Statin and Aspirin Pretreatment Are Associated with Lower Neurological Deterioration and Platelet Activity in Patients with Acute Ischemic Stroke

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Background: Aspirin and statin are recommended for the treatment of acute ischemic stroke. However, whether aspirin and statin pretreatment is associated with clinical outcomes has not been well addressed. This study aimed to evaluate the effect of pre-existing statin and aspirin use on platelet activation and clinical outcome in acute ischemic stroke patients. *Methods:* We conducted a prospective, multicenter observational study in patients with acute ischemic stroke. Platelet aggregation and platelet–leukocyte aggregates were measured on admission and during 7-10 days after admission. The primary outcome of the study was neurological deterioration (ND) within 10 days after admission. The secondary outcome was a composite of recurrent ischemic stroke, myocardial infarction, and death during the first 3 months after admission. Physical disability was evaluated using the modified Rankin Scale score at 3 months after admission. *Results:* Among 1124 enrolled patients, 270 (24%) experienced ND. Higher platelet aggregation and platelet–leukocyte aggregates on admission and during 7-10 days were associated with ND. Platelet aggregation and platelet–leukocyte aggregates on admission were significantly lower in the patients with pre-existing statin or aspirin use than those without treatment. Patients with prestroke concomitant statin and aspirin treatment had significantly lower incidence of ND than those without treatment. Diabetes mellitus, fasting glucose, platelet–leukocyte aggregates, and prestroke concomitant statin and aspirin use were independently associated with ND. *Conclusions:* Prestroke concomitant statin and aspirin use is associated with lower neurological deterioration and platelet activity in patients with acute ischemic stroke. **Key Words:** Neurological deterioration—platelet activation—ischemic stroke—outcome.

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Introduction

Neurological deterioration (ND) occurs during the acute phase in approximately one third of all ischemic stroke patients and is associated with increased mortality and long-term functional disability.[1,2] Atherothrombosis and inflammation play important roles in the pathogenesis of acute ischemic stroke.[3,4] Platelets play a critical role in triggering arterial thrombosis and in promoting atherogenesis.[3] Platelet activation and platelet–leukocyte aggregates has been described in patients with ischemic stroke.[5] Thus, aspirin is routinely recommended for the treatment of ischemic stroke within 24 hours of onset.[6] However, the benefits of prestroke aspirin use in patients with acute ischemic stroke remain unclear.

Statins are medications originally used for the control of hypercholesterolemia.[7] However, statins are effective in primary and secondary prevention of stroke.[8] Their long-term beneficial effects may be primarily mediated by their lipid-lowering effects. Statins may also work effectively in preventing recurrence or progression during the acute stage of stroke because they have antithrombotic, anti-inflammatory, and anti-oxidative effects aside from their cholesterol-lowering effect.[9,10] Statin therapy has been shown to reduce cardiovascular events and improve the outcome of myocardial infarction (MI).[11] Several observational studies have suggested that statin use after acute ischemic stroke was associated with better functional outcome and reduced mortality.[12,13] Although statin therapy is widely used in patients at high-risk for major vascular events, the benefits of pre-existing statin therapy in patients with acute ischemic stroke remain controversial. Multiple studies have demonstrated improved clinical outcomes in patients taking statins before stroke onset[14,15]; however, mechanisms conferring this protection have not been well studied.

Aspirin and statin are commonly recommended for the treatment of ischemic stroke patient.[6] However, whether aspirin and statin pretreatment are associated with ND or other clinical outcomes has not been well addressed. Thus, this prospective, multicenter cohort study aimed to evaluate if prior statin and aspirin treatment could reduce the ND and improve the functional outcome of patients with ischemic stroke. This study also investigated the effect of prior statin and aspirin treatment on platelet activity by assessing platelet aggregations and platelet–leukocyte aggregates.

Materials

Ethics Statement

This prospective study was jointly conducted by The People's Hospital of Deyang City, second, and third Affiliated Hospital of Wenzhou Medical College between March 2011 and June 2015. The study protocol was approved by the Ethics Committee at the participating hospitals. Written informed consent was obtained from each patient before study enrollment.

Study Population

Consecutive patients who underwent a first-ever ischemic stroke and were admitted to the above participating hospitals within 24 hours of the onset of stroke from March 2011 to June 2015 were evaluated. All patients were subjected to computed tomographic angiography or magnetic resonance angiography of the brain as well as color duplex ultrasound investigation of the carotid arteries. Common electrocardiogram (ECG), 24-hour Holter ECG (Type century3000, Beijing Greenland Technology Development Co. Ltd, Beijing, China), and echocardiogram were performed to reveal any possible cardio-embolic stroke. The inclusion criteria were (1) age ≥40 years old; (2) National Institutes of Health Stroke Scale (NIHSS) score <15; (3) the mechanism of stroke was atherothrombotic or small artery disease according to the Trial of ORG 10172 in the Acute Stroke Treatment classification system.[16] The exclusion criteria were (1) cardiac or any other determined or undetermined etiology of ischemic stroke; (2) history of carotid endoartectomy or carotid stent therapy; (3) in addition to aspirin, administration of other antiplatelet medication before stroke onset or poststroke; (4) usage of warfarin or heparin in the preceding 2 weeks or within 10 days after admission; (5) allergy to aspirin; (6) intravenous thrombolytic therapy; (7) blood platelet count $<100 \times 10^9$/L or $>450 \times 10^9$/L; (8) fever, hypoxia, or any relevant hemodynamic compromise at admission; (9) other conditions, such as asthma or severe cardiovascular, liver, or renal disease; and (10) individuals declined to participate in the study.

Demographic data, history of risk factors (i.e., hypertension, diabetes mellitus [DM], dyslipidemia, cigarette smoking), and history of previous vascular events (i.e., MI, angina) were obtained at baseline. Fasting blood samples were tested for blood sugar, hemoglobin A1c (HbA1c), total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol.

All enrolled patients were classified into prestroke alone statin use group (patients taking statins alone before stroke), prestroke alone aspirin use group (patients taking aspirin alone before stroke), prestroke concomitant statin and aspirin use group (patients taking concomitant statin and aspirin before stroke), and without prestroke statin or aspirin use group (patients did not take statins or aspirin before stroke).

Hospital Treatment

All patients received standard therapy based on the guidelines,[6] including aspirin (200 mg/day for 14 days and 100 mg/day thereafter, Bayer Healthcare Company Ltd, Beijing, China). The lipid-lowering regimens used for preventing ischemic stroke were also according to the guidelines and included statins (atorvastatin [Pfizer Pharmaceuticals Ltd, Beijing, China] or rosuvastatin [Astrazeneca Pharmaceuticals Ltd, Shanghai, China]) therapy with