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Original Article

Effects of Antiplatelet Agents on Functional Outcome and Cognitive Status in Patients with Acute Ischemic Stroke☆

CME

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SUMMARY

Background: The effect of antiplatelet agents for the treatment of acute stroke is less certain than that for the treatment of acute myocardial ischemia. In this study, we investigated whether antiplatelet agents (aspirin, clopidogrel, and ozagrel) demonstrated a favorable effect on functional outcome and cognitive status 3 months poststroke.

Methods: We randomly selected 24 hospitals from five different regions in China. Patients without recurrent stroke were recruited and neurological and neuropsychological examinations were performed on these patients at 3 months poststroke. Each patient was diagnosed as having favorable or poor functional outcome and normal cognition or cognitive impairment. Multivariate logistic regression analyses adjusted for sex, age, education, and neurological deficit at stroke onset were performed to examine whether antiplatelet agents exhibited a favorable effect on functional outcome and cognitive status at 3 months poststroke.

Results: Of the 518 eligible patients (aged 45–86 years, mean 63.01 ± 9.99 years), 167 (32.2%) were female. On the basis of univariate analysis, there were significant associations between functional outcome ($p = 0.048$) and cognitive status ($p = 0.026$) at 3 months poststroke and the use of antiplatelet agents in acute ischemic stroke. The adjusted odds ratio for favorable functional outcome was 1.81 (95% confidence interval: 1.09–2.99) and for normal cognition 1.67 (95% confidence interval: 1.02–2.74).

Conclusion: The use of antiplatelet agents in acute ischemic stroke may have a favorable effect on functional outcome and cognitive status in patients at 3 months poststroke.

1. Introduction

It is well known that antiplatelet agents, including aspirin and clopidogrel, play an important role in the prevention of myocardial and cerebral infarctions[1,2] and can improve the prognosis of acute myocardial infarction[3]. Previous clinical trials have evaluated the potential use of antiplatelet agents in acute ischemic stroke; however, these trials showed a nonsignificant trend in the improvement of functional outcome in stroke survivors[4,5]. The usefulness of antiplatelet agents for the treatment of acute stroke is less certain than that for the treatment of acute myocardial ischemia.

Although vascular dementia was very common[6], and our previous study showed cognitive impairment in patients poststroke[7], thus far, few clinical trials have examined cognitive status as an outcome measure of stroke[5,8]. Moreover, no clinical trials have investigated the cognitive effects of antiplatelet agent

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administration in acute stroke. Therefore, the aim of the present study was to examine the effectiveness of antiplatelet agents in patients with acute ischemic stroke on functional outcome and cognitive status at 3 months poststroke independent of demographic factors and neurological deficits at stroke onset.

2. Material and methods

2.1. Participants

We selected five regions that differed in geography and economy: northeast China, northern China, western China, central China, and southeast China. We randomly selected 24 hospitals from these five regions.

Patients with an acute ischemic stroke were admitted to the neurology department in the selected hospitals. The patients were screened between April 1, 2009 and April 30, 2010. Diagnosis of ischemic stroke was made on the basis of the presence of a sudden focal deficit and an associated lesion, as assessed using computed tomography or magnetic resonance imaging. Patients were eligible for participation in the study if they had experienced first-time ischemic stroke and had received treatment within 7 days of stroke. Patients were excluded on the basis of the following criteria: age < 45 years; demonstrated prestroke cognitive impairment [considered as a score of $\geq$ 55 on the short Informant Questionnaire on Cognitive Decline in the Elderly (s-IQCODE)][9]; or a history of concomitant cerebral and/or psychiatric disease that was likely to affect cognition, usefulness of intravenous recombinant tissue-type plasminogen activator (rt-PA) or contraindications for antiplatelet agents.

2.2. Collection of clinical data

The following variables were recorded for each eligible patient: demographics (sex, age, and years of education), neurological examination and medication in acute and convalescent phases of stroke. Older age was defined as $\geq$ 65 years. A low education level was defined as < 7 years of education. The National Institutes of Health Stroke Scale (NIHSS) was determined at onset and at 3 months poststroke[10]. Severe neurological deficit upon admission and at 3 months poststroke were individually defined as the NIHSS total scores $\geq$ 6 and $\geq$ 2, respectively[11]. Severe aphasia was determined as a language item score of NIHSS $\geq$ 2.

2.3. Evaluation of cognitive status

Prior to the formal interview, 48 neurological doctors from 24 hospitals were trained to perform the neurological and neuropsychological tests used in this study. The interviewers' inter-rater reliability for the cognitive tests exceeded 0.85. All patients without a disturbance in consciousness, severe aphasia, bilateral impaired movement, neglect, or recurrent stroke at 3 months poststroke were recruited for the study, and a battery of neuropsychological tests were performed on the patients. First, the patients underwent cognitive screening using the Montreal Cognitive Assessment with a cut-off score of 26[12]. To confirm cognitive impairment after stroke, the patients who did not pass the cognitive screening were asked to complete a battery of cognitive tests that lasted for approximately 30 minutes and covered four major cognitive domains: memory, which was assessed using the Fuld Object Memory test[13]; executive function, which was assessed using the Rapid Verbal Retrieve test[14]; visuospatial ability, which was examined using the Block Design subset of Wechsler for Adult Intelligence Scale-Revised[15]; and attention, which was measured using the Digit Span subset of the Wechsler for Adult Intelligence Scale-Revised[15]. These tests were selected because they do not require literacy for a successful performance.

2.4. Outcome measures

The cognitive outcome was assessed using previously described neuropsychological examinations. A deficit was defined as a performance below the 10th percentile relative to the education-adjusted normalized data. The limit scores for these tests have been previously established in several large surveys related to dementia in China[16,17]. In this study, the diagnosis of cognitive impairment after stroke was made according to the diagnosis criteria of vascular cognitive impairment[18] in patients who suffered from a stroke and exhibited a subsequent impairment in at least one cognitive domain. Patients without impaired cognitive function were classified as having normal cognition. An experienced neurologist determined the final diagnosis after a thorough examination of all of the clinical and neuropsychological data.

The modified Rankin Scale is a simplified overall assessment of function in which a score of 0 indicates the absence of symptoms and a score of 6 indicates death. Scores within 1 on the modified Rankin Scale indicate a favorable functional outcome[8].

2.5. Ethics

The protocols used in this study were approved by the ethics committees of all of the selected hospitals. Written informed consent was obtained from all of the patients or their legal guardians before any interviews were conducted.

2.6. Statistical analysis

All of the statistics were analyzed using SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL, USA). The primary aim of the analyses was to compare the prevalence of a favorable functional outcome and normal cognition at 3 months poststroke between the patients treated with and without antiplatelet agents. Thus, we calculated the crude and adjusted odds ratios (OR) with corresponding 95% confidence intervals (95% CI) using logistic regression. We adjusted for sex, age, level of education, and neurological deficit at stroke onset. A p value < 0.05 was considered significant.

3. Results

A total of 701 patients with acute stroke were screened. Upon admission, 85 patients were excluded because they were either younger than 45 years (16 cases); transient ischemic attack (16 cases), prestroke cognitive impairment (27 cases), cerebral disease or mental disorder (23 cases); or received intravenous rt-PA (3 cases). At the follow-up evaluation, 98 patients were excluded due to refusal (50 cases), death (3 cases), recurrent stroke (7 cases), severe aphasia (23 cases), or missing data (15 cases).

Of the 518 eligible patients (aged 45–86 years with a mean age of 63.01 ± 9.99 years), 167 (32.2%) were female, and 263 (50.8%) were admitted to the hospital within the first 48 hours of stroke onset. The average stay in the hospital was approximately 2 weeks. There were no significant differences in sex, age, or neurological deficit at stroke onset between patients who were treated with and without antiplatelet agents; however, patients with a high educational level were more likely to take the antiplatelet agents (Table 1).

Of the patients who were taking antiplatelet agents, 330 (75.9%) were administered with aspirin (dose 100–300 mg), 64 (14.7%) were taking clopidogrel (dose 75–300 mg), 32 (7.4%) were given dual antiplatelet agents (aspirin and clopidogrel), nine (2.1%) were