Cilostazol May Decrease Plasma Inflammatory Biomarkers in Patients with Recent Small Subcortical Infarcts: A Pilot Study

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Background: The mechanism of progressive neurological deficit in patients with recent small subcortical infarcts has not yet been clarified. Inflammatory biomarkers and the use of cilostazol may be associated with this phenomenon. *Methods:* Between May 2013 and April 2014, we evaluated consecutive first-ever patients with stroke due to recent small subcortical infarcts within 48 hours of onset. We divided patients into 2 groups according to the use of antiplatelet agents (cilostazol with or without aspirin versus aspirin alone). Plasma biomarkers such as matrix metalloproteinase-9, interleukin-6, high sensitive C-reactive protein, and amyloid β precursor protein (APP770, indicating endothelial dysfunction) were measured twice: (1) within 24 hours; and (2) 1 week after their admission. Multivariable logistic regression analyses were performed to identify the variables independently associated with progressive neurological deficit and poor functional outcome. *Results:* We analyzed 41 patients (male: 63.4%, mean age: 70.8 years). Most of the patients (90%) who were treated with cilostazol were concomitantly treated with aspirin. Matrix metalloproteinase-9 and high sensitive C-reactive protein were higher in patients with progressive neurological deficit compared with those without. APP770 were more likely to be decreased in cilostazol group compared with aspirin group. Multivariable analyses show that traditional risk factors such as age and National Institutes of Health Stroke Scale scores were independently associated with both progressive neurological deficit and poor functional outcome. *Conclusions:* Inflammatory biomarkers may be associated with progressive neurological deficit. Early initiation of cilostazol may decrease the levels of plasma biomarkers.
Key Words: Biomarkers—cilostazol—lacunar infarction—progression—small-vessel diseases—stroke outcomes.

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Introduction

Currently, cerebral small-vessel diseases (SVD) are focused on as risk factors for both stroke and cognitive decline.[1-3] An early blood–brain barrier breakdown and dysfunction are considered as causes of cerebral SVD.[4-6] Previously, we have revealed that increased pulse wave velocity (PWV) in patients with recent small subcortical infarcts (RSSI, formerly defined as acute lacunar infarcts) is a risk factor of both progressive neurological deficit (PND)[7] and recurrent ischemic stroke.[8] PND is a state of neurological worsening during a few days after the onset of stroke, which could lead to poor stroke outcome.[7,9] Increased PWV physiologically indicates microvascular dysfunction and PND in patients with RSSI, however, biochemical mechanisms have not yet been clarified.

Several studies suggests that PND may be preventive by using cilostazol, a selective inhibitor of phosphodiesterase 3 in accordance with antiplatelet and anti-inflammatory effect, in patients with noncardioembolic stroke,[10,11] and in particular in those with RSSI.[12,13] Inflammatory biomarkers play an important role regarding endothelial dysfunction in these patients.[14,15] Furthermore, some kind of amyloid β precursor protein, APP770, a novel plasma biomarker which suggests endothelial dysfunction and cognitive decline, has been recently established.[16] Assessing these biomarkers may contribute to clarify the mechanisms of PND and the protective effect of cilostazol in patients with RSSI.

In this pilot study, we aimed to clarify the mechanism of PND and protective effects of cilostazol by assessing plasma inflammatory biomarkers obtained during the acute phase of ischemic stroke in patients with RSSI. We hypothesized that patients treated with cilostazol would have lower levels of inflammatory biomarkers and lower risk of PND compared with patients treated with aspirin alone.

Methods

Study Design

Between May 2013 and April 2014, we enrolled consecutive first-ever patients with stroke with recent small subcortical infarcts (RSSI; formerly categorized as acute lacunar infarcts) who were admitted to Kawasaki Medical School Hospital within 48 hours of onset. We excluded patients having a history of either stroke or acute coronary syndrome, prescribing cilostazol before their admission because these histories could affect the values of biomarkers. This single-center observational study complied with the Declaration of Helsinki and was approved by the Institutional Review Board at the Kawasaki Medical School Hospital. Informed consent was obtained from all patients.

Treatment

Patients were treated according to the Japanese Guidelines for the Management of Stroke.[17] Because aspirin (160-300 mg daily) and cilostazol (200 mg daily) were clinically available as antiplatelet agents for patients who developed noncardioembolic acute ischemic stroke during this study period, patient eligibility for acute-phase therapy and choice of antiplatelets were determined by each physician according to these guidelines.

Baseline Assessment

We assessed age, sex, blood pressure, and known vascular risk factors such as hypertension, dyslipidemia, diabetes mellitus, chronic kidney disease, smoking habit, and alcohol consumption. We measured brachial-ankle PWV as an indicator of arteriosclerosis and endothelial dysfunction.[8,18] We divided patients into 2 groups according to the use of antiplatelet agents (cilostazol with or without aspirin versus aspirin alone). We defined stroke subtypes according to the Trial of Org 10172 in Acute Stroke Treatment criteria[19] and the STandards for ReportIng Vascular changes on nEuroimaging recommendations.[1] Stroke neurologists assessed the National Institutes of Health Stroke Scale (NIHSS) scores on admission (day 1), day 2, 3, 7, and at discharge. Progressive neurological deficit was defined as an increase of greater than or equal to 2 points in the NIHSS score during the 3 days after stroke onset.[7] The modified Rankin Scale (mRS) scores at discharge were assessed. We defined mRS scores of 0-2 as a good outcome and scores of 3-5 as a poor outcome.[20] Detailed information is provided in the Supplementary Material.

Magnetic Resonance Imaging

Patients underwent a 1.5T magnetic resonance imaging (MRI) of the brain (Signa EXCITE XL ver. 11.0: GE Healthcare, Milwaukee, WI), including diffusion-weighted imaging, fluid-attenuated inversion recovery (FLAIR) imaging, T2*-weighted gradient echo imaging, and 3D time-of-flight magnetic resonance angiography. RSSI was defined as infarcts of less than 15 mm in diameter as detected using diffusion-weighted imaging scans on admission.[1] Silent lacunar infarcts were defined as a focal lesion of greater than or equal to 3 mm in diameter, with hyperintensity on T2 weighted image and hypointensity on FLAIR images. White matter hyperintensities were defined as an irregular periventricular hyperintensity (Fazekas grade ≥3) and early confluent or confluent separate deep white matter hyperintense lesions (Fazekas grade ≥2) on T2 weighted image and FLAIR images. Cerebral microbleeds were defined as a focal area of signal loss in the brain parenchyma of size less than 5 mm on T2* scans.