Study Design for a Prospective Randomized Trial of Extracranial-Intracranial Bypass Surgery for Adults With Moyamoya Disease and Hemorrhagic Onset

—The Japan Adult Moyamoya Trial Group—

Abstract

This article summarizes the study design and organization of a multicenter, prospective randomized trial of extracranial-intracranial (EC-IC) bypass for treating adult patients with moyamoya disease who suffered episodes of intracranial bleeding. The Japan Adult Moyamoya Trial will determine whether the combination of EC-IC bypass with risk factor modifications affects the prognosis and the incidence of recurrent bleeding attacks. Direct bypass such as superficial temporal artery-middle cerebral artery anastomosis is essential and indirect bypass procedures alone such as encephalo-duro-arterio-synangiosis or encephalo-myo-synangiosis are not dealt with in this trial. Power calculations are based on an assumption of \(\alpha = 0.05\) with an annual event rate of 8% significant morbidity and mortality per year in the non-surgical group and 4% in the surgical group. The study has an 80% rate of accuracy for detection of a 20% difference between the two groups in events in a 5-year follow up.

Introduction

Moyamoya disease shows progressive occlusive lesions in the circle of Willis associated with the development of abnormally dilated moyamoya vessels in the region of the basal ganglia and thalamus, which act as collateral pathways to the cerebral cortex. Although most children with moyamoya disease suffer cerebral ischemia, approximately half of the adult patients show hemorrhagic episodes such as periventricular hemorrhage with intraventricular extension.

It is speculated that chronic hemodynamic over-stress might induce vascular wall pathologies such as pseudoaneurysm or vessel fragility, which lead to hemorrhagic events. Extracranial-intracranial (EC-IC) bypass surgery has been performed not only on the patients with ischemic episodes but also on those with cerebral hemorrhage with moyamoya disease under the hypothesis that bypass surgeries reduce the hemodynamic stress on the moyamoya vessels and prevent recurrent bleeding. However, the effect of these treatments has not yet been statistically and scientifically clarified, and the treatment guidelines for adult moyamoya disease with hemorrhagic onset are still controversial. To resolve these issues, the Japan Adult Moyamoya (JAM) Trial was designed.

Objectives

The primary objective is to determine whether the combination of EC-IC bypass with risk factor modifications affects the prognosis and the incidence of recurrent bleeding attacks. The secondary objectives are to determine surgical success in bypass formation and the incidence of recurrent bleeding attacks after the bypass surgery, to clarify the rate of recurrent bleeding attacks in the non-surgically treated group, and to determine the incidence of all other cerebrovascular strokes and death in the follow-up years.

Study Design

Patient eligibility and randomization

The inclusion and exclusion criteria are summarized in Table 1. Patients must fulfill all the clinical and radiological requirements. In addition, single photon emission computed tomography using N-isopropyl-4-[123I]iodoamphetamine is required. Quantitative measurement of cerebral blood flow in the resting state and after acetazolamide loading must be performed. All ineligible patients and all eligible but not randomized patients, including all patients treated by EC-IC bypass outside the trial for whatever reason at any participating center, are entered in the nonrandomized data base.

After informed consent is obtained, a computer-generated randomization scheme is applied and the patient is assigned to receive either the best medical care to modify risk factors or the best medical care plus EC-IC bypass.

Table 1 Patient eligibility

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<tr>
<th>Requirement</th>
<th>Description</th>
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<td>1. Clinical requirements</td>
<td>(1) Age: between 18 and 60 years at the time of the initial bleeding episode (2) Independent in daily life (modified Rankin disability scale 0–2) (3) Intracerebral hemorrhage, intraventricular hemorrhage, or subarachnoid hemorrhage within the preceding 12 months (4) At least one month has passed after the last stroke episode, either ischemic or hemorrhagic (5) At least one month has passed after the completion of acute phase treatment for the hemorrhage and for the related secondary pathophysiology (e.g. hydrocephalus)</td>
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<td>2. Radiological requirements</td>
<td>(1) Computed tomography/magnetic resonance imaging (a) Absence of extensive infarction spreading widely over the territory of a main arterial trunk (b) Absence of contrast enhancement in the infarcted area (2) Angiography (a) Occlusive lesions are present in the terminal portion of the intracranial internal carotid artery, or in the proximal portion of the anterior or middle cerebral arteries (b) Abnormal vascular network demonstrated in the region of basal ganglia and thalamus (moyamoya vessels) in the arterial phase (c) These findings are present bilaterally</td>
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<tr>
<td>3. Exclusion criteria</td>
<td>(1) Not independent in daily life (modified Rankin disability 3–5) (2) Atheroembolic cerebral disease, or cardiac arrhythmia which may cause thromboembolic complications (3) Malignant tumors or organ failure of the heart, liver, kidney, or lung (4) Unstable angina or myocardial infarction within the past 6 months (5) Hematological abnormality showing bleeding diathesis (6) Uncontrolled diabetes with a serum fasting blood glucose level of more than 300 mg/dl, or requiring insulin (7) Hypertension with a diastolic blood pressure of more than 110 mmHg (8) Treated by extracranial-intracranial bypass surgery before enrollment (9) Pregnancy</td>
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Correspondence to: Susumu Miyamoto, M.D., project director of Japan Adult Moyamoya Trial group, Department of Neurosurgery, National Cardiovascular Center, 5–7–1 Fujishirodai, Suita, Osaka 565–8565, Japan. Tel: +81–6–6833–5012, Fax: +81–6–6872–7486, e-mail: miy@hsp.ncvc.go.jp
Treatments and follow up

EC-IC bypass, if assigned, should be performed on both sides (unilateral procedures with an interval). Direct bypass procedures such as superficial temporal artery-middle cerebral artery anastomosis are essential. The surgeon can add an indirect bypass procedure with the direct bypass. However, only indirect bypass or high flow bypass graft such as venous graft or radial artery graft is not allowed.

The follow-up protocol is shown in Table 2. All patients, either surgical or medical, will be followed up for more than 5 years after enrollment, and their medical, neurological, and functional status reported.

Outcome events

The following items constitute the primary end point after enrollment: recurrent bleeding; complete stroke causing significant morbidity in daily life; significant morbidity or mortality from other causes; or additional performance of EC-IC bypass as decided by the participating neurologist in, for example, patients with progressive stroke or crescendo transient ischemic attack. The following items constitute the secondary end point in the prevention of recurrent bleeding which occurs 3 months after enrollment: recurrent bleeding on the same side as the previous bleeding; or related death or severe disability (modified Rankin disability scale 3–5). This is required because the operations are performed unilaterally at an interval by 3 months after enrollment.

Sample size and statistical analysis

The necessary sample size was calculated assuming that the incidence of end point events would be 8% per year in the non-surgically treated patients and 4% in the surgically treated patients. As the patients will be followed up for at least 5 years, a sample size of 80 patients per group has 80% accuracy to detect a difference of 20% in the 5-year accumulated event rates between the two groups with a significance level of 0.05. The primary analysis compared the length of time without treatment failure between the two groups using Kaplan-Meier survival analysis and Cox proportional hazard models.

Appendix: Study Organization

The Research Committee on Moyamoya Disease of the Japanese Ministry of Health, Labor and Welfare

Principal Investigator and Chair: Takashi Yoshimoto, M.D., Department of Neurosurgery, Tohoku University Graduate School of Medicine, Sendai, Miyagi

The Central Office of the Research Committee: Department of Neurosurgery, Tohoku University Graduate School of Medicine, Sendai, Miyagi; Takashi Yoshimoto, M.D. (Principal Investigator); Reizo Shirane, M.D. (Co-Principal Investigator); Yoshiko Yoshida, M.D. (Co-Principal Investigator)

Japan Adult Moyamoya (JAM) Trial Group

The Central Office and Data Management Center: Department of Neurosurgery, National Cardiovascular Center, Suita, Osaka; Susumu Miyamoto, M.D. (Principal Investigator); Jun C. Takahashi, M.D. (Co-Principal Investigator)

The Statistical Center: Department of Public Health, Tohoku University Graduate School of Medicine, Sendai, Miyagi; Ichiro Tsuji, M.D. (Principal Investigator)

The Randomization and Quality Control Center: Department of Clinical Epidemiology, Kyoto University Graduate School of Medicine, Kyoto; Tsuguya Fukui, M.D. (Principal Investigator)

Executive and Steering Committee: Takashi Yoshimoto, M.D. (Principal Investigator); Susumu Miyamoto, M.D. (Project Director and Co-Principal Investigator, Surgery); Yasushi Okada, M.D. (Co-Project Director and Co-Principal Investigator, Neurology); Tsuguya Fukui, M.D. (Co-Principal Investigator, Epidemiological); Ichiro Tsuji, M.D. (Co-Principal Investigator, Statistical); Yasuo Fukuuchi, M.D. (Co-Principal Investigator, Neurology); Takashi Ohmoto, M.D. (Co-Principal Investigator, Surgery); Yasuo Kuwabara, M.D. (Co-Principal Investigator, Radiology); Iyooi Nakagawara, M.D. (Co-Principal Investigator, Surgery); Izumi Nagata, M.D. (Co-Principal Investigator, Surgery)

Participating Centers: Chiba University Graduate School of Medicine, Chiba; Chugoku Rouai Hospital, Kure, Hiroshima; Gifu University Hospital, Gifu; Gunma University, Maebashi, Gunma; Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido; Iwate Medical University, Morioka, Iwate; Kita-Saito University, Sagamihara, Kanagawa; Kurashiki Central Hospital, Kurashiki, Okayama; Kyoto University Graduate School of Medicine, Kyoto; Nagaoka Chuo General Hospital, Nagaoka, Niigata; Nagasaki University, Nagasaki; Nagoya City University Medical School, Nagoya, Aichi; Nagoya Daini Red Cross Hospital, Nagoya, Aichi; Nakamura Memorial Hospital, Sapporo, Hokkaido; Nara Medical University, Kashiwara, Nara; National Cardiovascular Center, Suita, Osaka; National Kyushu Medical Center, Fukuoka; Research Institute for Brain and Blood Vessels-Akita, Akita; Sapporo Medical University, Sapporo, Hokkaido; Tenri Hospital, Tenri, Nara; Tokushima University Graduate School of Medicine, Sendai, Miyagi; Tokushima University, Tokushima; Tokyo Women’s Medical University, Tokyo

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