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Original Article

Improvement of Cerebrovascular Reserve by Percutaneous Transluminal Angioplasty for Symptomatic Middle Cerebral Artery Stenosis

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Objective: The purpose of this study was to investigate the efficacy of percutaneous transluminal angioplasty (PTA) for symptomatic middle cerebral artery stenosis by analyzing cerebral blood flow (CBF).

Methods: Between January 2016 and December 2018, six patients with symptomatic middle cerebral artery stenosis underwent CBF analysis by single-photon emission computed tomography (SPECT) with acetazolamide challenge before and after PTA for stenosis. They were retrospectively reviewed, and the blood flow in the area of the affected middle cerebral artery before and after angioplasty was compared.

Results: The mean stenosis rate and length of lesion before angioplasty were 76.4 ± 5.4% and 6.5 ± 2.1 mm, respectively. Balloon angioplasty without stenting was performed on all patients. The mean residual stenosis rate just after angioplasty was 45.4 ± 9.3%. No periprocedual complications developed, and there were no notable cerebral ischemic events during the postprocedural follow-up period. One patient underwent repeat angioplasty for restenosis. Although there was only a mild decrease in blood flow at rest, the cerebrovascular reserve (CVR) in the area of the affected middle cerebral artery was markedly decreased before angioplasty (mean, 3.6 ± 4.3%). After angioplasty, the CVR was significantly improved (mean, 18.0 ± 4.7%, $p < 0.01$).

Conclusions: PTA for symptomatic middle cerebral artery stenosis can be safely performed using appropriate interventional techniques for select patients. Reduced CVR due to stenosis can be improved after angioplasty, which may reduce the risk of cerebral ischemic events.

Keywords ▶ middle cerebral artery stenosis, percutaneous transluminal angioplasty, cerebrovascular reserve, single-photon emission computed tomography

Introduction

At present, the benefits of intervention for intracranial stenosis have not been established. The efficacy of bypass surgery for specific conditions, such as reduction of cerebral blood flow (CBF) and cerebrovascular reserve (CVR), has been demonstrated, but there are no definitive indications of percutaneous transluminal angioplasty (PTA).[1] We have determined its indications based on the findings of single-photon emission computed tomography (SPECT) and angiography, and we have performed PTA for intracranial stenosis. The objective of this study was to evaluate the efficacy of PTA for middle cerebral artery stenosis from the viewpoint of CBF analysis.

Materials and Methods

Before this study began, its protocol was approved by our institutional review board. Between January 2016 and December 2018, PTA was performed on 10 patients with middle cerebral artery stenosis, but CBF was not evaluated before procedure in four patients because the ischemic lesions extended early after onset. The subjects of this study were the remaining six patients in whom CBF was quantitatively evaluated by SPECT, including acetazolamide challenge before and after procedure.

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All patients underwent cerebral angiography before procedure. Based on the findings, the location and shape of the stenotic lesions were evaluated, and the length and stenosis rate (Warfarin–Aspirin Symptomatic Intracranial Disease [WASID] method) of the lesion were measured.[2] Quantitative evaluation of CBF by SPECT was performed using ^{123}I-iodoamphetamine (^{123}I-IMP) including acetazolamide challenge (autoradiography [ARG] method). Preprocedual evaluation was performed when symptoms stabilized at 2 weeks or more after onset of the cerebral ischemic event. Postprocedual evaluation was performed at 3 months or more after procedure. The PTA-treated stenotic lesion was evaluated with MRA or CTA, and when restenosis was suspected, and was then confirmed by cerebral angiography.

As a general rule, PTA for middle cerebral artery stenosis was considered when the following conditions were met:

1. Severe stenosis (≥70%) was present in the M1 segment.
2. A cerebral ischemic event considered to be associated with the hemodynamic mechanism developed in the area perfused by the target blood vessel.
3. The CVR was reduced (≤10%) in the area perfused by the target blood vessel.
4. Bending of the lesion was mild (≤45°) and short (≤10 mm).
5. The lesion was not markedly distal in the M1 segment; either the PTA balloon or the stent did not reach the M1–M2 junction at which the blood vessel widely becomes bent and narrow.
6. No small blood vessels, such as the perforating arteries, originated from a region close to the lesion, and there was no risk of occluding these by the PTA balloon.

Regarding the treatment strategy for cases in which PTA is considered, the objective, methods, and risk of PTA were explained to the patients and their families beforehand. The option of continuing medical treatment with antiplatelet therapy was also presented, and PTA was performed on patients who consented to it. To perform PTA, dual antiplatelet therapy (DAPT), including clopidogrel, was introduced 1 week or more before PTA. Procedure was performed under general anesthesia. Setting the activated clotting time (ACT) at 200 seconds or longer using heparin, the lesion was approached using a coaxial system, which comprised a 7Fr guiding catheter and a 5.2Fr DAC (Stryker Neurovascular, Fremont, CA, USA). Using a Gateway PTA balloon OTW (Stryker Neurovascular) for a normal or smaller vessel diameter to prevent overdilation, the balloon was inflated slowly at 2–6 atmospheric pressure, being a relatively low pressure, and inflation was completed when it was judged that the stenosis rate had reached 50% or more of the normal vessel diameter. When vessel dissection or restenosis (recoil) was noted after waiting for approximately 10 min, placement of a Wingspan (Stryker Neurovascular) was considered. However, neither the balloon diameter nor the inflation pressure was increased nor was a stent used when the vessel diameter improved from that before procedure and maintained a stable shape without recoil (even though the target vessel diameter had not been achieved). Heparin was not reversed, but neither was anticoagulant therapy continued. To prevent complications accompanying hyperperfusion, blood pressure was strictly controlled for several days. When a major change in digital subtraction angiography (DSA) was noted in the state of perfusion, such as increase in blood flow velocity and disappearance of dependence on collateral circulation in the vascular area treated by PTA, the risk of hyperperfusion was judged as high and sedation was completed after confirming favorable blood pressure control and the absence of complications accompanying hyperperfusion such as restlessness, convulsion, and hemorrhage. Regarding postprocedual antiplatelet therapy, DAPT was continued for at least 3 months until improvement of CVR was confirmed by SPECT and there were no clear findings of restenosis, followed by clopidogrel monotherapy.

CBF analysis was performed using nuclear medical imaging analysis software Neuro Flexer (Medi-Physics Co, Ltd, Tokyo, Japan). In this program, a template of each cerebral perfusion area of each cerebral artery prepared from axial cross-sectional views of normal brain magnetic resonance imaging (MRI) and atlas. The template was fitted to the patient's brain shape, and 0–3 regions of interest (ROIs) were automatically set in the area of the middle cerebral artery of each axial cross-sectional image of SPECT. The mean CBF in the area of the middle cerebral artery was determined to be the mean value of CBF in all ROIs. The CVR was calculated from the mean CBF at rest and after acetazolamide challenge.

$$\text{CVR (\%)} = [(\text{Mean CBF after acetazolamide challenge} - \text{mean CBF at rest})/\text{mean CBF at rest}] \times 100$$

Using these measurement results, CBF and CVR in the area of the affected middle cerebral artery were compared before and after procedure. Similarly, CBF in the area of the contralateral middle cerebral artery was measured, and the ratio of the mean CBF in the area of the affected middle

cerebral artery (CBF ratio) to the mean CBF in the area of the contralateral middle cerebral artery was calculated as 100%. Statistical analysis was performed using the paired *t* test, and $p < 0.05$ was regarded as significant:

CBF ratio (%) = (Mean CBF in the area of the affected middle cerebral artery/mean CBF in the area of the contralateral middle cerebral artery) × 100

Results

Mean age of the six patients was 61.0 ± 11.3 years, five of whom were females (**Table 1**). Five patients developed cerebral infarction and the sixth had a transient ischemic attack. All patients with cerebral infarction had scattered infarcts in the watershed area, which may have developed through the hemodynamic mechanism associated with the middle cerebral artery stenosis. The mean preprocedual stenosis rate was 76.4 ± 5.4%, and the mean length of the stenotic lesions was 6.5 ± 2.1 mm. The mean number of days from onset to PTA was 49 ± 21 days. PTA was performed on all patients by balloon inflation alone without stent placement. The mean stenosis rate was improved to 45.4 ± 9.3% immediately after PTA. No periprocedual complications developed in any patient and no cerebral ischemic event recurred throughout the postprocedual follow-up period, with a mean duration of 30.6 ± 13.6 months. As for periprocedual antiplatelet therapy, DAPT with cilostazol and clopidogrel was administered to three patients, and that with aspirin and clopidogrel were administered to the other three patients. DAPT was continued in one patient who developed restenosis, but the other patients did not develop obvious restenosis and their CVR was improved; therefore, DAPT was changed to clopidogrel monotherapy 3–4 months after procedure. In the patient who developed restenosis, repeat PTA was performed 10 months after procedure using a Wingspan to prevent restenosis. Reduction of CBF at rest was mild in all patients before procedure (CBF ratio at rest: 90.5 ± 2.2%), but the increase in blood flow after acetazolamide challenge was poor, and CVR was notably decreased (mean: 3.6 ± 4.3%). No significant increase was noted in CBF at rest after procedure compared with that before procedure (CBF ratio at rest: 95.5 ± 5.6%, $p = 0.09$), but blood flow after acetazolamide challenge was markedly increased in all patients, and the CVR was significantly improved (mean: 18.0 ± 4.7%, $p < 0.01$) compared with that before procedure (**Table 2**, **Fig. 1**).

Table 1 Patients' characteristics and postoperative status

Patient	Age(years)/sex	Onset pattern	Lesion length (mm)	Onset to PTA (days)	Antiplatelet drug	Preoperative stenosis (%)	Postoperative stenosis (%)	Perioperative complications	Restenosis (Retreatment)
1	65/F	TIA	9.0	41	CLP + CLZ	87	40	(–)	(–)
2	69/F	Stroke	9.0	32	CLP + CLZ	73	52	(–)	(–)
3	66/F	Stroke	7.3	46	CLP + CLZ	76	45	(–)	(–)
4	74/M	Stroke	4.9	58	CLP + ASA	71	44	(–)	(–)
5	51/F	Stroke	3.0	93	CLP + ASA	70	29	(–)	(–)
6	41/F	Stroke	6.0	28	CLP + ASA	79	59	(–)	(+)

ASA: aspirin; CLP: clopidogrel; CLZ: cilostazol; PTA: percutaneous transluminal angioplasty; TIA: transient ischemic attack

Table 2 Cerebral blood flow analysis

Patient	Preoperative		Postoperative	
	CBF ratio at rest (%)	CVR (%)	CBF ratio at rest (%)	CVR (%)
1	91	0	99	18
2	87	2	100	15
3	89	1	84	23
4	89	7	92	24
5	90	0	97	14
6	94	10	99	11

CBF: cerebral blood flow; CVR: cerebrovascular reserve

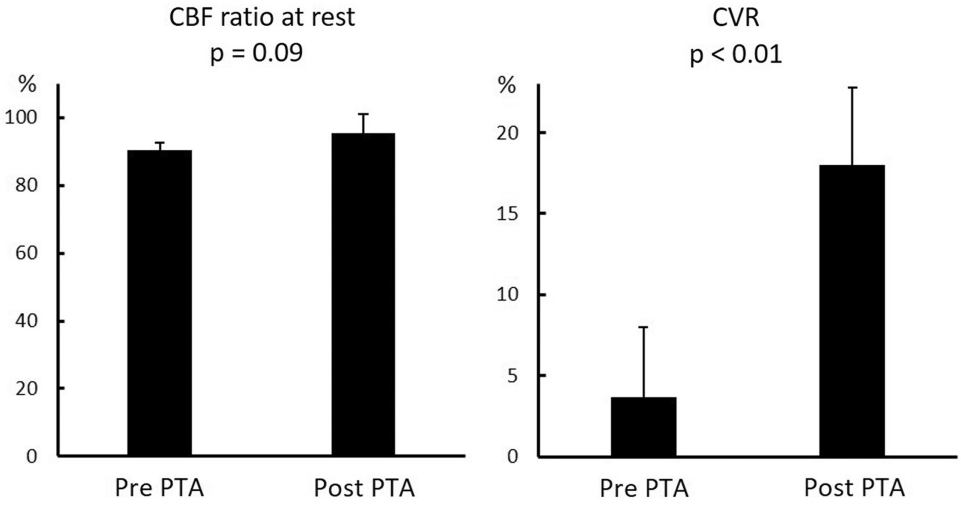

Fig. 1 Although the CBF ratio at rest was not significantly changed after angioplasty, the CVR was significantly improved. CBF: cerebral blood flow; CVR: cerebrovascular reserve

Case Presentation

The patient was a 66-year-old woman who presented with weakness of the right arm, dysarthria, and aphasia. MRI showed acute ischemic lesions scattered in the watershed area of the left cerebral hemisphere and severe stenosis in the M1 segment of the left middle cerebral artery (**Fig. 2A**). Treatment using argatroban and cilostazol (200 mg) was initiated. After completion of argatroban administration, DAPT was initiated by adding clopidogrel (75 mg) to cilostazol. On cerebral angiography, severe stenosis (76%) was noted in the proximal region of the M1 segment of the left middle cerebral artery (**Fig. 2B**). On SPECT, the CBF ratio at rest in the area of the left middle cerebral artery was 89%, but that after acetazolamide challenge was 66%, demonstrating marked laterality. The CVR of this area was markedly decreased to 1% (**Fig. 3A**). PTA for the stenotic lesion was planned to prevent recurrence of cerebral ischemic events. As the symptoms remitted, the patient was discharged home 14 days after onset with continuation of DAPT but she was readmitted and underwent PTA 46 days after onset.

Under general anesthesia, ACT was set at 200 sec or longer with 4000 units of heparin. A coaxial system of a 7Fr Fubuki (Asahi Intecc, Tokyo, Japan) and a 5.2Fr DAC were navigated to the left internal carotid artery. The normal diameter of the middle cerebral artery was less than 2.0 mm, and the lentuculostriate arteries originated from a region slightly distal to the stenotic lesion. To prevent vessel damage and occlusion of the perforating arteries by overdilation, a 1.5-mm balloon was selected. A Gateway PTA balloon (OTW 1.5 × 9 mm) was navigated and slowly inflated to an atmospheric pressure of 3 (**Fig. 2C**). The lesion was easily dilated, no vessel dissection or recoil was noted, and the stenosis rate had improved to 45% (**Fig. 2D**). No postprocedual anticoagulant therapy was performed and DAPT was continued. No perioperative complications developed. On SPECT performed 4 months after procedure, the CBF ratio in the area of the left middle cerebral artery after acetazolamide challenge was 78%, demonstrating a decrease in laterality compared with that before procedure, and the CVR of this area was markedly improved to 23% (**Fig. 3B**). Cilostazol administration was discontinued

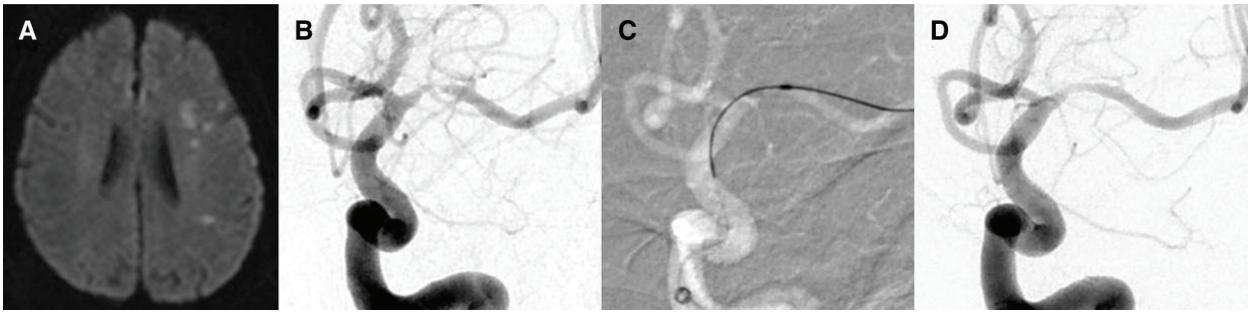

Fig. 2 (**A**) Diffusion-weighted MRI showed sporadic acute cerebral ischemic lesions at the left watershed area. (**B**) DSA showed severe stenosis in the proximal M1 segment of the left middle cerebral artery. (**C**) Angioplasty was performed using a 1.5 × 9-mm Gateway PTA balloon. (**D**) The stenosis lesion was sufficiently dilated without intraprocedural complications. DSA: digital subtraction angiography; MRI: magnetic resonance imaging

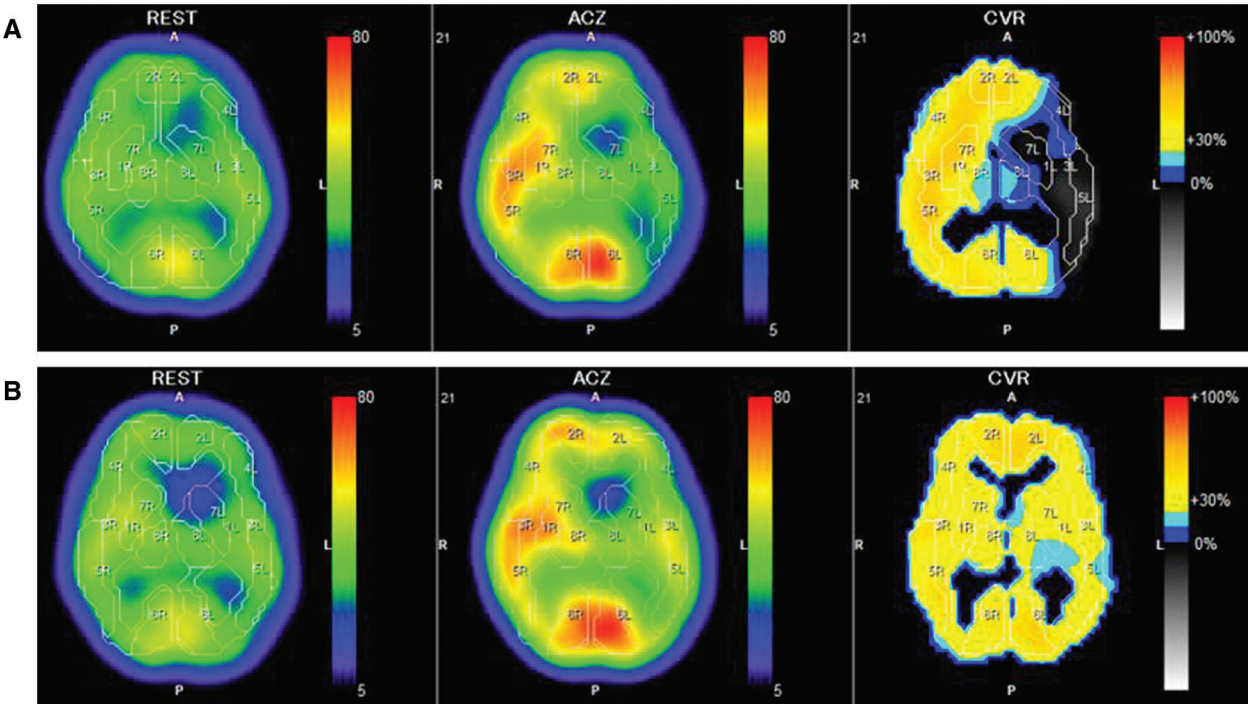

Fig. 3 (**A**) Preprocedual and (**B**) postprocedual CBF analysis. Note that the response of blood flow in the area of the left middle cerebral artery to ACZ challenge was increased and the CVR was also markedly improved after PTA. ACZ: acetazolamide; CBF: cerebral blood flow; CVR: cerebrovascular reserve; PTA: percutaneous transluminal angioplasty

at this time but clopidogrel monotherapy was continued. No cerebral ischemic event has recurred throughout the 38-month postprocedual follow-up period.

Discussion

Intracranial stenosis frequently develops in Asians, including Japanese, and the clinical course of asymptomatic lesions is relatively favorable. However, once symptoms develop, the risk of recurrence of cerebral ischemic events is high and therapeutic intervention is necessary.[3,4] In cases that cerebral ischemic events repeatedly develop in spite of medical treatment such as antiplatelet therapy and management of risk factors, a favorable outcome can be achieved by revascularization.[2,3,5–7] In the Japanese EC–IC Bypass Trial (JET) Study, bypass surgery was performed on patients with hemodynamic cerebral ischemia meeting specific criteria on quantitative evaluation of CBF. The effectiveness of bypass surgery for preventing cerebral ischemic events was confirmed by skilled operators and thorough periprocedual management.[1] Compared with bypass surgery, PTA is less invasive and more advantageous for recovering physiological antegrade blood flow. The technique is simple and applicable within a short time. However, sufficient

scientific evidence supporting its usefulness is lacking and there are no definitive indications. But appropriate procedure and periprocedual management may safely improve blood flow in regions distal to the stenotic lesion, leading to prevention of cerebral ischemic events for select patients, similarly to bypass surgery.[8,9] Therefore, judgment of the indications and procecual strategy are also important for PTA.

As a general rule, the indications for revascularization are limited to refractory stenotic lesions against medical treatment. However, as neurological function may markedly deteriorate due to a recurring cerebral infarction, judging whether the lesion is resistant to medical treatment at onset of the first cerebral ischemic event is ideal. A severely stenotic lesion (70%) was identified in a subanalysis of the WASID Study[10] and a lesion causing hemodynamic cerebral ischemia was identified in the Groupe d'Etude des Stenoses Intra-Craniennes Atheromateuses symptomatiques (GESICA) Study[6] as a significant risk factor for the recurring of cerebral ischemic events. In studies investigating intracranial stenosis by quantitative evaluation of CBF, when the CVR was reduced, the incidence of recurrence was significantly high even though CBF at rest was not reduced.[11,12] In the JET Study, bypass surgery was to be performed when the case met both conditions of reduced CBF at rest and CVR. However, when the CVR was reduced in cases of severe symptomatic intracranial stenosis manifesting hemodynamic cerebral ischemia, subjects were likely to be resistant to medical treatment, suggesting that revascularization be considered.[13] At our institution, excluding cases in which symptoms are progressively aggravated in the acute phase, cerebral angiography and SPECT, including acetazolamide challenge, are performed on patients who develop cerebral ischemic events considered to be caused by intracranial stenosis, and the indication of revascularization is carefully judged by evaluating the stenotic lesion and CBF. When a stenotic lesion is likely to cause hemodynamic cerebral ischemia and the CVR is reduced, revascularization is considered even though CBF at rest is not reduced. The area of the middle cerebral artery, particularly, has a neurologically important function. In addition, collateral circulation in the area of the middle cerebral artery cannot be acquired through either the anterior or posterior communicating artery, and it is mainly dependent on blood flow through the small cortical branches of other vascular regions. Therefore, the significance of revascularization of middle cerebral artery stenosis may be high.

Even in cases in which revascularization is recommended, to perform PTA safely it is necessary to select the patients carefully and perform procedure using an appropriate technique with appropriate timing, similarly to bypass surgery. Previous large-scale randomized clinical studies, the Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) Study[14] and the Vitesse Intracranial Stent *Study* for Ischemic Stroke Therapy (VISSIT) Study,[15] compared medical treatment and PTA with stenting (PTAS) for symptomatic intracranial stenosis, but the efficacy of PTAS was not demonstrated because many periprocedual complications developed in both studies. Herein, the subjects were patients within 30 days of the onset of cerebral ischemic events, but the median time to enrollment after onset was 7 days; procedure was performed within 3 days after randomization in the SAMMPRIS Study, whereas in the VISSIT Study, the median time to enrollment after onset was 9 days, and procedure was performed within 2 days after randomization. As the time to procedure after onset was short, effects of antiplatelet drugs might not have been sufficient at the time of procedure. Basically, the risk of recurrent cerebral ischemic events is high and complications are likely to occur by the intervention for unstable lesions in the acute phase. Indeed, poor outcomes of PTA performed in the acute phase have been reported by studies other than large-scale studies.[16] Based on these studies, in the Wingspan Stent System Post Market Surveillance (WEAVE) Trial,[17] patients at 8 days or more after onset of the cerebral ischemic events were selected, and procedure was performed 7 days or more after the initiation of DAPT (median time to treatment after onset: 22 days), resulting in a low incidence of periprocedual complications. For our patients, preprocedual DAPT was performed for a sufficient duration, and PTA was performed at the earliest time of 28 days after onset, resulting in the absence of periprocedual complications. Based on the above, we might consider it important to perform antiplatelet therapy for a sufficient duration and then PTA after the acute phase to achieve a favorable outcome.

Many cases of cerebral infarction developing in the periprocedual period of PTA occur in the perforating arteries, so one possible cause is that dilation of the stenotic lesion distorts and moves plaque out of the lesion and occludes the origin of the perforating arteries (snowplow effect).[18] Therefore, when revascularization is considered for a middle cerebral artery, in which the perforating arteries originate from a region close to the stenotic lesion, PTA may not be appropriate. The Mori classification is considered as a reference criterion to select lesions appropriate for PTA, that is, those for which PTA can be performed relatively safely in

patients having a comparatively linear and short stenotic lesion with no problem regarding the access route (Type A) because both the complication rate and restenosis rate are low.[19] As a general rule at our institution and based on the above, intervention is performed after the acute phase to increase the safety of revascularization. To select between bypass surgery and PTA, PTA is prioritized for patients in whom angioplasty is considered safe when the lesion is relatively linear and short with no access problems and the bifurcation of the perforating arteries not close to the lesion.

The WEAVE Trial[17] clarified that the correct use of a Wingspan by skilled interventionalists in appropriately selected patients is relatively safe, but the outcomes of stent placement in intracranial stenosis remain poor compared with those of medical treatment. As vessel opening by a balloon alone was sufficiently effective to improve CBF and prevent cerebral infarction, PTA without stent placement should be attempted as the initial treatment.[7,20,21] As the lesions were atherosclerotic, they cannot in many cases be dilated sufficiently using a balloon alone, and 45% stenosis remained on average immediately after procedure in our patients. However, it was sufficiently effective to improve CVR, even though stenosis remained, suggesting it had clinical significance. On the other hand, postprocedual restenosis is likely after PTA using a balloon alone, and restenosis frequently develops when the initial dilation is insufficient.[22] In our patient (No. 6), who required retreatment for restenosis, a 59% stenosis rate remained after the first PTA, no improvement of CVR was observed on SPECT at 6 months after procedure, suggesting that restenosis had developed earlier. If a stent is placed in the initial PTA, the possibility of acquiring sufficient dilation increases, but conversely, in-stent stenosis or thrombotic occlusion may be induced because of foreign body placement. Moreover, recovery from vessel rupture and perforating artery occlusion caused by overdilation is impossible even though a stent is placed. Thus, greater importance should be placed on preventing overdilation rather than acquiring satisfactory dilation in the initial treatment to prevent the use of a stent and other complications.

In this study, we selected patients with symptomatic middle cerebral artery stenosis based on the above criteria and performed PTA using the technique described above. Thus, it was possible to complete revascularization safely without causing periprocedual complications. In addition, significant improvement of the reduced CVR, which is considered a risk factor for the recurrence of cerebral ischemic events, was demonstrated. No cerebral ischemic events recurred during the follow-up period, suggesting the efficacy of PTA to prevent cerebral infarction.

There were several limitations in this study. First, patients who underwent PTA and those who continued medical treatment were not compared; thus, the superiority of PTA over medical treatment was not demonstrated. Moreover, as this was a retrospective study, no objective numerical criterion was set for the distance between the stenotic lesion and the M1–M2 junction or between the stenotic lesion and the bifurcation of the perforating arteries something to which attention should be paid to judge the indication of PTA. Furthermore, preprocedual evaluation of CBF by SPECT was performed 2 weeks or more after onset, and the postprocedual evaluation was performed 3 months or more after procedure when completion of DAPT was considered, but these time points were not based on a validated index. However, examination time points were not consistent among past reports, and currently, there is no clear index concerning the time points appropriate for evaluating CBF.[1,7,11,13] In the future, clear criteria for evaluating anatomical characteristics of stenotic lesions and the timing of evaluation of CBF should be investigated to obtain highly objective and reliable data. Further studies are necessary to clarify whether PTA for intracranial stenosis is effective in preventing cerebral infarction.

Conclusion

PTA for symptomatic middle cerebral artery stenosis accompanied by reduction of the CVR can be safely applied by carefully judging the indications and employing an appropriate technique, which may improve the CVR and contribute to preventing recurrence of cerebral ischemic events.

Disclosure Statement

The authors declare no conflict of interest.

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