The Therapeutic Strategy and Outcome of Endovascular Therapy for Acute Stroke with Cerebral Proximal Artery Occlusion due to Atherosclerotic Artery Stenosis

Kosuke Kakumoto,1 Yukihiro Sankoda,1 Shigenari Kin,1 Kei Harada,2 and Kenji Uda3

Objective: While intracranial mechanical thrombectomy has been established as a treatment, atherothrombotic brain infarction due to stenosis of major cerebral arteries is occasionally difficult to treat as severe stenosis persists after recanalization, eventually requiring percutaneous transluminal angioplasty (PTA) or stent placement. The contents and results of mechanical thrombectomy for atherothrombotic brain infarction that we have encountered are presented.

Methods: The subjects were 17 patients diagnosed with atherothrombotic brain infarction among the 99 patients with cerebral infarction accompanied by major intracranial artery occlusion treated at our hospital during the 30 months from January 2014 and June 2016. Recanalization graded as Thrombolysis in Cerebral Infarction (TICI) 2b or higher was regarded as effective, and the outcome was evaluated using the modified Rankin Scale (mRS).

Results: The responsible lesion was located at the origin of the internal carotid artery (ICA) in three patients, in the ICA siphon in four patients, middle cerebral artery (MCA) in five patients, vertebral artery (VA) in two patients, and basilar artery (BA) in three patients. Effective recanalization was achieved in 82.4%, the mRS score was 0-2 in 52.9%, and the postoperative mRS score was the same as before treatment in 11.8%.

Conclusion: The outcome of intracranial mechanical thrombectomy for atherothrombotic brain infarction accompanied by major intracranial artery stenosis was favorable in many patients, and aggressive treatment is considered recommendable. In addition, safe and appropriate execution of additional treatments for residual stenotic lesions leads to favorable outcomes.

Keywords ▶ atherothrombotic brain infarction, Penumbra system, stent retriever

Introduction

With the advent of the Penumbra system and stent retrievers, the recanalization rate and outcome after intracranial mechanical thrombectomy have been improved.1,2 Moreover, five randomized controlled trials (RCTs) demonstrated the usefulness of mechanical thrombectomy.3–7 However, some patients with atherothrombotic brain infarction accompanied by stenosis of major intracranial arteries require percutaneous transluminal angioplasty (PTA) or stent placement for severe residual stenosis or reclosure after mechanical thrombectomy and are difficult to treat. Here, we report the contents and results of intracranial mechanical thrombectomy that we performed for atherothrombotic brain infarction.

Subjects

The subjects were 17 patients diagnosed with atherothrombotic brain infarction among the 99 patients (102 lesions) with brain infarction accompanied by occlusion of major intracranial arteries who underwent mechanical thrombectomy.
at our hospital during the 30 months from January 2014 to June 2016.

Methods

Intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) was regarded as the first choice according to its guidelines, and mechanical thrombectomy was performed under local anesthesia in patients with no indication for rt-PA thrombolysis and those who did not respond to it. If the procedure was difficult to continue due to marked body movements during the treatment, sedatives such as diazepam, dexmedetomidine hydrochloride, and propofol were used as necessary. Endovascular treatment was performed by femoral artery puncture, in principle. As the guiding catheter, 9 Fr OPTIMO (Tokai Medical, Aichi, Japan) was used for anterior circulation lesions, and 6 Fr FUBUKI (Asahi Intecc, Tokyo, Japan) was used for posterior circulation lesions, unless there were problems with the puncture site. At our hospital, the Penumbra MAX series (Penumbra, Alameda, CA, USA) was introduced in January 2014, and stent retrievers were introduced in July, the same year. While a direct aspiration first pass technique (ADAPT) using the Penumbra system was performed as the first choice, stent retrievers were used as an additional treatment if thrombectomy was difficult with the Penumbra system. Also, stent retrievers were used as the first choice by the operator’s judgment. Recanalization was evaluated using the modified Thrombolysis in Cerebral Infarction (TICI) grade, and TICI 2b or higher grades were regarded as effective recanalization. In addition, the outcome was evaluated using the modified Rankin Scale (mRS) and was judged to be favorable when the mRS score was ≤2 or was not changed from the preoperative level.

Patients in whom stenosis was observed in the recanalized vessel and those who were considered to have developed A to A embolism due to the stenotic lesion were diagnosed with atherothrombotic brain infarction. PTA was performed in patients who showed severe stenosis after thrombectomy, had a narrow area of brain infarction on preoperative MRI diffusion weighted image (DWI), and were judged to have a low risk of hemorrhage. Also, stent placement was performed in patients who developed restenosis after PTA.

In patients in whom navigation of the thrombectomy device was difficult due to severe stenosis of the cervical internal carotid artery (ICA), carotid artery stenting (CAS) was performed first. CAS was also performed first in patients who were suggested to have vulnerable plaque by high intensity of the plaque at the origin of the internal carotid (IC) on cervical MRA and judged to have A to A embolism due to plaque rupture because they were considered at a high risk of plaque rupture by the passage of the thrombectomy device during the procedure.

Results

Table 1 summarizes the characteristics of the patients. Table 2 compares the outcomes between patients with atherothrombotic brain infarction and other patients. The stenosed vessels were the IC in seven (siphon in four, origin in three), middle cerebral artery (MCA) in five (M1 in four, M1 distal-M2 in one), vertebral artery (VA) in two, and basilar artery (BA) in three patients. In all three patients with stenosis at the origin of IC, the MCA was occluded due to A to A embolism. CAS was performed, followed by thrombectomy, in two (Table 1, Cases 8 and 9), and additional CAS was performed later in one patient (Case 14). In two (Cases 11 and 12) of the four patients with stenosis of the IC siphon, reocclusion was observed on the day of recanalization, and retreatment was necessary. In Case 11, PTA was performed as the initial treatment, but, as reocclusion was observed, stenting was added at retreatment. In Case 12, intravenous thrombolysis with rt-PA was performed, and as recanalization was confirmed on DSA performed immediately after the treatment, only examinations were performed at that time, but reocclusion occurred after 4 hours. After thrombectomy, additional PTA was performed for severe stenosis at C4 of the IC. Details of Case 11 are described in the case presentation below. In one patient each with IC siphon stenosis and MCA stenosis (Cases 12 and 16), the vessels were reoccluded shortly after recanalization due to thrombus formation at the site of stenosis. Therefore, although after intravenous thrombolysis with rt-PA, multiple antiplatelet agents (aspirin at 200 mg, clopidogrel at 300 mg, p.o., and ozagrel sodium at 80 mg, i.v.) were administered, this resulted in angiographic confirmation of suppression of thrombus formation, and no reocclusion was noted. Stenosis progressed in a patient in whom the stenosed MCA was recanalized by stent retriever thrombectomy (Case 3), and Superficial temporal artery (STA)-MCA bypass was added after 9 months.

If intravenous thrombolysis with rt-PA was performed, basically, the administration of antiplatelet drugs was initiated by performing head MRI after 24 hours and confirming the absence of hemorrhagic change. After dual-antiplatelet
Table 1  Patient characteristics and outcome of endovascular therapy

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<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Occlusion site  (stenosis site)</th>
<th>ASPECTS-DWI/pc-ASPECTS</th>
<th>t-PA</th>
<th>D2N</th>
<th>D2P</th>
<th>P2R</th>
<th>Device</th>
<th>PTA/ CAS</th>
<th>TICI</th>
<th>NIHSS before procedure</th>
<th>NIHSS 24 h after procedure</th>
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*pc-ASPECTS, ASPECT: Alberta Stroke Program Early CT Score; BA: basilar artery; CAS: carotid artery stenting; D2N: door to needle time; D2P: door to puncture time; DWI: diffusion-weighted magnetic resonance imaging; IC: internal carotid artery; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; P: Penumbra; PTA: percutaneous transluminal angioplasty; pc-ASPECTS: posterior circulation-acute stroke prognosis early CT score; P2R: puncture to recanalization time; S: Solitaire; T: Trevo XP; TICI: thrombolysis in cerebral infarction; VA: vertebral artery
therapy was continued for 3 months; it was shifted to mono-
antiplatelet therapy without recurrence of cerebral infarc-
tion. Cases 4, 7, and 14 developed cerebral infarction during
oral treatment with 100 mg aspirin. No reocclusion was
observed after thrombectomy, and the administration of
75 mg clopidogrel was added. Even after intravenous rt-PA
therapy, loading doses of aspirin (200 mg) and clopidogrel
(300 mg) were administered intraprocedural through the
gastric tube in patients who needed CAS with thrombec-
tomy (Cases 8 and 9), those who needed stenting for severe
stenosis (Case 11), and those in whom thrombus formation
progressed at the site of stenosis during thrombectomy ther-
apy (Case 16). Case 17 showed severe stenosis of the BA,
and as reocclusion was considered likely to be fatal. There-
fore, 200 mg aspirin and 300 mg clopidogrel were adminis-
tered after PTA, and no reocclusion was observed.

As for the therapeutic results, the effective recanaliza-
tion rate was 82.4%, and favorable outcomes were
observed in 64.7% (mRS ≤2 in 52.9% and premorbid mRS
was maintained in 11.8%). Both the effective recanaliza-
tion rate and the percentage of good prognoses were
higher in patients with atherothrombotic infarction com-
pared with others.

Details of Cases 9, 11, 16, and 6 are presented below.

### Case Presentation

#### Case 9
This patient had M1 occlusion associated with right IC
stenosis (Fig. 1B and 1C). Pretreatment cervical MRA
showed severe stenosis of the right IC, head MRA
showed occlusion of the right M1, and a diagnosis of A
to A embolism due to severe IC stenosis was made. Fol-
lowing intravenous thrombolysis with rt-PA, DSA was
performed. Right common carotid angiography (CCAG)
showed severe stenosis at the origin of the right IC and
occlusion of the right M1 similarly to MRA. Since pas-
sage of the device through the site of severe stenosis
involved the risk of distal embolism and ICA occlusion
due to dissection, CAS was considered necessary before
intracranial thrombectomy. After 200 mg aspirin and
300 mg clopidogrel were administered via the nasoga-
stric tube, CAS was performed first using Carotid Wall-
stent (Stryker, Kalamazoo, MI, USA) (Fig. 1E and 1F).
Then, ADAPT was performed using Penumbra 5MAX
ACE, resulting in TICI3 recanalization (puncture to
recanalization time [P2R] 50 min) (Fig. 1G). After the
absence of hemorrhagic change was confirmed by head
MRI on the day after treatment, the administration of

<table>
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<th>Table 2</th>
<th>Baseline characteristics of the study population</th>
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<td>Patients with AS (n = 17)</td>
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<td>Age, yr</td>
<td>69 ± 9.26</td>
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<tr>
<td>Male sex, n (%)</td>
<td>13 (76.5%)</td>
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<tr>
<td>Risk factor, n (%)</td>
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<tr>
<td>Hypertension</td>
<td>9 (52.9%)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>5 (29.4%)</td>
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<tr>
<td>Dyslipidemia</td>
<td>8 (47.1%)</td>
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<tr>
<td>Atrial fibrillation</td>
<td>3 (17.6%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>3 (17.6%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1 (5.9%)</td>
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<tr>
<td>History of stroke or TIA</td>
<td>3 (17.6%)</td>
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<tr>
<td>Occlusion site, n (%)</td>
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<tr>
<td>Internal carotid artery</td>
<td>5 (29.4%)</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>7 (41.2%)</td>
</tr>
<tr>
<td>Vertebral artery</td>
<td>2 (11.8%)</td>
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<tr>
<td>Basilar artery</td>
<td>3 (17.6%)</td>
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<tr>
<td>Posterior cerebral artery</td>
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<td>Anterior cerebral artery</td>
<td>0</td>
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<tr>
<td>Baseline NIHSS score</td>
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<tr>
<td>rt-PA</td>
<td>70.60%</td>
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<tr>
<td>D2N</td>
<td>45 ± 26.17</td>
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<td>D2P</td>
<td>60.5 ± 39.25</td>
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<td>P2R</td>
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<td>D2R</td>
<td>116 ± 33.24</td>
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<td>Onset to recanalization time</td>
<td>169 ± 60.31</td>
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<td>TICI ≥2b</td>
<td>82.40%</td>
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<td>Favorable outcome</td>
<td>64.70%</td>
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AS: atherosclerotic stenosis; D2N: door to needle time; D2P: door to puncture time; D2R: door to recanalization
time; NIHSS: National Institutes of Health Stroke Scale; P2R: puncture to recanalization time; rt-PA: recombinant
tissue plasminogen activator; TIA: transient ischemic attacks; TICI: thrombolysis in cerebral infarction
EVT for AIS due to Atherosclerotic Artery Stenosis

and stenting was performed using Integrity BMS 4.0 mm × 22 mm (Medtronic, Santa Rossa, CA, USA). Although satisfactory vascular patency could be achieved (Fig. 2L), the patient developed extensive brain infarction and, subsequently, hemorrhagic infarction, resulting in mRS6 (Fig. 2G–2I).

Case 16

The patient has M1 occlusion with stenosis from the right M1 distal to M2 (Fig. 3A). Intravenous thrombolysis with rt-PA was performed (door to needle time [D2N]: 23 min), and recanalization was confirmed on DSA (Fig. 3B). Stenosis was observed, but as intravenous rt-PA therapy had been performed, the patient was observed without antiplatelet medication. Since reocclusion was noted after 4 hours, ADAPT was performed using Penumbra 5MAX ACE, resulting in recanalization, but thrombus formation was noted after 10 minutes (Fig. 3C). DSA showed a series of stenotic lesions from the M1 distal to M2 inferior trunk, and a diagnosis of atherosclerosis was made. However, the judgment of whether the M2 superior trunk was truly stenosed or appeared stenosed as thrombus formation was difficult. Trevo XP 3.0 mm × 20 mm (Stryker) was deployed in the superior trunk (Fig. 3D) as the M2 superior trunk was also diagnosed with atherosclerosis because

100 mg aspirin and 75 mg clopidogrel was continued. Following 2-week rehabilitation at our hospital, the patient was discharged to home in a state of mRS0. After discharge, the patient was followed-up by our department as an outpatient. Since no recurrence of cerebral infarction was observed on head MRI after 3 months, and carotid ultrasonography confirmed the absence of abnormalities at the site of stenting, the antiplatelet therapy was reduced to aspirin alone.

Case 11

This patient had right IC occlusion associated with C5 stenosis (Fig. 2). ADAPT was performed two times using Penumbra 5MAX ACE, and while a large amount of thrombus was retrieved, recanalization could not be achieved. TICI3 recanalization was obtained by Solitaire FR 6 mm × 30 mm (Medtronic, Minneapolis, MN, USA) + Penumbra 5MAX ACE (door to puncture time [D2P]: 58 min, P2R: 29 min) (Fig. 2J). For severe residual stenosis, PTA (8 atm, 4 min) using SHIDEN 3.0 × 20 mm (Kaneka Medix, Osaka, Japan) was performed, and while satisfactory dilatation was achieved (Fig. 2K), the site was reoccluded after 12 hours. Recanalization was obtained by ADAPT using Penumbra 5MAX ACE, PTA (8 atm, 4 min) was performed using SHIDEN 4.0 mm × 20 mm, and stenting was performed using Integrity BMS 4.0 mm × 22 mm (Medtronic, Santa Rossa, CA, USA). Although satisfactory vascular patency could be achieved (Fig. 2L), the patient developed extensive brain infarction and, subsequently, hemorrhagic infarction, resulting in mRS6 (Fig. 2G–2I).

Fig. 1 In Case 9, DWI on admission shows early ischemic changes in the right insular cortex (A), and subcortical white matter of the corona radiata (B). MRA shows occlusion of the M1 segment of the right MCA (C), and right ICA stenosis (D). Right CCAG shows ICA stenosis at origin (E). Following carotid artery stenting (F), the 5MAX ACE is advanced to the occlusion site, and the thrombus is removed completely by ADAPT (G). ADAPT: a direct aspiration first pass technique; CCAG: common carotid angiography; ICA: internal carotid artery; DWI: diffusion-weighted magnetic resonance imaging; MCA: middle cerebral artery
Fig. 2 In Case 11, DWI on admission shows early ischemic changes in the cortex and subcortical white matter of left parietal lobe and corona radiata (A–C). Left CCAG (lateral view) after the thrombus is removed by the 3MAX ACE and Solitaire (Medtronic, Santa Rossa, CA, USA) stent shows severe ICA stenosis (J). Left CCAG after balloon PTA shows dilatation of the lesion (K). After 12 h, the left ICA has become occluded again (L), and DWI shows that the high-intensity area has expanded (D–F). Left ICAG after re-treatment (balloon PTA and stenting) shows good dilatation (M). However, post-procedural DWI (G–I) shows high-intensity area has expanded to a greater degree than noted on pre-procedural DWI (D–F). CCAG: common carotid angiography; DWI: diffusion-weighted magnetic resonance imaging; ICA: internal carotid artery; ICAG: internal carotid angiography; PTA: percutaneous transluminal angioplasty

of poor stent expansion. Since stenosis involved two branches, and as there was a possibility of occlusion of both shoud vascular dissection be induced by PTA, anti-platelet medication was judged to be safer if it could prevent reocclusion. Since thrombus formation progressed even after the use of Trevo XP (Fig. 3E), 80 mg of ozagrel sodium was administered by intravenous (iv) drip infusion, and 200 mg of aspirin was administered through the gastric tube. Since no reocclusion occurred during 30-minute observation, the procedure was ended (Fig. 3F), and the patient was discharged to home in a state of mRS0.

Case 6
The patient suffered left VA occlusion associated with severe left VA stenosis following chronic occlusion of the right VA (Fig. 4A). After intravenous thrombolysis with rt-PA (D2N: 70 min), DSA slowly visualized the V3 portion and BA via the collaterals (Fig. 4C and 4D). ADAPT was performed using Penumbra 3MAX, and TICI3 recanalization was achieved (D2P: 87 min, P2R: 40 min), but severe stenosis persisted in the left VA after recanalization (Fig. 4E and 4F). The right VA was occluded, and as brain infarction was also expected to extend to the BA and posterior cerebral artery (PCA) territories, PTA (6 atm, 3 min) was performed using Gateway 2.0 × 9 mm (Stryker) at the site of residual stenosis (Fig. 4G). Since restenosis was not observed after 30 minutes, the treatment was ended without stenting (Fig. 4H). The patient was discharged to home in a state of mRS0.

Discussion
In this study, we evaluated treatment in the acute period of atherothrombotic brain infarction associated with major intracranial artery stenosis. The Penumbra system is used as the first choice at our hospital. In addition, our policy is to first perform ADAPT and, if recanalization cannot be achieved, to add stent retriever thrombectomy. We adopted this strategy because the recanalization rate by ADAPT has been reported to be comparable to that by stent retriever thrombectomy, and thrombus can be aspirated from a position near the occluded area without lesion crossing, so thrombectomy is considered to be performed safely even when information concerning the
areas distal to the site of occlusion is unavailable. Moreover, in many patients, whether or not there are concurrent atherosclerotic lesions is unknown before the procedure, and the lesion is found to be atherosclerotic only after recanalization. The risk of plaque rupture and intimal damage or dissection, which may be induced by passage of the device, is considered to be reduced by ADAPT using the Penumbra system.\textsuperscript{(11)}

According to Yoon et al.,\textsuperscript{(1)} 22.9\% of the patients who underwent intracranial mechanical thrombectomy for ultra-acute phase brain infarction had atherostenotic lesions, and the percentage of patients who had favorable outcomes with an mRS score of ≤2 was significantly higher in these patients than in those of other disease types. They suggested a significantly lower National Institute of Health Stroke Scale (NIHSS) score and a significantly higher effective recanalization rate as reasons for this difference and speculated that these patients might have a smaller amount of occlusive plaque or better developed collaterals and ischemic tolerance due to stenotic lesions. Similar results were obtained at our hospital by comparison between atherothrombotic brain infarction and other diseases (Table 2).

We performed CAS in two patients with stenosis of the IC origin and obtained favorable outcomes in both patients. Stenosis is considered to have been caused by thrombus formation associated with severe stenosis in one and rupture of vulnerable plaque in the other patient. In both patients, a 9 Fr OPTIMO was guided to the common carotid artery (CCA), and Carotid GuardWire Percusurge (Medtronic) to the external carotid artery (ECA), and flow reversal was induced by blocking the blood flow with a balloon. Furthermore, FilterWire EZ (Stryker) was placed in the distal part of the ICA to minimize further enlargement of brain infarction during the procedure. In addition, to reduce the risk of distal embolism and reocclusion due to intra- or
except for the use of heparin at ≤10000 units for angiography or the prevention of deep venous thrombosis.\textsuperscript{14,15} However, antiplatelet agents are considered essential in CAS or for the prevention of thrombus formation at sites of stenosis. As the outcome is exacerbated by hemorrhage, even if recanalization can be achieved, we used antiplatelet agents after confirming the narrowness of the infarct area by pretreatment MRI and maintained the blood pressure low after treatment,\textsuperscript{16} to avoid hemorrhagic complications. There has also been a report of cases in which an uneventful course without hemorrhagic complications could be obtained by performing CAS with dual-antiplatelet therapy using 100 mg aspirin and 75 mg clopidogrel following intravenous thrombolysis with rt-PA.\textsuperscript{17}

Many patients with VA or BA occlusion treated at our hospital showed satisfactory outcomes. Particularly, all the five patients with atherothrombotic brain infarction showed favorable outcomes, with the mRS score after 3 months being ≤2 in three and remaining unchanged at three from before treatment in two patients. In the

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**Fig. 4** In Case 6, the right VA was occluded at the origin (A), and the left VA arose from the aorta (B). Left VAG shows VA occlusion, and the basilar artery is supplied via the collateral artery (anterior-posterior view [C], lateral view [D]). DSA after thrombectomy with Penumbra 3MAX (Penumbra, Alameda, CA, USA) shows successful recanalization with severe atherosclerotic stenosis at the left VA (anterior-posterior view [E] and lateral view [F]). A balloon catheter was positioned within the stenotic lesion, and PTA was performed (6 atm, 3 minutes) (G). Left VAG after balloon PTA shows good dilatation of the lesion (H). PTA: percutaneous transluminal angioplasty; VA: vertebral artery; VAG: vertebral artery angiography.
Basilar Artery International Cooperation Study (BASICS) study, which is a prospective registry study about the treatment and outcome of acute BA occlusion, the mRS score was ≥4 in 68% of the patients, and the mortality rate was 36% but high at 50% in those who were severely ill at treatment.\(^9\) In the ENDOSTROKE study, the mRS score was ≤2 in 34%, and the mortality rate was 35%, of the patients who were endovascularly treated for BA occlusion.\(^9\) In this study, the TICI 2b-3 effective recanalization rate was 79%, and the development of collaterals and the use of stent retrievers were considered independent predictors of recanalization.\(^9\) While TICI3 recanalization could be achieved in all patients treated at our hospital, the device used was the Penumbra system in four and Solitaire stent in one patient, and favorable results could also be obtained using the Penumbra system. Additional PTA was performed for severe stenotic lesions persisting after recanalization in four of the five patients, and no stenosis that would require retreatment has been observed after the procedure. We did not perform stenting in our patients because reocclusion due to elastic recoil or acute occlusion due to arterial dissection was not observed after PTA, but there have been reports that satisfactory outcomes could be obtained by stenting\(^{20,21}\) and that the risk of distal embolism due to dissection or plaque rupture can be reduced by primary stenting without PTA.\(^{22}\) Also, as there has been a report of cases that developed restenosis 3 weeks after treatment and required stenting in the chronic period,\(^{10}\) careful follow-up is necessary after treatment.

Patients with stenotic lesions need long-term follow-up after thrombectomy, and it is considered necessary to evaluate additional treatments each time the risk of brain infarction increases due to progression of stenosis.

### Conclusion

Intracranial mechanical thrombectomy for atherothrombotic brain infarction associated with major intracranial artery stenosis was reported. Many patients with atherothrombotic brain infarction showed favorable outcomes compared with other patients, and aggressive treatment is considered recommendable. However, reocclusion due to vascular stenosis is often observed after recanalization, and multimodal treatments including additional PTA and stenting is necessary. In addition, it is necessary to individually evaluate early introduction of antiplatelet agents for the prevention of reocclusion even after intravenous thrombolysis with rt-PA in patients with a narrow infarct area and a low possibility of hemorrhagic changes.

### Disclosure Statement

Neither the first author nor any of the coauthors have any conflicts of interest to disclose regarding this paper.

### References


