Long-Term Effects on Preventing Stroke after Endovascular Treatment or Bypass Surgery for Intracranial Arterial Stenosis

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Background: Intracranial arterial stenosis (ICAS) is an important cause of ischemic stroke worldwide due to its higher risk of recurrence with medical therapy. Although some large randomized studies failed to show the superiority of surgical treatment compared with medical therapy, the results of medical therapy are not sufficient. There are patients who still benefit from surgical treatment. This retrospective analysis aimed to evaluate the long-term efficacy of surgical therapy with percutaneous transluminal angioplasty and/or stenting (PTA/PTAS) or extracranial-intracranial (EC/IC) bypass surgery for patients with ICAS. *Methods*: Between October 2005 and December 2016, 55 ICAS patients were treated with PTA/PTAS or EC-IC bypass surgery. Their electronic medical records were retrospectively reviewed and analyzed. The primary outcome was all adverse events beyond 30 days after a revascularization procedure. *Results*: We performed 21 cases (35%) of PTA, 4 cases (7%) of PTAS, and 34 cases (58%) of EC-IC bypass surgery and the median follow-up duration was 66 months (range 1-144 months). The occurrence rate of the primary outcome was 10.2% and only 1 patient (1.8%) experienced ipsilateral disabling ischemic stroke beyond 30 days. The long-term functional independent survival rate was 83.6%. *Conclusions*: We demonstrated a long-term favorable outcome of combined surgical intervention for ICAS patients with PTA/PTAS and EC-IC bypass surgery, and the result was better than previously reported outcomes of medical therapy. Additional multicenter studies are required to draw firm conclusions on the efficacy of reduction of recurrent stroke in patients with ICAS.
Key Words: Intracranial arterial stenosis—percutaneous transluminal angioplasty—stenting—EC-IC bypass

Introduction

Intracranial arterial stenosis (ICAS) is one of the most important causes of ischemic stroke worldwide, especially in Asia. It has a high risk of recurrent infarction with medical therapy compared with other stroke subtypes.[1-4] Because of the risk of recurrence, randomized studies have been conducted to show the superiority of surgical treatment with bypass or endovascular treatment using stenting, but the aim has never been achieved. The Extracranial/Intracranial (EC/IC) Bypass Study demonstrated that outcomes of patients undergoing surgical revascularization therapy were worse than of those receiving medical therapy.[5] In 2 large trials, the stenting and aggressive medical management for preventing recurrent stroke in intracranial stenosis (SAMMPRIS) trial and the Vitesse Stent Ischemic Therapy trial, the investigators could not

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prove the superiority of percutaneous transluminal angioplasty and stenting (PTAS) for preventing stroke.[6-9] These unfavorable results in the surgical treatment of ICAS led to negative comments in guidelines developed by the American Heart Association and the American Stroke Association, which do not recommend EC/IC bypass nor stenting for initial treatment of symptomatic major intracranial artery stenosis.[10]

The aforementioned results in surgical treatments were primarily due to perioperative complications. Compared with the EC/IC Bypass Study,[5] the Japanese EC-IC Bypass Trial (JET) study, conducted with rigorous patient selection including objective hemodynamic assessment, demonstrated the superiority of surgical treatment because it had a low periprocedural complication rate.[11] Endovascular treatment of submaximal angioplasty alone or stenting with devices other than Wingspan stent may be considered as a treatment option, which could demonstrate the advantages of a surgical approach with limited complications.[1,6,7,9,12-14] Additionally, identifying high-risk medical therapy subgroups that are likely to benefit from such potential treatment is an important issue.[7,9,14,15] However, long-term outcomes remain unclear in patients who underwent EC-IC bypass surgery with low perioperative complication or intervention with other techniques under appropriate application.

We have performed endovascular treatment and superficial temporal artery-middle cerebral artery (STA-MCA) bypass for mainly symptomatic ICAS patients who are affected by hypoperfusion for more than 10 years. This retrospective analysis evaluates the long-term efficacy of surgical therapy for patients with ICAS.

Patients and Methods

Patients and Study Setting

This study was implemented at a single institution. In total, 59 surgical treatments, endovascular therapy, or STA-MCA bypass surgery were performed on 55 patients between October 2005 and December 2016. Patients with at least 1 month of clinical follow-up were included; those who needed emergency treatment were excluded. Patients with a lesion that was not attributable to atherosclerosis, such as moyamoya disease, were also omitted. The electronic medical records of each patient were retrospectively reviewed to collect information, including baseline characteristics, performed intervention, and technical and clinical outcomes. The research protocol was approved by the Japanese Red Cross Nagoya Daini Hospital institutional ethics committee and written informed consent was waived because of the retrospective design.

Surgical treatment was performed for patients with severe intracranial stenosis (70%-90%), except for 1 patient with retreatment with moderate stenosis of 65%, involving the internal carotid, middle cerebral, basilar, or intracranial dominant vertebral arteries, who had previously received medications. Most patients were symptomatic and presented with a transient ischemic attack (TIA) or stroke attributable to the territory of the target lesion. Asymptomatic patients, especially those with clinically significant hypoperfusion or progressing severe stenosis, were carefully considered as candidates for surgical intervention.

Treatment Strategies

Percutaneous angioplasty (PTA) was performed on patients with the following conditions; initiating sufficient and appropriate medical therapy consisting of antiplatelet drugs, statins, and risk factor control, accessible to the lesion with low risk, short lesion (<10 mm) without severe vascular calcification, and not involving any perforating arteries. Local anesthesia was used for PTA and the strategy was submaximal balloon angioplasty. We additionally used coronary balloon expandable stents in cases of deficient dilatation, lesion recoil, and dissections. In patients whose ischemic mechanisms were hemodynamic but they did not meet these criteria, STA-MCA bypass was offered. In symptomatic cases, we waited for about 2-4 weeks from onset to surgical procedure in order to pass the phase of unstable cerebral perfusion with medical therapy, except in patients whose neurological symptoms were worsening rapidly.

Follow-up and Outcome Measures

Patients underwent postprocedure clinical evaluation measured as modified Rankin Scale (mRS) score on the day of discharge and at the latest follow-up; they also had regular inspection with magnetic resonance imaging and, if necessary, computed tomography angiography or conventional angiography. Patients were evaluated by physicians in the outpatient department.

The primary outcome was all adverse events including any stroke, death, or other procedure-related complications beyond the periprocedural period, defined as 30 days after a revascularization procedure. The secondary outcome was the incidence of any stroke, other neurological complications, or all-cause death occurring within 30 days.

Results

During the study period, we performed 21 cases (35%) of PTA, 4 cases (7%) of PTAS, and 34 cases (58%) of STA-MCA bypass for 55 patients. Three patients had multiple procedures; 2 of them needed retreatment due to restenosis and another one underwent STA-MCA bypass for symptomatic stenosis and was then treated with staged PTAS strategy for a contralateral asymptomatic tandem lesion. Baseline characteristics are summarized in Table 1. Among these patients, the mean age was 63.6 years (range 39-80 years) and most were male (70.9%). The median duration of follow-up in all patients was 66 months (range

Table 1. *Baseline characteristics of patients*

Baseline characteristics	N = 59 (cases)/55 (patients), No. (%)
Age, years ± SD*	63.6 ± 9
Male*	39 (70.9)
Procedure	
PTA	21 (35)
PTAS	4 (7)
STA-MCA anastomosis	34 (58)
Risk factors	
Hypertension	41 (69)
Hyperlipidemia	37 (63)
Diabetes	19 (32)
Smoking (Current and former)	29 (49)
Coronary artery disease	11 (19)
Previous stroke/TIA	19 (32)
Presentation	
Ischemic stroke	36 (61)
TIA	10 (17)
Asymptomatic	13 (22)

Abbreviations: PTA, percutaneous transluminal angioplasty; PTAS, percutaneous transluminal angioplastystenting; SD, standard deviation; STA-MCA, superficial temporal artery-middle cerebral artery; TIA, transient ischemic attack.

*Population parameter is number of patients.

1-144 months). Concomitants of vascular risk factor were detected in many patients, including hypertension (69%), hyperlipidemia (63%), diabetes (32%), smoking (49%), coronary artery disease (19%), and previous stroke or TIA (32%). Initial clinical presentation was ischemic stroke in most patients (61%) and 13 patients (22%) were asymptomatic. Location and severity of stenosis are shown in Table 2. Middle cerebral artery (MCA) was the most frequent lesion, followed by internal cerebral artery (ICA) stenosis. The mean preprocedural stenosis rate was 83.2% (range 65%-95%).

The primary outcome occurred in 6 patients (10.2%); 1 patient underwent PTA/PTAS and the others had STA-MCA bypass (Table 3). One patient in the STA-MCA bypass group, who used anticoagulant drug for atrial fibrillation, died at 60 months after the revascularization therapy due to intracranial hemorrhage, 2 had ischemic stroke, 1 had chronic subdural hematoma, 1 needed treatment for wound infection, and another one in PTA/PTAS group died because of pleural empyema. Ipsilateral disabling ischemic stroke in the vascular distribution of the treated artery beyond 30 days occurred in 1 patient (1.8%), and no stroke event was detected during the follow-up period, especially in PTA/PTAS patients. Only 2 patients (3.4%) met the secondary outcome at the 30-day follow-up period; 1 had an ipsilateral disabling ischemic stroke and another had hyperperfusion syndrome. All of them had STA-MCA bypass and no patient who underwent PTA or PTAS suffered major periprocedural complications. Technical success was defined as residual stenosis of less than or equal to 50% for PTA/PTAS and as bypass patency on magnetic resonance angiography obtained on the day after the surgery for STA-MCA bypass. The technical success rate of PTA/PTAS was 96% and the average postprocedural stenosis rate was 41.2% (range 25%-85%), and that of STA-MCA bypass was 100%.

Functional outcome was measured using mRS at discharge and at latest follow-up. The average score of mRS was .87 (median 1, range 0-4) at the preprocedural point, .95 (median 1, range 0-5) at discharge, and 1.05 (median 0, range 0-6) at the latest follow-up. Of the 10 patients who presented with clinical worsening on the mRS after discharge, 1 patient had a brain infarction, 1 had parenchymal brain hemorrhages, 1 had chronic heart failure, 1 had pleural infection, and 4 had fractures. The long-term functional independent survival (mRS $\geq$ 2) rate was 87.3%, and 89.1% of all patients could walk with no assistance (mRS $\geq$ 3; Table 4).

Discussion

The purpose of this study was to evaluate the long-term efficacy of surgical intervention for ICAS patients. Indeed, we demonstrated long-term effectiveness to prevent recurrent stroke and good functional outcomes in ICAS patients treated with PTA/PTAS or STA-MCA bypass. None of the patients suffered ischemic stroke in PTA/PTAS and only 2 patients (5.9%) with STA-MCA bypass presented with recurrent infarction. The long-term rate of all adverse events in the present study was 10.2% and compared favorably with the 23.9% of 3-year event risk in the PTAS group of the SAMMPRIS trial. Furthermore, the

Table 2. *Lesion location and severity of intracranial arterial stenosis*

Lesion location	PTA/PTAS (n = 25, No. [%])	STA-MCA Bypass (n = 34, No. [%])	Total (n = 59, No. [%])
ICA	9 (36)	6 (18)	15 (25)
MCA	6 (24)	28 (82)	34 (57)
BA	3 (12)	0 (0)	3 (5)
VA	7 (28)	0 (0)	7 (12)
Severity of stenosis*	82.8% (65%-95%)	83.5% (70%-95%)	83.2% (65%-95%)

Abbreviations: ICA, internal cerebral artery; MCA, middle cerebral artery; STA-MCA, superficial temporal artery-middle cerebral artery, VA, vertebral artery; BA, basilar artery.

*Data are presented as mean percentage (range).

Table 3. *Results of primary and secondary outcomes and technical success*

	PTA/PTAS (n = 25, No. [%])	STA-MCA Bypass (n = 34, No. [%])	Total (n = 59, No. [%])
All adverse events including any stroke, death, or other procedure related complications beyond 30 days	1 (4)	5 (14.7)	6 (10.2)
Any stroke, other neurological complications, or all-cause death within 30 days	0 (0)	2 (5.9)	2 (3.4)
Disabling ischemic stroke in the territory of treated artery beyond 30days	0 (0)	1 (2.9)	1 (1.8*)
Technical success	24 (96)	34 (100)	58 (98.3)
Postprocedural stenosis	41.20%	-	-

Abbreviation: STA-MCA, superficial temporal artery-middle cerebral artery.
*The percentage was calculated using the number of patients as the denominator (n = 55).

14.9% risk of any stroke or death in the medical group in the SAMMPRIS trial was higher than that of our findings. From the point of view of the same primary endpoints in SAMMPRIS, the occurrence rate of endpoints in this study was 9.1%, which was considered superior to the rate in the medical arm of the SAMMPRIS trial.[7] Vitesse Stent Ischemic Therapy, another randomized control study that found an increased 12-month risk of added stroke or TIA with balloon-expandable stent, reported a 9.4% incidence rate of stroke in the medical group within 1 year, which was higher than our stroke risk rate of 7.3% within our 6-month median follow-up period.[9] These comparisons show that our surgical treatment strategy has the potential to improve outcomes of patients with ICAS.

Previous studies reported periprocedural stroke or death rates of 0%-8.3% with angioplasty.[12,16-18] Similarly, no complications were reported in the PTA/PTAS group of the present study within 30 days. The failure of the SAMMPRIS trial was primarily attributable to the higher incidence of periprocedural stroke than was expected.[6,12] A posthoc analysis of data collected in the SAMMPRIS trial showed that the most frequent types of periprocedural stroke were local perforator ischemic strokes.[19] Perforator occlusion by the displacement of debris or plaque shifting has been considered as the cause of periprocedural stroke after stenting.[20,21] It has been argued that the exclusion of patients presenting with perforator syndrome from SAMMPRIS could have averted half of the ischemic stroke complications.[20] Considering these results, the favorable outcome of periprocedural complications in the present study seems to be because of our strict patient selection. Additionally, one of the most important strategies is to ensure a sufficient waiting period before the procedure, because it is generally known that higher complication rates are reported in acute cases with unstable symptoms.[1,22]

Table 4. *Modified Rankin scale*

Score	Total (n = 55, No. [%])		
	Pretreatment	Discharge	Latest follow-up
0	27 (49.1)	26 (47.3)	34 (61.8)
1	15 (27.3)	15 (27.3)	4 (7.3)
2	7 (12.7)	9 (16.4)	10 (18.2)
3	5 (9.1)	2 (3.6)	1 (1.8)
4	1 (1.8)	2 (3.6)	1 (1.8)
5	0 (0)	1 (1.8)	3 (5.5)
6	0 (0)	0 (0)	2 (3.6)

Surgical revascularization using STA-MCA bypass surgery failed to prove efficacy for internal carotid artery occlusive disease compared with medial therapy in the EC/IC Bypass Study.[5] However, the study was criticized because of the large number of patients who were operated on outside of the study and the lack of hemodynamic assessment during patient selection.[23,24] After that, 2 randomized controlled trials (RCTs) were conducted to prove the superiority of STA-MCA bypass applied for restricted patients who showed obvious hemodynamic impairment with objective indicators.[11,25] The JET study demonstrated a significant reduction of complete stroke, death, and recurrent ipsilateral stroke in the surgical group after 2 years of follow-up, and reported no perioperative death or impairment complication.[11] On the other hand, the carotid occlusion surgery study (COSS) study, implemented in the United States and Canada, did not show a significant result to recommend bypass surgery for patients with internal carotid artery occlusion, mainly because of its significant perioperative stroke rate (15%).[25,26] In Japanese guidelines for the management of stroke (2015 version), EC-IC bypass surgery has been recommended under the same criteria used in JET.[27] There is a report from the European Association of Neurological Surgeons arguing that EC-IC bypass surgery might be beneficial if it is performed with a perioperative stroke rate lower than 7%-10%,[23] and another from the Cerebrovascular Section of the American Association of Neurological Surgeons and Congress of Neurological Surgeons stating that hemodynamic symptoms intractable to medical treatment may benefit from surgery performed with low perioperative morbidity.[28] According to these results, EC-IC bypass surgery is still considered as a potential option for ICAS patients. We reported 2 disabling neurological complications (5.9%) after STA-MCA bypass including 1 perioperative ischemic stroke (2.9%), and 3 ipsilateral ischemic strokes (8.8%) that occurred during the follow-up period after surgery. The rate of perioperative complication was acceptable and the long-term result was far better than that of COSS.[26] The difference of follow-up duration between this study and JET could explain why our rate of long-term ipsilateral ischemic stroke occurrence was higher than that of JET (3.1%).[11]

We acknowledge that there are several limitations to this study. First, this is a small size retrospective single center study. Second, we compared our results with previous RCTs because of the lack of a medical control arm. Previous RCTs performed endovascular therapy with stents for almost all cases, but we used stents for a limited number of cases of endovascular procedure and also performed STA-MCA bypass, so we should not simply compare both results. However, one of the most important issues facing this topic is the detection of characteristics that make patients suitable for each surgical intervention, and in the present study, we provided some evidence to help solve this problem. Additional prospective investigations are needed to clarify the efficacy of surgical intervention for ICAS and to determine definitive criteria for patient selection.

Conclusions

The long-term result of combined surgical intervention for ICAS with PTA/PTAS and STA-MCA bypass was shown in this study. Only 2 patients had neurological complications in the first 30 days and 2 patients presented with recurrent ipsilateral ischemic stroke beyond 30 days. Selecting an appropriate surgical strategy for each patient has the potential to reduce recurrent stroke in patients with ICAS. Further multicenter studies with a larger cohort are required to draw firm conclusions for the efficacy on reduction of recurrent stroke in patients with ICAS.

Supplementary Materials

Supplementary data to this article can be found online at doi:10.1016/j.jstrokecerebrovasdis.2018.12.039.

References

1. Holmstedt CA, Turan TN, Chimowitz MI. Atherosclerotic intracranial arterial stenosis: risk factors, diagnosis, and treatment. Lancet Neurol 2013;12:1106-1114.
2. Gorelick PB, Wong KS, Bae H-J, et al. Large artery intracranial occlusive disease: a large worldwide burden but a relatively neglected frontier. Stroke 2008;39:2396-2399.
3. Wong LK. Global burden of intracranial atherosclerosis. Int J Stroke 2006;1:158-159.
4. Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. N Engl J Med 2005;352:1305-1316.
5. The EC/IC Bypass Study Group. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. N Engl J Med 1985;313:1191-1200.
6. Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med 2011;365:993-1003.
7. Derdeyn CP, Chimowitz MI, Lynn MJ, et al. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. Lancet 2014;383:333-341.
8. Zaidat OO, Castonguay AC, Fitzsimmons BF, et al. Design of the Vitesse Intracranial Stent Study for Ischemic Therapy (VISSIT) trial in symptomatic intracranial stenosis. J Stroke Cerebrovasc Dis 2013;22:1131-1139.
9. Zaidat OO, Fitzsimmons BF, Woodward BK, et al. Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis. JAMA 2015;313:1240-1248.
10. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:2160-2236.
11. Ogasawara K, Ogawa A. JET Study (Japanese EC-IC bypass trial). Nihon Rinsho 2006;64(Suppl 7):524-527.
12. Dumont TM, Sonig A, Mokin M, et al. Submaximal angioplasty for symptomatic intracranial atherosclerosis: a prospective Phase I study. J Neurosurg 2016;125:964-971.
13. Ma Y, Gu Y, Tong X, et al. The Carotid and Middle cerebral artery Occlusion Surgery Study (CMOSS): a study protocol for a randomised controlled trial. Trials 2016;17:544.
14. Zaidat OO, Castonguay AC, Nguyen TN, et al. Impact of SAMMPRIS on the future of intracranial atherosclerotic disease management: polling results from the ICAS symposium at the International Stroke Conference. J Neurointerv Surg 2014;6:225-230.
15. Derdeyn CP, Fiorella D, Lynn MJ, et al. Impact of operator and site experience on outcomes after angioplasty and stenting in the SAMMPRIS trial. J Neurointerv Surg 2013;5:528-533.
16. Nguyen TN, Zaidat OO, Gupta R, et al. Balloon angioplasty for intracranial atherosclerotic disease: periprocedural risks and short-term outcomes in a multicenter study. Stroke 2011;42:107-111.
17. Marks MP, Wojak JC, Al-Ali F, et al. Angioplasty for symptomatic intracranial stenosis: clinical Outcome. Stroke 2016;37:1016-1020.
18. Marks MP, Marcellus ML, Do HM, et al. Intracranial angioplasty without stenting for symptomatic atherosclerotic stenosis: long-term follow-up. Am J Neuroradiol 2005;26:525-530.
19. Derdeyn CP, Fiorella D, Lynn MJ, et al. Mechanisms of stroke after intracranial angioplasty and stenting in the SAMMPRIS Trial. Neurosurgery 2013;72:777-795.
20. Abou-Chebl A, Steinmetz H. Critique of "Stenting Versus Aggressive Medical Therapy for Intracranial Arterial Stenosis" by Chimowitz et al in the New England Journal of Medicine. Stroke 2012;43:616-620.
21. Levy EI, Hanel RA, Boulos AS, et al. Comparison of periprocedure complications resulting from direct stent placement compared with those due to conventional and staged stent placement in the basilar artery. J Neurosurg 2003;99:653-660.

22. Kasner SE, Chimowits MI, Lynn MJ, et al. Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. Circulation 2006;113: 555-563.
23. Hänggi D, Steiger HJ, Vajkoczy P, et al. The role of MCA-STA bypass surgery after COSS and JET: the European point of view. Acta Neurochir Suppl 2014;119:77-78.
24. Ausman JI, Diaz FG. Critique of the extracranial-intracranial bypass study. Surg Neurol 1986;26:218-221.
25. Powers WJ, Clarke WR, Grubb RL, et al. Extracranial-intracranial bypass surgery for stroke prevention in hemodynamic cerebral ischemia. JAMA 2011;306:1983-1992.
26. Grubb RL, Powers WJ, Clarke WR, et al. Surgical results of the Carotid Occlusion Surgery Study. J Neurosurg 2013;118:25-33.
27. Joint Committee on guidelines for the management of stroke. Japanese guidelines for the management of stroke 2015. Tokyo: Kyowa Kikaku; 2015:135-136.
28. Amin-Hanjani S, Barker FG, Charbel FT, et al. Extracranial-intracranial bypass for stroke—is this the end of the line or a bump in the road? Neurosurgery 2012;71:557-561.