Preventive Effect of Cilostazol on Pneumonia in Patients with Acute Cerebral Infarction

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Background: The antiplatelet drug cilostazol decreases the risk of ischemic stroke recurrence in patients with chronic cerebral infarction. Additionally, cilostazol reduces the occurrence of pneumonia in these patients. The purpose of this study was to investigate whether cilostazol is effective for preventing pneumonia in patients with acute cerebral infarction. *Materials and Methods:* A total of 199 consecutive Japanese patients with noncardioembolic acute cerebral infarction, who visited our hospital from January 2010 to April 2016, were retrospectively assessed by using medical records. We compared changes in the occurrence of pneumonia between cilostazol (n = 127) and noncilostazol (n = 72) groups. *Results:* A total of 76% of patients in the cilostazol group were not administered other antiplatelet drugs. The median duration until cilostazol administration was 5 days (interquartile range = 2-8 days) after the onset of cerebral infarction. A total of 8.0% of the cohort was accompanied by pneumonia. The incidence of pneumonia in the cilostazol group was significantly lower than that in the noncilostazol group (4.7% versus 13.9%, $P = .02$). Within 30 days after acute cerebral infarction, the presence of neurological deterioration in the cilostazol group tended to be lower compared with the noncilostazol group, but this difference was not significant (5.5% versus 12.5%, $P = .08$). *Conclusions:* These findings suggest that cilostazol is effective for preventing pneumonia in patients with acute cerebral infarction. **Key Words:** Cilostazol—pneumonia—cerebral infarction—acute phase.

Introduction

Pneumonia is one of the major complications that occur in patients with acute cerebral infarction, negatively affecting mortality and functional outcome.[1-5] The inflammatory response to infection exacerbates brain damage after acute cerebral infarction.[6,7] As independent risk factors, older age, stroke severity, and dysphagia affect the occurrence of pneumonia after acute cerebral infarction.[2-4,6,7] Dysphagia occurs in these patients at frequencies ranging from 23% to 50%.[8] Dysphagia is highly related to the incidence of aspiration, consequently causing pneumonia.[5] Therefore, development of drugs that improve swallowing function in these patients is important.[2,3] The antiplatelet drug cilostazol is used for preventing recurrence of cerebral infarction in patients with chronic cerebral infarction.[9,10] Additionally, cilostazol is reported to have an ameliorating effect on swallowing function in these patients.[11-15] However, the efficacy of cilostazol in patients with acute cerebral infarction remains to be determined.[16-19] Therefore, in this study, we investigated whether cilostazol reduces the occurrence of pneumonia in patients with acute cerebral infarction.

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Materials and Methods

Patients

A total of 199 consecutive Japanese patients with noncardioembolic acute cerebral infarction, who visited our hospital from January 2010 to April 2016, were retrospectively assessed using medical records. The survey was performed during the admission period. The exclusion criteria were as follows: cardiogenic cerebral embolism, severe disturbance of consciousness, endotracheal intubation, discontinuation of cilostazol by adverse effects, and pneumonia within 72 hours after admission. To avoid counting patients with community-acquired pneumonia, we excluded the occurrence of pneumonia within 72 hours after admission. We compared changes in the occurrence of pneumonia between cilostazol (n = 127) and noncilostazol (n = 72) groups. Patients received cilostazol (200 mg/day), aspirin (100 mg/day), or clopidogrel (75 mg/day) without regard to this study. Ozagrel sodium (160 mg/day) was intravenously administrated for 3-14 days (mean 8.7 ± 2.4 days). Alternatively, argatroban was infused continuously at 60 mg/day for the first 2 days, and then it was infused at 10 mg/day until the next 5 days (mean 4.6 ± .3 days). Most patients received edaravone (60 mg/day) for 3-14 days (mean 8.1 ± 2.1 days). This study was conducted in accordance with the Declaration of Helsinki and its amendments. The aim and protocol of this study were approved by the Ethics Committee of Osaka Medical College (#2303).

Definition of Pneumonia

The diagnosis of pneumonia was done in accordance with the criteria of the U.S. Centers for Disease Control and Prevention.[20] Briefly, clinically defined pneumonia was determined by the presence of a new and persistent infiltrate or consolidation on at least 1 chest x-ray or computed tomography with one of the following clinical signs: fever (temperature ≥37.5°C on 2 consecutive measurements or a single measurement of ≥38.0°C), leukopenia (<4000 white blood cells/mm^3) or leukocytosis (≥12,000 white blood cells/mm^3), and altered mental status in people older than 70 years old with no other recognized cause. Additionally, clinically defined pneumonia further required 2 of the following signs: new onset of purulent sputum or increased respiratory secretions, new onset or worsening cough or dyspnea, rales, and worsening gas exchange.

Clinical Assessment

We collected data concerning head computed tomography or magnetic resonance imaging plus magnetic resonance angiography, electrocardiography, carotid artery ultrasound examinations, and cardiac ultrasonography. The stroke subtype was classified according to these findings and the Trial of Org 10172 in Acute Stroke Treatment criteria.[21] Additionally, larger lacunar-type infarcts were separately assessed because they often cause progressive motor deficits.[22] Stroke severity was evaluated by the National Institutes of Health Stroke Scale score at admission.[23] Swallowing function was evaluated by the functional oral intake scale (FOIS) for estimating change in the functional eating abilities of patients with stroke and dysphagia.[24,25] FOIS scores of lower than or equal to 6 and lower than or equal to 3 indicated the presence of dysphagia and a tube feeding-dependent condition, respectively. The A^2DS^2 score was used for predicting poststroke pneumonia. The A^2DS^2 score was graded into low (0-4) and high (5-10) scores.[26,27] Severity of leukoaraiosis was graded according to the Fazekas scale because it is an independent risk factor of pneumonia in acute cerebral infarction through impairment of cognition and consciousness.[27] The total Fazekas score was calculated by adding the periventricular and subcortical scores and graded into normal (0-2) and severe (3-6) scores.[27] The presence of a poor nutritional status was defined by serum albumin levels of 3.0 mg/dL or lower at admission.[28] Angiotensin-converting enzyme inhibitors decrease the occurrence of poststroke pneumonia,[29] whereas acid-suppressive drugs, such as proton pump inhibitors (PPIs), increase occurrence of poststroke pneumonia.[30,31] Therefore, internal use of these drugs was also examined. Functional outcome was evaluated by the modified Rankin scale at discharge.[32] Neurological deterioration was defined as stroke recurrence or at least a 1-point increase in the National Institutes of Health Stroke Scale score.[18]

Statistical Analysis

Statistical analyses were performed by version 12.0.1 of JMP statistical software (SAS Institute Inc., Cary, NC). Values are expressed as the mean ± standard deviation or median (interquartile range) for continuous variables. Continuous variables were assessed using the Student *t* test or the Mann–Whitney *U* test. Means of changes in FOIS scores from admission to discharge in the 2 groups were compared using the Mann–Whitney *U* test. Categorical variables were analyzed by the χ^2 test or Fisher exact test. The threshold for significance was $P < .05$. Univariate and multivariate analyses were performed using the Cox proportional hazards model to investigate the predictors of pneumonia. The Cox proportional hazards model was used to estimate the relative risk (hazard ratio [HR]) and 95% confidence interval (CI). Variables that were significant on univariate analysis at $P < .10$ were included in multivariate analyses. Pneumonia-free survival was estimated by the Kaplan–Meier method and compared by the log-rank test.