Comparison of Effects between Clopidogrel and Cilostazol on Cerebral Perfusion in Nonsurgical Adult Patients with Symptomatically Ischemic Moyamoya Disease: Subanalysis of a Prospective Cohort

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Background and purpose: Adult patients with symptomatically ischemic moyamoya disease (MMD) initially undergo medical treatment alone including antiplatelet drugs when symptomatic cerebral hemispheres do not exhibit hemodynamic compromise. The purpose of the present study subanalyzing the same patient cohort used in a previous study was to determine which antiplatelet drug, clopidogrel or cilostazol, provides better improvement of cerebral perfusion in such patients. *Methods:* All patients without cerebral misery perfusion on ^{15}O gas positron emission tomography (PET) did not undergo revascularization surgery and were treated with medication alone, including antiplatelet therapy. Patients ≥50 years and <50 years initially received clopidogrel and cilostazol, respectively. When a patient suffered side effects of an antiplatelet drug, they were switched to the other antiplatelet drug. Cerebral blood flow (CBF) in the symptomatic hemisphere was measured at inclusion and at 2 years after inclusion using ^{15}O gas PET. *Results:* Of 68 patients, 31 and 38 were treated with clopidogrel and cilostazol, respectively, for 2 years after inclusion. For patients treated with clopidogrel, CBF did not differ between first and second PET. For patients treated with cilostazol, CBF was significantly greater in the second PET than in the first PET. On multivariate analysis, cilostazol administration was an independent predictor of CBF improvement in the symptomatic hemisphere (95% confidence interval, 1.34-139.20; P =.0271). *Conclusions:* Cilostazol improves cerebral perfusion better than clopidogrel in adult patients with symptomatically ischemic MMD not accompanied by misery perfusion.

Key Words: Moyamoya disease—adult—hemodynamic compromise—antiplatelet drug

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Introduction

Moyamoya disease (MMD) is a chronic, occlusive cerebrovascular disease of unknown etiology characterized by bilateral steno-occlusive changes in the terminal portion of the internal carotid artery (ICA) and an abnormal vascular network at the base of the brain.[1,2] Revascularization surgery is generally employed as the standard surgical treatment for MMD with the onset of ischemic symptoms.[3] This procedure prevents further cerebral ischemic attacks.[4,5] In particular, for pediatric MMD with ischemic symptoms, revascularization surgery is universally recommended, regardless of the severity of MMD, because the juvenile brain is still developing.[6-8] In contrast, although several investigators have recommended selective revascularization surgery for adult patients with ischemic presentation and hemodynamic compromise,[9,10] no clear guidelines for this selection are available.

We previously conducted a prospective evaluation of 70 adult patients showing symptomatically ischemic MMD without cerebral misery perfusion on positron emission tomography (PET) and conducted follow-up with medication alone including an antiplatelet drug for 2 years.[11] The incidence of recurrent ischemic events was 3% per 2 years and in patients without recurrent ischemic events, cerebral blood flow (CBF) in the affected cerebral hemisphere was significantly increased at 2 years after inclusion compared to at inclusion.[11] Those findings suggest that patients without misery perfusion should initially receive medical treatment alone and undergo revascularization surgery if ischemic symptoms recur.[11] While all patients included in that study received either clopidogrel or cilostazol, which antiplatelet drug is more effective for adult patients with symptomatically ischemic MMD has remained unclear.

Clopidogrel is a thienopyridine derivative and blocks activation of platelets by adenosine diphosphate by selectively and irreversibly inhibiting the binding of this agonist to its receptor on platelets, thereby affecting adenosine diphosphate-dependent activation of the GpIIb-IIIa complex, the major receptor for fibrinogen present on the platelet surface.[12,13] In contrast, cilostazol is a phosphodiesterase III inhibitor that has not only antiplatelet effects, but also antioxidative and vasodilation effects through increasing intracellular cyclic adenosine monophosphate and endothelial nitric oxide synthase activity.[14]

The purpose of the present study was thus to subanalyze the same patient cohort used in our previous study[11] and to determine which antiplatelet drug, clopidogrel or cilostazol, results in better improvement of cerebral perfusion in adult patients with symptomatically ischemic MMD.

Methods

Study Design

The present study was designed as a prospective, observational study. This protocol was reviewed and approved by the institutional ethics committee. Written, informed consent was obtained from patients or their next of kin prior to participation.

Patients

Seventy-one consecutive patients who visited from May 2008 to September 2015 and met the following inclusion criteria were prospectively entered into the present study[11]: (1) presence of MMD according to the diagnostic criteria of the Research Committee on Spontaneous Occlusion of the Circle of Willis of the Ministry of Health, Labor, and Welfare, Japan; (2) age >30 but <60 years; (3) modified Rankin disability scale score 0 or 1; (4) presence of episodes of carotid territory ischemic symptoms that had occurred ≤3 months before presentation to our department; (5) absence of major cerebral infarction on magnetic resonance imaging; and (6) absence of misery perfusion in the symptomatic cerebral hemispheres on brain ^{15}O gas PET according to the methods described below (see "***Brain ^{15}O Gas PET Study and Definition of Misery Perfusion***" section).

Patients who received anticoagulants at inclusion or during the 2-year follow-up period were excluded from the present study. Patients with further ischemic symptoms during the 2-year follow-up period were also excluded.

Management and Follow-up

No patients underwent revascularization surgery and all received antiplatelet therapy such as clopidogrel or cilostazol. Clinicians intentionally administered clopidogrel at 75 mg/day for patients ≥50 years old and cilostazol at 200 mg/day for patients <50 years old. When a patient suffered side effects of an antiplatelet drug, the clinician changed the pharmacotherapy to the other antiplatelet drug (i.e., changed clopidogrel to cilostazol, or changed cilostazol to clopidogrel).

Patients visited our outpatient clinic at 8-week intervals after inclusion.[11] At these visits, clinicians checked clinical conditions, including blood pressure and blood biochemistry.[11] Based on these data, each patient received medical treatments. Attempts were made to keep systolic blood pressure below 140 mmHg, hemoglobin A1c below 6.5%, and low-density lipoprotein cholesterol below 140 mg/dL. Efforts were also made to keep each patient from smoking.

Brain ^{15}O Gas PET Study and Definition of Misery Perfusion

PET studies were performed using a SET-3000GCT/M scanner (PET/CT; Shimadzu, Kyoto, Japan) for all patients.[11] These studies were performed between 3 weeks and 3 months after the last ischemic event.[11] CBF was determined while the subject continuously