Lessons Learned From Moyamoya Disease: Outcome of Direct/Indirect Revascularization Surgery for 150 Affected Hemispheres

Miki FUJIMURA¹ and Teiji TOMINAGA²

¹Department of Neurosurgery, National Hospital Organization, Sendai Medical Center, Sendai, Miyagi; ²Department of Neurosurgery, Tohoku University Graduate School of Medicine, Sendai, Miyagi

Abstract

Moyamoya disease is a chronic, occlusive cerebrovascular disease with unknown etiology characterized by bilateral steno-occlusive changes at the terminal portion of the internal carotid artery and an abnormal vascular network at the base of the brain. Recent advances in molecular biology and genetic research have provided better understanding of the pathophysiology of moyamoya disease, but surgical revascularization still remains the preferred treatment for this entity. The present study investigated the clinical course of 106 consecutive patients with moyamoya disease who underwent superficial temporal artery-middle cerebral artery anastomosis with indirect pial synangiosis in 150 hemispheres. The outcomes of surgery on the operated hemisphere were favorable, with no cerebrovascular event during the outpatient follow-up period (mean 58.4 months) in 89.3% (134/150). Two patients suffered hemorrhagic events on the operated hemisphere during the follow-up period (2/150, 1.33%), one of whom suffered deteriorated neurological status after hemorrhage. Despite the favorable long-term outcome, the incidence of temporary neurological deterioration due to cerebral hyperperfusion was 18.0% (27/150), but no patients suffered permanent neurological deterioration directly caused by hyperperfusion. In conclusion, direct/indirect revascularization surgery is a safe and effective treatment for moyamoya disease, although the issue of bleeding/re-bleeding remains to be solved. Postoperative cerebral hyperperfusion and peri-operative infarction are potential complications of this procedure, so we recommend intensive postoperative care and cerebral blood flow measurement in the acute stage, because the management of hyperperfusion is contradictory to that of ischemia.

Key words: moyamoya disease, surgical management, extracranial-intracranial bypass, surgical complication, long-term outcome

Introduction

Moyamoya disease is a chronic, occlusive cerebrovascular disease with unknown etiology characterized by bilateral steno-occlusive changes at the terminal portion of the internal carotid artery and an abnormal vascular network at the base of the brain.³,²⁸) Extracranial-intracranial (EC-IC) bypass such as superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis is generally employed as the standard surgical treatment for moyamoya disease to prevent cerebral ischemic attacks by improving cerebral blood flow (CBF).⁷,¹¹,¹³,²³) Recent advances have been made in understanding the molecular biology and pathophysiology of moyamoya disease, and new genetic mutations and deletions have been identified,¹⁴,¹⁸) but surgical revascularization remains the preferred treatment for moyamoya disease patients with ischemic symptoms.⁷,¹¹,¹³,²³) The present study investigated the long-term outcomes of combined (direct/indirect) revascularization procedures in a single institute performed under standardized surgical indications and postoperative management protocol. The concept of revascularization surgery for moyamoya disease is discussed based on its intrinsic genetics and histological background.

Patients and Methods

The present study included 106 consecutive patients
with moyamoya disease, 30 men and 78 women aged 2–69 years (mean 33.1 years), surgically treated in 150 hemispheres between March 2004 and November 2010. The inclusion criteria of this study, corresponding to our surgical indications for STA-MCA anastomosis, included all of the following items: presence of ischemic symptoms, apparent hemodynamic compromise on N-isopropyl-p-[123I]iodoamphetamine single-photon emission computed tomography ([123I]-IMP SPECT), independent activity of daily living (modified Rankin scale scores 0–2), and absence of major cerebral infarction.2,4,5) All hemispheres that did not match these criteria were excluded from the initial surgery. Once hemodynamic compromise was confirmed, the patients underwent revascularization surgery. All patients underwent STA-MCA (M4) anastomosis with encephalo-duro-myo-synangiosis (Fig. 1).2,4,5) All patients satisfied the diagnostic criteria of the Research Committee on Spontaneous Occlusion of the Circle of Willis, of the Ministry of Health, Labour and Welfare, Japan, except for four patients with ‘probable moyamoya disease’ showing unilateral involvement.9) All patients were strictly followed up in our institutes for more than 12 months with a mean follow-up period of 58.4 months. The presence or absence of cerebral ischemic symptoms including stroke and transient ischemic attack (TIA), and occurrence of any intracranial hemorrhagic event such as intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) were investigated based on the patient’s records.

CBF was routinely measured by [123I]-IMP SPECT 1 and 7 days after surgery in all patients (Fig. 2A).5) 1.5-T or 3-T magnetic resonance (MR) imaging and MR angiography were routinely performed within 2 days after surgery (Fig. 2B).17) MR imaging included

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**Fig. 1** Intraoperative photographs of left superficial temporal artery (STA)-middle cerebral artery (MCA) anastomosis. A: The M4 segment of the right MCA was explored, and anastomosis between the STA stump and MCA was performed. B: Low power magnification view after anastomosis (arrow).

**Fig. 2** Representative case of a 31-year-old woman presenting with cerebral infarction. A: N-isopropyl-p-[123I]iodoamphetamine single-photon emission computed tomography scans in the acute stage after right superficial temporal artery (STA)-middle cerebral artery (MCA) anastomosis demonstrating marked increase in cerebral blood flow on the hemisphere operated on (arrows). B: Magnetic resonance angiogram after revascularization surgery demonstrating the STA-MCA bypass as a thick high signal (arrow).

**Fig. 3** Status of revascularization surgery for moyamoya disease in the intrinsic physiological reorganization system. Suzuki’s grading could indicate the compensatory nature of moyamoya disease, so called ‘intracranial carotid to extracranial carotid system (IC-EC) conversion’ as a physiology of moyamoya disease. Concept of revascularization surgery for moyamoya disease includes both vascular reconstruction by extracranial-intracranial (EC-IC) bypass and consolidation for future arteriogenesis by indirect pial synangiosis.
diffusion-weighted, T2*-weighted, fluid-attenuated inversion recovery, and T2-weighted images. The diagnostic criteria for symptomatic cerebral hyperperfusion included all of the following items: presence of a significant focal increase in CBF at the site of the anastomosis, which is responsible for the apparent neurological signs including focal neurological deficit and/or severe headache due to hemorrhagic changes; apparent visualization of STA-MCA bypass by MR angiography and the absence of any ischemic changes by diffusion-weighted MR imaging; and absence of other pathologies, such as compression of the brain surface by the temporal muscle inserted for indirect pial synangiosis, TIA, and seizure. The occurrence of symptomatic cerebral hyperperfusion after revascularization surgery was evaluated by 123I-IMP SPECT in the acute stage.

Results

No cerebrovascular events occurred in 134 of the 150 operated hemispheres (89.3%) of 106 patients during the outpatient follow-up period (Table 1). TIA was detected in 13 operated hemispheres (8.6%) during the outpatient follow-up period, but all patients with onset of TIA showed disappearance or improvement of ischemic attack during the follow-up period. One patient with ischemic onset (1/150, 0.66%) suffered minor completed stroke in the operated hemisphere during paroxysmal arterial fibrillation due to thyrotoxicosis 6 months after the revascularization surgery. One patient with ischemic onset (1/150, 0.66%) developed ICH of the ipsilateral thalamus 3 years after successful revascularization surgery, and suffered deterioration of modified Rankin scale score from 0 to 3 after the hemorrhage.

Table 1  Long-term outcome of superficial temporal artery-middle cerebral artery anastomosis with pial synangiosis during the outpatient follow-up period

<table>
<thead>
<tr>
<th>Cerebrovascular event</th>
<th>No. of hemispheres</th>
<th>Incidence (%)</th>
<th>Neurological status</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cerebrovascular event</td>
<td>134/150</td>
<td>89.3</td>
<td>N/A</td>
</tr>
<tr>
<td>TIA</td>
<td>13/150</td>
<td>8.6</td>
<td>N/A</td>
</tr>
<tr>
<td>Cerebral infarction*</td>
<td>1/150</td>
<td>0.66</td>
<td>mRS 2 → 2</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>2/150</td>
<td>1.33</td>
<td>mRS 0 → 0</td>
</tr>
<tr>
<td>SAH</td>
<td>1/150</td>
<td>mRS 0 → 3</td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>1/150</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Minor completed stroke during paroxysmal arterial fibrillation due to thyrotoxicosis. ICH: intracerebral hemorrhage, mRS: modified Rankin scale before and after the cerebrovascular events, N/A: not applicable, SAH: subarachnoid hemorrhage, TIA: transient ischemic attack.

Two patients with hemorrhagic onset developed rebleeding (2/150, 1.33%), one from contralateral ICH and one from ipsilateral SAH, but neither patient suffered deterioration of their neurological status. Postoperative MR angiography showed the patency of the STA-MCA bypass in all 106 patients with 150 operated hemispheres.

None of the 106 patients suffered peri-operative cerebral infarction in any of the 150 hemispheres, except for the following four patients. Three patients (3/150, 2.0%) presented with pseudolaminar necrosis in part of the cerebral cortex supplied by the STA-MCA bypass in the sub-acute stage probably due to thrombo-embolism, which did not affect their long-term neurological status. One patient (1/150, 0.66%) with an atherosclerotic background presented with cerebral infarction 3 days after surgery in the ipsilateral occipital lobe due to intensive blood pressure control for symptomatic SAH due to hyperperfusion. However, this infarction did not affect her long-term activity of daily living.

Twenty-six patients (27/150 hemispheres, 18.0%) demonstrated temporary neurological deterioration, including mild focal neurological signs, due to postoperative focal cerebral hyperperfusion between 2 and 14 days after surgery. Postoperative MR imaging/MR angiography did not show any ischemic changes, and showed the STA on the operated hemisphere as thick high signal intensity in all 27 hemispheres. Postoperative SPECT demonstrated significant intense increases in CBF at the sites of anastomosis in all 27 hemispheres. Twenty-two patients (23/150 hemispheres, 15.3%) demonstrated transient focal neurological deficit due to focal hyperperfusion that mimicked ischemic attack, starting between 2 and 9 days after surgery and persisting for several days. The anatomical location and temporal profile of the hyperperfusion were completely in accordance with the transient neurological signs in all 22 patients. Four patients (4/150 hemispheres, 2.6%) complained of severe headache and demonstrated symptomatic cerebral hyperperfusion associated with SAH in three patients (2.0%) or with ICH at the right frontal sub-cortex in one patient (0.66%). No patient suffered permanent neurological deficit due to cerebral hyperperfusion. No patient suffered delayed neurological deterioration due to cerebral hyperperfusion during the follow-up period.

Discussion

Planning of revascularization surgery for moyamoya disease should especially consider the intrinsic anatomical and/or physiological background.
of this rare entity. The histopathological characteristics of moyamoya disease include intimal hyperplasia and medial thinness. These histopathological changes are known to be occur in the peripheral pial arteries as well as major arterial trunks such as the carotid fork and proximal MCA, so the intrinsic fragility of the recipient artery must be appreciated during the anastomosis. Consideration of the macroscopic anatomy requires preservation of the trans-dural anastomosis via the middle meningeal artery, occipital artery, and STA during surgery, which have all spontaneously developed preoperatively due to the compensatory nature of moyamoya disease.

The concepts of revascularization surgery for moyamoya disease include both microsurgical reconstruction by EC-IC bypass and consolidation for future EC-IC arteriogenesis by indirect pial synangiosis (Fig. 3). Both procedures may attempt to convert the vascular supply for the brain from the intracranial carotid to the extracranial carotid system (IC-EC). The natural pathophysiological course of moyamoya disease, as demonstrated by Suzuki’s angiographic staging, suggests that ‘IC-EC conversion’ of the vascular supply is consistent with an intrinsic compensatory reorganization process of this entity. Therefore, the concept of revascularization surgery for moyamoya disease should be based on the idea to support the intrinsic compensatory nature of moyamoya disease rather than to eradicate the pathophysiology of this entity.

Surgical revascularization prevents cerebral ischemic attack by improving CBF in patients with moyamoya disease. Direct revascularization surgery such as STA-MCA anastomosis has been established as an effective procedure for patients with ischemic symptoms, providing long-term favorable outcomes. A series of 450 revascularization procedures for moyamoya disease, in which the direct revascularization technique was used in 95.1% of adults and 76.2% of pediatric patients, obtained a surgical morbidity rate of 3.5%, mortality rate of 0.7%, and cumulative 5-year risk of perioperative or subsequent stroke or death of 5.5%, indicating that revascularization surgery in patients with moyamoya disease carries low risk and is effective at preventing future ischemic events. In contrast to the promising effect of revascularization surgery for patients with ischemic onset, whether surgical revascularization has potential for preventing future re-bleeding in patients with hemorrhagic onset remains controversial. This issue remains to be elucidated in the currently on-going Japan Adult Moyamoya trial. In the present study, 150 direct revascularization procedures for patients with ischemic symptoms provided high cure/improvement rates of ischemic symptoms, with mortality rate of 0%. However, two patients developed intracranial hemorrhage on the operated hemisphere during the outpatient follow-up period, and one patient had significantly deteriorated activity of daily living due to thalamic hemorrhage. Therefore, surgical revascularization markedly ameliorates the risk of future ischemic stroke, but the effect for preventing hemorrhage remains to be clarified in a future study.

Revascularization surgery for moyamoya disease provides favorable long-term outcome, but involves some potential complications as summarized in Table 2. Symptomatic cerebral hyperperfusion after the direct revascularization technique is characterized by transient focal neurological deterioration mimicking ischemic symptoms. Such cerebral hyperperfusion is a cause of transient neurological deterioration during the acute stage after STA-MCA anastomosis for moyamoya disease. The incidence of temporary neurological deterioration due to hyperperfusion is 16.7% to 38.2%, if mild focal neurological signs are included. Furthermore, our most recent study using routine postoperative CBF measurement by 123I-IMP SPECT after STA-MCA (M4) anastomosis for moyamoya and nonmoyamoya disease patients showed that the incidence of symptomatic hyperperfusion was significantly higher in the moyamoya disease group.

### Table 2 Potential complications in the acute stage after superficial temporal artery (STA)-middle cerebral artery anastomosis with indirect pial synangiosis for moyamoya disease

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Procedure</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral ischemia</td>
<td>direct</td>
<td>anti-platelet agent hydration/antioxidant</td>
</tr>
<tr>
<td>thrombo-embolism</td>
<td>direct/indirect</td>
<td>anti-platelet agent surgical decompression/EMS revision</td>
</tr>
<tr>
<td>hemodynamic ischemia</td>
<td>direct/indirect</td>
<td>anti-platelet agent surgical decompression/EMS revision</td>
</tr>
<tr>
<td>watershed shift</td>
<td>direct</td>
<td>BP lowering/antioxidant</td>
</tr>
<tr>
<td>brain compression by EMS graft</td>
<td>indirect</td>
<td></td>
</tr>
<tr>
<td>HP</td>
<td>direct</td>
<td>BP lowering/antioxidant</td>
</tr>
<tr>
<td>focal HP with transient neurological deficit</td>
<td>direct</td>
<td></td>
</tr>
<tr>
<td>hemorrhage due to HP</td>
<td>indirect</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>indirect&gt;direct</td>
<td>hematoma evacuation</td>
</tr>
<tr>
<td>subdural hematoma</td>
<td>indirect</td>
<td>spine drainage/revision</td>
</tr>
<tr>
<td>CSF leakage</td>
<td>indirect/direct</td>
<td></td>
</tr>
</tbody>
</table>

(26/121 hemispheres, 21.5%) than in the non-moyamoya disease group (0/28, 0%). In the present study, the incidence of symptomatic hyperperfusion was as high as 18.0%, again indicating that symptomatic hyperperfusion should be recognized a possible complication of direct revascularization surgery for moyamoya disease.

The reason why moyamoya disease patients have higher risk for symptomatic cerebral hyperperfusion is undetermined. The intrinsic anatomical vulnerability of the pial artery structure, such as medial thinness and waviness and duplication of the internal elastic lamina, may lead to fragility of the peripheral arteries in the vascular territory of the STA-MCA bypass. Excessive production of reactive oxygen species during revascularization may also affect the vascular permeability, and thus result in transient neurological deterioration and/or hemorrhagic complications. Recent studies using dura mater, arachnoid membrane, and serum obtained from patients with moyamoya disease have demonstrated that the expression of vascular endothelial growth factor (VEGF) and matrix metalloproteinase (MMP)-9 were significantly increased in moyamoya patients, such increased expression of VEGF and MMP-9 in patients with moyamoya disease may contribute, at least in part, to the vulnerability to cerebral hyperperfusion.

The concepts of revascularization surgery for moyamoya disease include both microsurgical reconstruction by EC-IC bypass and consolidation for future arteriogenesis leading to EC-IC anastomosis by indirect pial synangiosis. The intrinsic pathology is important to understand such as anatomical fragility of the recipient artery and the presence of spontaneously developed transdural anastomosis during surgery. Direct/indirect revascularization surgery is a safe and effective treatment for moyamoya disease with ischemic symptoms, although the issue of bleeding/re-bleeding remains to be solved. Postoperative cerebral hyperperfusion and peri-operative infarction are potential complications of this procedure, so we recommend intensive postoperative care and CBF measurement in the acute stage, because the management of hyperperfusion is contradictory to that of ischemia.

References

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Address reprint requests to: Miki Fujimura, MD, PhD, Department of Neurosurgery, National Hospital Organization, Sendai Medical Center, 2–8–8 Miyagino, Miyagino-ku, Sendai 983–8520, Japan. e-mail: fujimur@nsg.med.tohoku.ac.jp