Effects With and Without Clopidogrel Loading Treatment for Acute Ischemic Cerebrovascular Disease Patients: A Retrospective Cohort Study

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Objectives: We investigated the effectiveness of clopidogrel loading (CL) treatment compared with usual clopidogrel non-loading (NL) treatment for acute ischemic cerebrovascular disease. *Methods:* We screened consecutive 1072 patients with ischemic cerebrovascular disease within 48 hours of symptom onset admitted to our hospital. Eligible patients were divided into the CL group (300 mg on day 1, followed by 50-75 mg once daily) and NL group (50-75 mg once daily). The incidence proportion of neurologic deterioration during hospitalization was compared between the 2 groups using logistic regression analysis. *Results:* A total of 224 patients, 39 in CL group and 185 in NL group, were enrolled. The frequency of neurologic deterioration did not significantly differ between the 2 groups (risk ratio [95% confidence interval]: 1.47 [.88-2.46]). On the preset subgroup analysis according to stroke subtype, the frequency of neurologic deterioration in CL group was significantly higher in branch atheromatous disease (risk ratio: 2.44 [1.67-3.55]) and was not different statistically in transient ischemic attack (risk ratio: 0). The analysis adjusted by several confounders showed that the incidence proportion of neurologic deterioration was not significantly different in large artery atherosclerosis (adjusted odds ratio: 1.06 [.23-4.84]) as crude analysis. The incidence proportion of adverse events was not significantly different between the 2 groups. *Conclusions:* The effect of CL therapy differed by stroke subtypes in preventing neurologic deterioration. CL therapy appeared to be ineffective in branch atheromatous disease. Therefore, the choice of CL therapy should carefully be made according to stroke subtypes. **Key Words:** Acute stroke—clopidogrel—loading—antiplatelet—neurologic deterioration.

Introduction

Clopidogrel is considered to be effective for ischemic cerebrovascular disorder prevention. In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events trial for patients with previous manifestations of atherosclerotic disease, long-term administration of 75 mg clopidogrel daily was superior to 325 mg aspirin daily in reducing the risk of ischemic stroke, myocardial infarction, or vascular death, and the safety profile of clopidogrel was at least as good as that of aspirin.[1] Based on this trial, it is recommended that patients receive clopidogrel monotherapy as well as aspirin for secondary stroke and transient ischemic attack (TIA) prevention in the current treatment guidelines for ischemic stroke and TIA of the European Stroke Organization[2] and the American Heart Association/American

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Stroke Association.[3] On the other hand, the Japanese Guidelines for the Management of Stroke 2015 recommend a daily dose of 160- 300 mg aspirin for stroke recurrence prevention in the acute phase (within 48 hours from onset) and clopidogrel monotherapy in the chronic phase.[4]

Quoted as the "aspirin dilemma," aspirin negates the antithrombotic effect in blood concentration-dependent manner[5] and also causes adverse effects such as gastrointestinal bleeding.[6] On the other hand, clopidogrel is expected to play an important role as an acute treatment for ischemic cerebrovascular disease, as the superiority of clopidogrel over aspirin has been elucidated with respect to antiplatelet activity as well as to anti-inflammatory effect.[7,8]

As experienced in clinical settings, there are some cases that suffer from the worsening of stroke symptoms in the acute to subacute phase. Such neurologic deterioration cases account for 13%-40% of all acute or subacute strokes,[9-16] and most of those worsening occur within first 48-72 hours of onset.[9] Therefore, strong antiplatelet treatment in earlier stage may be more effective to prevent neurologic deterioration.

Although several studies support the effectiveness of clopidogrel loading (CL) treatment in acute coronary syndrome requiring percutaneous coronary intervention,[17-19] it is not sufficiently verified in cases of cerebrovascular disease.

The aims of our study were to investigate the effectiveness and safety of CL treatment (300 mg on day 1, followed by 75 mg or 50 mg quaque die) compared with usual clopidogrel non-loading (NL) treatment (75 mg or 50 mg quaque die) for patients of acute ischemic cerebrovascular disease in our clinical setting. As a dosage regimen, clopidogrel 75 mg daily is usually recommended, sometimes 50 mg daily depending on age, body weight, and general condition on prescribing information of clopidogrel in Japan.

Methods

Ethics Statement

All procedures in this study were approved by the ethical committee of the Research Institute for Brain and Blood Vessels–Akita. All patients consented with a written document.

Study Participants

By our inclusion and exclusion criteria as described below, we consecutively screened acute ischemic cerebrovascular disease patients within first 48 hours of symptom onset admitted to our hospital between January 2009 and December 2012. Eligible patients were those who met the following inclusion criteria: (1) age of 20 years or older, (2) diagnosis of acute ischemic stroke or TIA, and (3) clopidogrel treatment taken within 24 hours after admission. The exclusion criteria were (1) diagnosis of cardioembolism, (2) treatment with intravenous recombinant tissue plasminogen activator or intra-arterial urokinase thrombolysis, (3) clopidogrel dose of less than 50 mg daily, and (4) discharge within 48 hours after admission. Enrolled patients were divided into 2 groups based on the treatment received, namely CL group and NL group.

Procedure

Neurologists or neurosurgeons assessed the neurologic severity of the patients, using the National Institutes of Health Stroke Scale (NIHSS)[20] on admission and discharge, as well as at the time of symptom exacerbation if any. The patients were carefully monitored for any clinical changes by trained staff during hospitalization. Upon hospital admission, all patients were diagnosed by brain imaging with either magnetic resonance imaging (MRI) or computed tomography, as well as an electrocardiogram, and had in principle another brain imaging around 7 days after admission. Stenotic lesions in main arteries were assessed by the findings of magnetic resonance angiography, three-dimensional computed tomographic angiography, and carotid ultrasonography by neuroradiologists, neurologists, or neurosurgeons. All patients were then classified into cardioembolism, large artery atherosclerosis (LAA), small vessel occlusion (SVO), stroke of other determined etiology, or stroke of undetermined etiology (negative evaluation/2 or more causes identified/incomplete evaluation) basically according to the Trial of Org 10712 in Acute Stroke Treatment (TOAST) subtype classification system[21] or TIA. Intracerebral lesions with a diameter of 15 mm or more and lesions extending to the surface of the pontine base were defined as branch atheromatous disease (BAD),[22,23] which is classified as negative evaluation.

At baseline, all patients have had their clinical and medication history taken and their general condition for vascular risk factors had been examined. The severity of stenosis of corresponding artery based on the magnetic resonance angiography findings was classified into no steno-occlusion, moderate (less than 90% stenosis), severe (90%-99% stenosis), and occlusion (a complete loss of distal flow signal). The stenosis severity assessed by other modalities was divided into no steno-occlusion, moderate (less than 70% stenosis), severe (70%-99% stenosis), and occlusion (a complete loss of distal flow signal).

We undertook systematic management for patients based on the Japanese guideline.[24] The standard treatment included intravenous antithrombotic agents, such as ozagrel, argatroban, or sometimes heparin, plus edaravone immediately after admission unless thrombolytic therapy was indicated. Either of oral antiplatelet agents, that is, clopidogrel, cilostazol, or aspirin, was administered in consideration of history (gastrointestinal bleeding, tachycardia, arrhythmia, and so on). In the case of infarction recurrence under antiplatelet or anticoagulant therapy, dual antiplatelet therapy (DAPT) or combination therapy of antiplatelets and anticoagulants was adopted according to the stroke subtype.