Ozagrel for Patients With Noncardioembolic Ischemic Stroke: A Propensity Score-Matched Analysis

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Background and Purpose: Ozagrel sodium (ozagrel), a thromboxane A2 synthesis inhibitor, is used for ischemic stroke patients in several countries, despite a lack of strict evidence of its benefits. We investigated whether ozagrel was beneficial for patients with atherothrombotic stroke or lacunar infarction. *Methods:* This was a retrospective observational study using the Diagnosis Procedure Combination database in Japan. We identified patients with atherothrombotic stroke or lacunar infarction who were admitted to 781 hospitals from July 1, 2010 to March 31, 2012. Propensity score-matched analyses were performed separately for patients with atherothrombotic stroke and those with lacunar infarction, which balanced differences in baseline characteristics between patients who received ozagrel (ozagrel group) and those who did not (control group) in each stroke subtype. The modified Rankin Scale scores at discharge and occurrence of hemorrhagic complications after admission were compared between the ozagrel and control groups. *Results:* After the propensity score matching, 2726 pairs of patients with atherothrombotic stroke and 1612 pairs of patients with lacunar infarction were analyzed. Ordinal logistic regression analyses showed that ozagrel use was not significantly associated with modified Rankin Scale score at discharge in patients with atherothrombotic stroke (odds ratio: .99; 95% confidence interval: .88-1.11) or in those with lacunar infarction (odds ratio: 1.00; 95% confidence interval: .87-1.16). The occurrence of hemorrhagic complications did not differ significantly between the ozagrel and control groups. *Conclusion:* The present study suggested that ozagrel was safe to use but did not improve functional outcomes in patients with atherothrombotic or lacunar infarction. **Key Words:** Ischemic stroke—ozagrel—propensity score matching—Diagnosis Procedure Combination database—antiplatelet therapy—stroke recurrence.

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Introduction

Ozagrel sodium (ozagrel), a thromboxane A2 synthesis inhibitor, is used for patients with noncardioembolic stroke in China, Korea, and Japan.[1-3] In the Japanese guideline for managing patients with acute ischemic stroke, it is recommended to start administering ozagrel for patients with noncardioembolic ischemic stroke, including atherothrombotic stroke and lacunar infarction, within 5 days after onset, using a dose of 80 mg twice a day for 14 days.[2,4] Although it is recommended in the Japanese guideline, this recommendation was based on a single randomized control trial published more than 20 years ago.[4] Therefore, we investigated the effects of ozagrel on outcomes in patients with acute ischemic stroke in current clinical settings.

The aim of the present study was to investigate the effects of ozagrel on outcomes in patients with noncardioembolic stroke.

Methods

This study was approved by the Institutional Review Boards and Ethics Committee of The University of Tokyo. Because of the anonymous nature of the data, informed consent was waived.

Study Design and Setting

The present study was a retrospective cohort study using the Diagnosis Procedure Combination (DPC) database. The DPC database is a Japanese administrative claims and discharge abstract database. A detailed profile of the database is provided elsewhere.[5] Briefly, data for approximately half of all patients admitted to hospitals in Japan are recorded in the database. In 2012, more than 1000 hospitals, including all 82 academic hospitals, participated in the database. The attending physicians take charge of data recording for individual patients.

The following data are recorded for each patient: demographic characteristics; diagnoses; outcomes; receipt of procedures; drug use; and several disease-specific data including the Japan Coma Scale (JCS) score,[6] modified Rankin Scale (mRS) score, and day of onset for stroke patients. Diagnoses were recorded by both the International Classification of Diseases (10th revision; ICD-10) codes and text data in Japanese. Main diagnoses, preexisting comorbidities, and complications after admission were separately recorded.

Selection of Participants

The survey period of the present study was July 1, 2010 to March 31, 2012. Patients were included if they were admitted to hospitals for atherothrombotic stroke or lacunar infarction within 1 day of stroke onset and treated with oral antiplatelet drugs during hospitalization. The diagnosis of atherothrombotic stroke was detected by ICD-10 code I633, whereas the diagnosis of lacunar infarction was identified by ICD-10 code I638 with text data of "lacunar infarction." When patients were admitted to the same hospitals with ischemic stroke twice or more during the survey period, only data from their first admission were used for subsequent analyses.

Patients meeting the following criteria were excluded: age of <40 years, diagnosis of atrial fibrillation or use of warfarin or dabigatran during hospitalization, use of heparin during hospitalization, preexisting comorbidity of malignancy or coagulopathy, receipt of thrombolysis with recombinant tissue plasminogen activator, and receipt of endovascular therapy or surgical revascularization procedures. We excluded patients with impaired consciousness with reference to a previous study.[4] Patients with impaired consciousness were defined as those with two-digit or three-digit JCS scores on admission.[6] Patients who initially received ozagrel at 1 day or more after hospital admission were also excluded. Then, atherothrombotic stroke and lacunar infraction patients were divided into two groups based on whether they received ozagrel on admission (ozagrel group) or did not (control group).

Data Collection and Processing

The following diseases were collected as preexisting comorbidities in accordance with the ICD-10 codes: hypertension, diabetes mellitus, dyslipidemia, chronic obstructive pulmonary diseases, heat failure, atrial fibrillation, chronic kidney diseases, liver cirrhosis, malignancy, coagulopathy, dementia, peripheral arterial diseases, and previous stroke. The presence of previous stroke was also identified by whether patients were previously admitted to the same hospital with ischemic stroke.

As indicators of disease severity, JCS and mRS scores on admission were identified for each patient. We also collected data on ambulance service use.

Information on use of the following drugs on admission was collected: edaravone; argatroban; antihypertensive drugs, including nicardipine and diltiazem; glycerol; and mannitol. Magnetic resonance imaging (MRI) examinations on admission were also identified. As drugs used within 3 days of hospital admission, oral antiplatelet agents and antacids were identified. We also detected whether patients received statins within 7 days of hospital admission.

As hospital characteristics, we identified hospital volume, hospital type (academic or non-academic), and availability of thrombolysis with recombinant tissue plasminogen activator. Hospital volume was defined as the total number of patients with acute ischemic stroke admitted to each hospital during the survey period. Stroke care unit admissions were also identified.