Effects of Extracranial–Intracranial Bypass for Patients With Hemorrhagic Moyamoya Disease
Results of the Japan Adult Moyamoya Trial

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Background and Purpose—About one half of those who develop adult-onset moyamoya disease experience intracranial hemorrhage. Despite the extremely high frequency of rebleeding attacks and poor prognosis, measures to prevent rebleeding have not been established. The purpose of this study is to determine whether extracranial–intracranial bypass can reduce incidence of rebleeding and improve patient prognosis.

Methods—This study was a multicentered, prospective, randomized, controlled trial conducted by 22 institutes in Japan. Adult patients with moyamoya disease who had experienced intracranial hemorrhage within the preceding year were given either conservative care or bilateral extracranial–intracranial direct bypass and were observed for 5 years. Primary and secondary end points were defined as all adverse events and rebleeding attacks, respectively.

Results—Eighty patients were enrolled (surgical, 42; nonsurgical, 38). Adverse events causing significant morbidity were observed in 6 patients in the surgical group (14.3%) and 13 patients in the nonsurgical group (34.2%). Kaplan–Meier survival analysis revealed significant differences between the 2 groups (3.2%/y versus 8.2%/y; P=0.048). The hazard ratio of the surgical group calculated by Cox regression analysis was 0.391 (95% confidence interval, 0.148–1.029). Rebleeding attacks were observed in 5 patients in the surgical group (11.9%) and 12 in the nonsurgical group (31.6%), significantly different in the Kaplan–Meier survival analysis (2.7%/y versus 7.6%/y; P=0.042). The hazard ratio of the surgical group was 0.355 (95% confidence interval, 0.125–1.009).

Conclusions—Although statistically marginal, Kaplan–Meier analysis revealed the significant difference between surgical and nonsurgical group, suggesting the preventive effect of direct bypass against rebleeding.

Clinical Trial Registration—URL: http://www.umin.ac.jp/ctr/index.htm. Unique identifier: C000000166.

See related article, p 1245.

Moyamoya disease is a unique cerebrovascular disease characterized by progressive occlusion of the bilateral internal carotid arteries at their terminal portions and unusual secondarily formed vascular networks (moyamoya vessels) that act as collateral pathways. Unlike pediatric patients, who usually present with transient ischemic attacks (TIAs) or cerebral infarction, about one half of adult patients have intracranial hemorrhage that seriously affects their prognosis. Long-term hemodynamic stress to the collateral vessels is thought to induce vascular pathologies leading to hemorrhage. Although the rate of recurrent bleeding is known to be extremely high, no therapeutic method of preventing rebleeding attacks has yet been established. Extracranial–intracranial bypass surgery is often used for ischemic moyamoya disease, and angiographic diminishment of moyamoya vessels can be observed after surgery, which is regarded as decreased hemodynamic stress to these vessels. A hypothesis has therefore emerged that bypass surgery can also reduce this stress, even in hemorrhagic moyamoya disease, and prevent rebleeding attacks. In fact, many cases of bypass surgery for hemorrhagic moyamoya disease have been reported, but all are retrospective studies and the benefit of bypass surgery has not yet been scientifically clarified. To resolve this, the Japan Adult Moyamoya (JAM) Trial was conducted in Japan.

Stroke is available at http://stroke.ahajournals.org

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planned in 1999. The study started in 2001, and follow-up of all enrolled patients was completed in 2013.

Methods

Patient Eligibility

This study is a multicentered, prospective, randomized, controlled trial to clarify the effect of bypass surgery on moyamoya disease with hemorrhagic onset. Twenty-two institutes with sufficient surgical experience with moyamoya disease participated in the study. The target was adult patients who had experienced episodes of intracranial bleeding within the preceding year and could be observed for 5 years after enrollment. The diagnosis of moyamoya disease was made according to the diagnostic guidelines proposed by the Ministry of Health and Welfare of Japan. Table 1 lists all the inclusion and exclusion criteria. The study office carefully checked the radiological data and determined eligibility for the trial in each case.

Table 1. Patient Eligibility for the JAM Trial

<table>
<thead>
<tr>
<th>Clinical requirements</th>
<th>Radiological requirements</th>
<th>Angiography</th>
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<tbody>
<tr>
<td>Age: between 16 and 65 years at the time of the initial bleeding episode</td>
<td>Lack of large infarction spread widely over the territory of a main arterial trunk</td>
<td>Angiographic findings should satisfy the diagnostic criteria of the spontaneous occlusion of the circle of Willis (moyamoya disease) published by the Ministry of Health, Labor, and Welfare of Japan:</td>
</tr>
<tr>
<td>Independent in daily life (modified Rankin disability scale score of 0–2)</td>
<td>Lack of contrast enhancement in the infarcted area</td>
<td>Occlusive lesions should exist in the terminal portion of the intracranial internal carotid artery or in the proximal portion of the anterior or middle cerebral arteries</td>
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<tr>
<td>Intracerebral hemorrhage, intraventricular hemorrhage, or subarachnoid hemorrhage occurring within the preceding 12 months</td>
<td></td>
<td>An abnormal vascular network in the region of basal ganglia and thalamus (moyamoya vessels) is demonstrated in the arterial phase of angiography</td>
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<tr>
<td>At least 1 month since the last stroke episode, either ischemic or hemorrhagic</td>
<td></td>
<td>These findings should be demonstrated on both sides</td>
</tr>
<tr>
<td>At least 1 month since the completion of acute phase treatment for hemorrhage and for related secondary pathophysiology (eg, hydrocephalus)</td>
<td>Exclusion criteria</td>
<td></td>
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<tr>
<td></td>
<td>Not independent in daily life (modified Rankin disability scale score of 3–5)</td>
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<td></td>
<td>Atherosclerotic carotid or cardiac arrhythmia that may cause thromboembolic complications</td>
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<td>Malignant tumors or organ failure of the heart, liver, kidney, or lung</td>
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<td>Unstable angina or myocardial infarction within the past 6 months</td>
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<td>Hematologic abnormality showing bleeding diathesis</td>
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<td>Uncontrolled diabetes mellitus showing a serum fasting blood glucose level &gt;300 mg/dL, or requires insulin</td>
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<td>Hypertension with a diastolic blood pressure of &gt;110 mm Hg</td>
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<td></td>
<td>Treated with extracranial–intracranial bypass surgery before enrollment</td>
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</table>

Sample Size

At the beginning of the study, the optimal sample size was calculated on the assumption that the incidence of adverse neurological events would be 8%/y in the nonsurgical group and 4%/y in the surgical group. The follow-up period was 5 years, and the sample size of 160 (80 patients per group) was expected to have 80% of the statistical validity required to detect a difference between the 2 groups with a significance level of 0.05. However, this number was reduced to 80 in January 2006 because the number of patients eligible for the study was revealed to be far smaller than expected. The number of new registration was 13.2/y at that time point, which meant that the completion of the study would be later than 2018. Then, the JAM Trial Executive and Steering Committee determined that the original sample size would be impossible to attain within the adequate study period. The calculation of 80% statistical power told us that the number of 80 patients would be able to detect the statistical significance if the event rate of the surgical group was <2.8%/y when that of the nonsurgical group was set to be 8%/y.

Randomization

According to computed tomography and digital subtraction angiography performed at the onset of intracranial hemorrhage, the study office estimated the bleeding point in each case as type A (bleeding from collateral vessels in the anterior circulation) or type B (bleeding from those in the posterior circulation). After informed consent was obtained, a computer-generated randomization scheme was applied, and the patient was assigned to receive either conservative medical care alone (nonsurgical group) or medical care plus extracranial–intracranial bypass (surgical group). To ensure a balance between these groups with respect to the bleeding point, a randomization scheme was performed separately within type A and type B (stratified randomization). This was required because the outcome could differ between hemorhages of the basal ganglia (type A) and those of the thalamus (type B), although such a difference had not been proven. To avoid inclusion bias and ensure the quality of the trial, all ineligible patients and patients who were eligible but did not participate in this study for whatever reason were reported and checked by the study office. Bypass surgery for these nonparticipants was prohibited unless a legitimate reason compelled it, such as frequent TIAs or progressive ischemic stroke.

Surgical Treatment

Extracranial–intracranial bypass, if assigned to the surgical group, was performed on both sides (each side at some interval within 3 months after enrollment) by a registered neurosurgeon at each institute. As the operative maneuver, a direct anastomotic procedure such as superficial temporal artery–middle cerebral artery anastomosis was required. Indirect bypass procedures can be added to direct bypass; however, indirect bypass alone was not permitted, nor was high-flow bypass such as venous graft or radial artery graft.

Patient Follow-Up

Table 2 shows the follow-up protocol. Each patient was observed for 5 years after enrollment by a pair of neurosurgeons and a neurologist in each participating institute. Postprocedure inpatient events were also handled by this pair. Blood pressure medication was given to patients with hypertension to control it. The use of anticoagulants or antiplatelet drugs was not allowed unless the patient was having significant cerebral ischemic attacks. The patients’ medical, neurological, radiological, and functional status was checked and reported every year. Both bleeding time and coagulation time were also monitored.

End Points

The following items constitute primary end points: (1) recurrent bleeding; (2) completed stroke causing significant morbidity; (3) significant morbidity or mortality from other medical cause; or (4) requirement for extracranial–intracranial bypass for a nonsurgical
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Patient because of progressive ischemic stroke or crescendo TIAs, as determined by a registered neurologist. Significant morbidity was defined as having a modified Rankin disability scale score of ≥3. The following items constitute a secondary end point: (1) recurrent bleeding occurring later than 3 months after enrollment or (2) related death or significant morbidity. This was because surgical operations were to be performed on each side at some interval within 3 months after enrollment. Asymptomatic bleeding incidentally detected by MRI in the routine follow-up examination was not regarded as an end point. All the adverse events were reported to the central office of the trial, and end points were finally adjudicated in the executive and steering committee consisted of neurologists and neurosurgeons who were not blinded to the allocation.

Statistical Analysis

All statistical analyses were executed by 2 statisticians in the statistical center of the trial (listed in the Appendix). Statistical analysis with a Kaplan–Meier survival analysis and a Cox proportional hazard model was used to compare the length of time without an adverse event for each group. The unpaired 2-group t test, χ² for independence test, and Fisher exact probability test were used to compare baseline characteristics of the 2 groups. All analyses were performed with IBM SPSS software, version 20 (IBM Software Group, Chicago, IL).

Ethical Considerations

All institutes participating in the JAM Trial received the approval of the committee of bioethics at each center. The JAM Trial was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR, ID: C000000166, 2005), which was approved by the International Committee of Medical Journal Editors.

Results

Randomization, Treatment, and Follow-Up

Figure 1 demonstrates the flow diagram of the JAM Trial. During the period of January 2001 to June 2008, 213 patients were assessed for eligibility. After 133 patients were excluded for the reasons listed in Figure 1, 80 patients were enrolled in the JAM Trial and randomized: 42 to the surgical group and 38 to the nonsurgical group. Table 3 summarizes the baseline characteristics of the patients.
In the surgical group, all patients but 1 underwent bilateral direct anastomotic bypass. One patient received direct bypass on one side and indirect bypass on the other side because no cortical artery feasible for direct anastomosis could be identified in the operative field. In the nonsurgical group, all patients were treated conservatively with no protocol violation. All patients but 1 were observed until the occurrence of adverse events compatible with end points or until 5 years had elapsed after enrollment. The murder of 1 patient in the surgical group at the point of 1.95 years after enrollment ended that patient’s follow-up. The event-free period of this case was included in the statistical analysis. However, this event was dealt with as a dropout and not as an end point because it had no relation to the patient’s medical issues. The mean follow-up period was 4.32 years (4.46 years in the surgical group and 4.17 in the nonsurgical group).

**Study Outcomes**

The last patient completed the 5-year follow-up in June 2013. Table 4 shows the outcomes of the patients. The primary end point was observed in 6 (14.3%) in the surgical group and 13 (34.2%) in the nonsurgical group. In the surgical group, 5 patients experienced rebleeding attacks and 1 patient had a completed ischemic stroke during the follow-up period. In the nonsurgical group, 12 patients experienced rebleeding attacks and 1 patient had crescendo TIAs requiring emergent bypass surgery as determined by the attendant neurologist. Accordingly, the secondary end point was observed in 5 (11.9%) in the surgical group and 12 (31.6%) in the nonsurgical group. Cox regression analysis revealed that the hazard ratios of the surgical group compared with the nonsurgical group were 0.391 (95% confidence interval, 0.148–1.029) as to the primary end point and 0.355 (95% confidence interval, 0.125–1.009) as to the secondary end point. Figure 2 shows the Kaplan–Meier cumulative curves for the analysis of the primary and secondary end points. The log-rank test revealed that the surgical group was at significantly lower risk than the nonsurgical group for both the primary end point (3.2%/y versus 8.2%/y; \( P = 0.048 \)) and the secondary end point (2.7%/y versus 7.6%/y; \( P = 0.042 \)).

**Perioperative Complications**

Among the 84 surgical procedures for the 42 patients in the surgical group, perioperative complications were observed in 8 cases (9.5%). Symptoms of local hyperperfusion around the anastomotic sites were the most frequent (3 cases). Other perioperative events consisted of TIA, seizure, local vaso-genic edema, scalp bedsore, and tear of a subcutaneous drain-age tube. Seven of the 8 events were clinically transient, and no sequelae remained. One patient with local hyperperfusion syndrome showed a deterioration in modified Rankin disability scale score. This event, however, was not severe enough to fulfill the criteria of the end point.

**Discussion**

It is known that about one half of the adult patients with moyamoya disease have intracranial hemorrhage, whereas most pediatric cases present with cerebral ischemia.1–3 Typically, the hemorrhage involves the thalamus and basal ganglia with

<table>
<thead>
<tr>
<th>Table 4. Details of Outcomes and Cox Regression Analysis</th>
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<tbody>
<tr>
<td><strong>Surgical Group (n=42)</strong></td>
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<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Primary end point</td>
</tr>
<tr>
<td>14.3</td>
</tr>
<tr>
<td>Recurrent bleeding</td>
</tr>
<tr>
<td>11.9</td>
</tr>
<tr>
<td>Completed stroke</td>
</tr>
<tr>
<td>2.4</td>
</tr>
<tr>
<td>Crescendo TIA (bypass required)</td>
</tr>
<tr>
<td>0.0</td>
</tr>
<tr>
<td>Secondary end point</td>
</tr>
<tr>
<td>recurrent bleeding or</td>
</tr>
<tr>
<td>related death/severe</td>
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<tr>
<td>11.9</td>
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</tbody>
</table>

CI indicates confidence interval; and TIA transient ischemic attack.
frequent perforation to the ventricles. It is speculated that long-term hemodynamic overstress can induce pathological change in the dilated collateral vessels such as lenticulostral arteries, choroidal arteries, and other basal moyamoya vessels, which leads to the bleeding.1,2 The rupture of microaneurysms formed in the collateral vessels has also been recognized.7 Such bleeding attacks, which are potentially fatal, seriously affect the patient’s prognosis.8

The natural history of hemorrhagic moyamoya disease is extremely poor because of the high rate of recurrent bleeding attacks. Kobayashi et al9 reported that 33.3% of the patients who were conservatively treated had rebleeding attacks during the follow-up period of mean 6.7 years and estimated the annual rebleeding rate to be 7.09%/y. Because the majority of the patients were in their 30s to 50s at the onset of hemorrhage,3,10 this annual rate indicates that, over a long period, rebleeding attacks seriously threaten their lives. No therapeutic method for preventing rebleeding attacks, however, has been established. No evidence exists that treatment of hypertension reduces the rebleeding rate. Even the relationship between hypertension and intracranial hemorrhage in moyamoya disease has not been proven.

At present, the only promising strategy is extracranial–intracranial bypass. In ischemic moyamoya disease, angiography often demonstrates that moyamoya vessels can diminish after bypass surgery.4 It is likely that the dominant bypass flow reduces the burden on moyamoya vessels to maintain the cerebral blood flow, which results in relief of hemodynamic stress. Microaneurysms in collateral vessels that disappear after surgery have also been reported.11,12 Consequently, a hypothesis has emerged that bypass surgery can also reduce the long-term hemodynamic stress in hemorrhagic moyamoya disease and prevent rebleeding attacks. In fact, some authors have reported the effectiveness of bypass for hemorrhagic moyamoya disease. Kawaguchi et al13 revealed that superficial temporal artery–middle cerebral artery bypass reduced the rate of hemorrhagic and ischemic stroke. Karasawa et al14 reported that patients who had undergone bypass surgery experienced rebleeding attacks less frequently than those treated conservatively. Several authors, on the contrary, failed to reveal the effectiveness of bypass.8,15 A multicenter retrospective questionnaire study conducted by Fujii et al15 revealed that rebleeding attacks were less frequent in patients who had undergone bypass surgery than in the nonsurgical cases, but the difference was not statistically significant. All previous reports, however, were retrospective studies that potentially contain various biases. Consequently, the effectiveness of bypass surgery on hemorrhagic moyamoya disease has remained unclear.

The JAM Trial, which is the first prospective, randomized, controlled trial focused on moyamoya disease, has demonstrated how bypass surgery affects patients’ prognosis and the rebleeding rate in hemorrhagic moyamoya disease. Kaplan–Meier survival analysis revealed that direct bypass surgery significantly decreased the rate of both all adverse events (primary end point) and rebleeding attacks (secondary end point) during the following 5 years. These results strongly suggest that the newly established bypass flow can influence the hemodynamic state of the collateral vessels and lessen their overstress. This study required direct anastomotic bypass because indirect bypass alone can fail to establish sufficient extracranial–intracranial collateral flow in adult patients.14 To ensure the quality of the trial, every institute was requested to report all patients who were assessed for eligibility but were not enrolled in the study, and bypass surgery for these cases was prohibited. In addition, no protocol violation was observed regarding the enrolled patients.

Care must be taken when interpreting the results of the JAM Trial. First, the result was statistically marginal. Kaplan–Meier survival analysis revealed the significant benefits of bypass surgery, but the \( P \) values of the primary and secondary
end points were 0.048 and 0.042, respectively, which are close to 0.05. In the Cox regression analysis, the upper limit of the 95% confidence interval of the hazard ratio was 1.029 for the primary end point and 1.009 for the secondary end point, both of which slightly exceed 1.0. Therefore, the authors cannot declare with assurance that bypass surgery is absolutely superior to conservative therapy. This difference can be attributed to the small sample size. As mentioned earlier, the optimal sample size initially calculated was larger. Hemorrhagic moyamoya disease, however, is not common, and recruitment of patients with good modified Rankin disability scale scores was far more difficult than expected. Considering that an excessively long registration period would degrade the quality of this trial, the number of the cases was reduced.

Second, some limitations apply to the JAM Trial regarding generalization. All institutes participating in the trial had sufficient experience with direct bypass surgery for moyamoya disease, and only registered surgeons were allowed to operate on patients. Consequently, the rate of perioperative complications, including transient events, turned out to be 9.5%, and permanent severe disability was not observed. The authors think that ensuring the quality of surgeons is indispensable to this kind of randomized trial involving surgery. As for interpretation of the results, however, it should be emphasized that the results do not necessarily apply to all neurosurgical institutes.

Third, and perhaps most important, the JAM Trial has only revealed the effect of bypass surgery within 5 years and does not suggest an improved prognosis for the surgical group thereafter. It is well known that recurrent bleeding can take place >10 years after the initial attack.9 Therefore, patients enrolled in the JAM Trial should be observed for longer periods in the future. The JAM Trial Executive and Steering Committee has already decided to continue with patient follow-up and report the 10-year results. Subanalyses regarding the site of initial and recurrent hemorrhage, hemodynamic impairment evaluated by single-photon emission computed tomography, and angiographic reduction of moyamoya vessels after bypass surgery should also be performed, and the results should be reported.

Conclusions
Although statistically marginal, the JAM Trial revealed that direct bypass surgery for adult patients with hemorrhagic moyamoya disease reduces the rebleeding rate and improves a patient’s prognosis during the 5 years after enrollment. To determine the long-term benefits of surgery, further follow-up is required.

Appendix: Study Organization
The Research Committee on Moyamoya Disease of the Japanese Ministry of Health, Labour and Welfare

Principal Investigator and Chair
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2005 to 2013: Nobuo Hashimoto, MD, PhD

JAM Trial Group

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Randomization and Quality Control Center
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Disclosures
None.

References
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