treatment.[4] The imaging outcomes reported were deviated from our study. The reason for this was predicted to be that the treatment outcomes included in the meta-analysis were from the 1990s and early 2000s, and the treatment devices were older. There are 6 references reported since 2013 using the currently used advanced devices. Literatures were summarized in Table 6.[19-24] In each report, the endovascular procedures

Table 6 Literature review on endovascular treatment of middle cerebral artery aneurysms

	This study (2024)	Link et al[21] (2018)	Kadkhodayan et al[20] (2015)	Gory et al[23] (2014)	Mortimer et al[24] (2014)	Kim et al[19] (2013)	Abla et al[22] (2013)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Average age (SD)	60.3 ±10.5	57.0 ±15.0	57.0	53.2	53.0	56.7	60.2 ±10.7
Male sex	37 (48)	26 (28)	95 (27)	42 (32)	98 (33)	13 (43)	13 (43)
Average follow-up periods (SD) month	38.0 ± 26.0	–	24.0	16.3	–	–	17.1
Treatment procedures							
Single cath	31 (38)	50 (54)	86 (25)	23 (18)	–	17 (57)	21 (62)
Double cath	15 (18)	0 (0)	0 (0)	10 (7)	–	8 (26)	0 (0)
Balloon	12 (15)	24 (26)	230 (66)	79 (60)	–	2 (7)	1 (3)
Stent	22 (29)	19 (20)	26 (8)	19 (15)	–	3 (10)	12 (35)
FD	0 (0)	0 (0)	4 (1)	0 (0)	–	0 (0)	0 (0)
Number of aneurysms	80	93	346	131	300	30	34
Non-Rup	80 (100)	53 (57)	251(73)	90 (39)	56 (19)	27 (90)	19 (56)
Rup		40 (43)	95 (27)	41 (61)	244 (81)	3 (10)	15 (44)
Imaging outcomes							
CO+NR	72 (90)	80 (85)	346 (94)	130 (99)	274 (91)	28 (93)	25 (73)
Clinical outcomes							
mRS: 0–2	77 (96)	59 (81)	336 (97)	–	219 (73)	–	22 (64)
mRS: 3–6	3 (4)	34 (19)	10 (3)	–	81 (27)	–	12 (36)
Complications							
Sym Iinf	4 (5)	18 (19)	47 (14)	6 (5)	17 (6)	2 (7)	4 (12)
ICH	0 (0)	2 (2)	9 (3)	12 (9)	18 (6)	1 (3)	7 (21)
Death	0 (0)	0 (0)	10 (3)	7 (3)	45 (15)	0 (0)	5 (15)

cath: catheter
CO: complete occlusion
FD: flow diverter
ICH: intracranial hemorrhage
mRS: modified Rankin Scale
NR: neck remnant
Rup: rupture
Sym Inf: symptomatic infarction

included the use of single or double catheter and flow diverter, balloon-assisted technique, and stent placement. The good imaging outcomes ranged from 73–99%, and the outcomes were improved compared to the meta-analysis reported by Smith et al.[4] Good imaging outcomes and favorable clinical outcomes were higher when the percentage of ruptured aneurysms was lower.

However, Gory and Mortimer achieved good angiographic outcomes immediately after treatment despite the high percentages of ruptured aneurysms,[23,24] possibly due to the timing of embolic state assessment. Immediately after aneurysm rupturing, it is in hypercoagulable state and accentuates embolic state, and which may be contributed the high CO+NR ratios in the immediate period. Ruptured aneurysms may be recurrence even if adequate embolization is achieved immediately after treatment.[25] In our study, we compared the angiographic outcomes between the initial and recurrent groups. During the follow-up phase, both groups had high rates of good clinical outcomes (CO + NR). Almost half of the patients in the initial group (43.1%) with NR in the immediate phase transitioned to CO at the 6-month follow-up. Therefore, NR may considered an acceptable aneurysmal embolic status in the initial treatment of unruptured MCA aneurysms. Previous studies reported that the changes in aneurysmal embolic state approximately 6 months posttreatment following image improvement were induced by thrombosis progression.[26,27] However, one of the weak points of endovascular treatment is recurrence after treatment; Lecler et al reported that recurrence after endovascular treatment occurs in about 11% of cases.[28] At our institution, we have seen recurrence in 5% (4/80 aneurysms) after an average follow-up of 38 months. All recurrent aneurysms were in non-stented patients, suggesting that the use of stents may reduce recurrence in the medium term.

The pre- and post-stent groups had similar imaging and clinical outcomes with low complication rates. However, the pre-stent group had more narrow-neck aneurysms than the post-stent group. The higher proportion of patients in the pre-stent group (61.5%) who received treatment using the single-catheter procedure indicates that their aneurysms, which had simple shapes such as a narrow neck, were selectively treated. Likewise, fewer patients (27.8%) were treated using the single-catheter procedure in the post-stent group, and more patients received endovascular treatment using other procedures, such as the use of double catheter (27.8%), balloon-assisted technique (18.5%), and stent placement (40.7%). Therefore, even difficult-to-treat aneurysms can be effectively managed with adjunctive techniques to achieve good outcomes. The higher complication rate among the post-stent group than among the pre-stent group was likely due to the higher rate of thromboembolic complications following endovascular treatment using stents.[29,30]

Although more complex procedures may adequate embolization for difficult aneurysms such as the wide neck, they are associated with increased thrombotic complications.[31-33] DAPT is generally recommended for patients receiving endovascular treatment with stent placement to reduce the risk of thrombotic complications.[33] DAPT (aspirin [100 mg] and clopidogrel [75 mg]) is usually administered 14 days before endovascular treatment.[34] However, about 20% of Japanese patients are resistant to clopidogrel due to cytochrome P450 2C19 gene mutation[35]; thus, TEG6s (Haemonetics Corporation, Boston, USA) should be measured before endovascular treatment to confirm response to clopidogrel. If resistance to clopidogrel and thrombotic complications occur, prasugrel (3.75 mg) is recommended. The current antithrombotic protocols in our institution for stent placement recommend that patients undergoing endovascular treatment receive preoperative DAPT and then 5000 units of heparin and 30 mg of argatroban continuously for 12 h after surgery. So far, no severe bleeding complications have been reported when our protocols were followed. To date, the duration of antithrombotic therapy remains unclear. In our practice, if the embolic state is stable and there is no incidence of stroke, we discontinue the administration of antiplatelet agents 2 years after endovascular treatment, even among patients with stent placement.[36]

Limitations

This study had some limitations. First, our single-center retrospective review may not be generalizable to other populations. However, it provided evidence on the efficacy of endovascular treatment for MCA aneurysm in preventing rupture. Second, our limited sample may have overestimated the effects of endovascular treatment. This study was small cohort and there was a possibility of a statistical type 2 error. Thus, larger sample sizes are required to establish the efficacy of our procedures. Third, the choice of endovascular technique, which was left to the operators' discretion, resulted in inconsistency in technique selection. Fourth, the aneurysmal embolic state was confirmed using MRI findings, a technique that is less accurate than DSA. Finally, patients were only followed up for an average duration of 3 years. A longer follow-up period is needed to evaluate the long-term hemorrhage control effect of coil embolization.

CONCLUSIONS

Endovascular treatment of unruptured MCA aneurysm is safe and effective in preventing rupture and achieving good embolization of narrow-neck aneurysms without using a stent as well as wide-neck aneurysms using double catheter, balloon-assisted techniques, or stent placement. Thrombotic complications should be carefully monitored, particularly when using such complex procedures. Endovascular treatment of unruptured MCA aneurysms is a favorable treatment option depending on the experience of the institution.

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DECLARATIONS

Ethics approval

All procedures performed in studies involving human participants 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. The study was approved by the Bioethics Committee of the Nagoya University Graduate School of Medicine (No. 2020-0404).

Consent to participate and publish

Informed consent was obtained from all individual participants included in the study. Patients signed informed consent regarding publishing their data.

Conflicts of interest

Takashi Izumi has a technical guidance contract with Medtronic. No conflicts of interest for other authors.

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