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Clinical Study

Clopidogrel plus aspirin *versus* aspirin alone for preventing early neurological deterioration in patients with acute ischemic stroke

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ABSTRACT

Recent studies have suggested that combination antiplatelet therapy may be superior to monotherapy in the treatment of acute stroke. However, additional prospective studies are needed to confirm this finding. The present trial compared the efficacy and safety of clopidogrel plus aspirin versus aspirin alone in the treatment of non-cardioembolic ischemic stroke within 72 hours of onset. Six hundred and ninety patients aged ⩾40 years with minor stroke or transient ischemic attack (TIA) were identified for enrollment. Experienced physicians determined baseline National Institutes of Health Stroke Scale scores at the time of admission. All patients were randomly allocated (1:1) to receive aspirin alone (300 mg/day) or clopidogrel (300 mg for the first day, 75 mg/day thereafter) plus aspirin (100 mg/day). The main endpoints were neurological deterioration, recurrent stroke, and development of stroke in patients with TIA within 14 days of admission. After 43 patients were excluded, 321 patients in the dual therapy group and 326 patients in the monotherapy group completed the treatment. Baseline characteristics were similar between groups. During the 2 week period, stroke deterioration occurred in nine patients in the dual therapy group and 19 patients in the monotherapy group. Stroke occurred after TIA in one patient in the dual therapy group and three patients in the monotherapy group. Similar numbers of adverse events occurred in both groups. This study showed that early dual antiplatelet treatment reduced early neurological deterioration in patients with acute ischemic stroke, compared with antiplatelet monotherapy. These results imply that dual antiplatelet therapy is superior to monotherapy in the early treatment of acute ischemic stroke.

1. Introduction

In the acute stages of transient ischemic attack (TIA) and minor ischemic stroke, patients are at high risk of an unstable clinical course, including recurrence or deterioration of stroke. Most of these unfavorable events occur in the initial 48–72 hours after symptom onset and have deleterious effects on the recovery of neurological functions [1–4]. Thrombolysis has been demonstrated to be an effective method of treating acute ischemic stroke, but it cannot be used in most patients due to strict indications, such as the limited time window after the onset of stroke. Thus, guidelines recommend early antiplatelet treatment for most patients with acute ischemic stroke [5,6]. Two large trials established the efficacy of aspirin in the treatment of acute ischemic stroke [7,8], and guidelines currently recommend the use of aspirin in the acute stage [5,6]. A recent study comparing the efficacy and safety of cilostazol to aspirin found that cilostazol use was feasible for the treatment of acute ischemic stroke [9]. A recent review and meta-analysis showed that dual antiplatelet therapy appears to safely and effectively reduce stroke recurrence and combined vascular events in patients with acute ischemic stroke or TIA, compared with monotherapy [10]. In addition, two recent studies showed trends towards reduced ischemic stroke recurrence with dual antiplatelet therapy in the acute stage compared with monotherapy [11,12]. However, additional prospective studies are needed to further test this apparent superiority of combination antiplatelet therapy over antiplatelet monotherapy in the treatment of acute stroke. The present study aimed to assess whether combination therapy with clopidogrel and aspirin reduced the recurrence or deterioration of stroke more effectively than aspirin monotherapy in northern Han Chinese patients.

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2. Methods

2.1. Participants

Between September 2010 and October 2012, 690 patients aged ⩾40 years with minor stroke or TIA (⩽72 hours of onset) were identified as eligible for enrollment in this study. Minor stroke was defined by a National Institutes of Health Stroke Scale (NIHSS) score ⩽7 at the time of randomization. TIA was defined as the complete recovery of neurological deficit within 1 hour of onset. The exclusion criteria were (1) cardioembolic stroke, (2) anticoagulation therapy before stroke onset or definite indication for anticoagulation, (3) current peptic ulceration or history of systemic bleeding, (4) platelet count <100,000/mm [3] or coagulopathy, (5) major surgery or trauma in the previous 3 months, (6) coexisting severe systemic disease, such as terminal malignancy or serious renal or liver disease, (7) pregnancy, breastfeeding, or planned pregnancy during the course of the trial, (8) known contraindication to clopidogrel or aspirin, (9) suitability for thrombolysis, and (10) NIHSS score >8. Our institutional ethics committee approved the study protocol and all patients or family members provided written informed consent.

2.2. Procedures

The patients were randomly allocated (1:1) to receive aspirin alone (300 mg/day) or clopidogrel (300 mg for the first day, 75 mg/day thereafter) plus aspirin (100 mg/day). Randomization was performed by blindly choosing a table tennis ball from a box with the number 1 or 2 written on it to represent dual or single antiplatelet therapy. In addition to antiplatelet treatment, routine management of arterial blood pressure and blood glucose and lipid levels (atorvastatin, 40 mg/day) was conducted according to published guidelines [5,6].

At baseline, all patients underwent electrocardiography, chest radiographs, and brain MRI and magnetic resonance angiography (MRA). Demographic characteristics and vascular risk factors were also collected. Blood samples were collected at baseline for biochemical and hematological measurements, to identify patients with clear contraindications to the trial medications, and to provide baseline data to monitor the safety profiles of the medications over the course of the trial.

Acute ischemic stroke or TIA was confirmed by clinical symptoms and brain MRI (including diffusion-weighted imaging [DWI]) and MRA findings. Experienced physicians determined baseline NIHSS scores at the time of admission. Drugs were administered to enrolled patients immediately after neurological evaluation. The NIHSS was administered twice each day (morning and evening) until the 14th day after admission.

The main study endpoints were neurological deterioration, recurrent stroke, and development of stroke in patients with TIA within 14 days after admission. Neurological deterioration, including recurrent stroke, was defined as an increase of ⩾2 points in NIHSS score. Stroke recurrence was defined as additional neurological deficit and corresponding positive lesions on DWI. The development of stroke in patients with TIA was defined as continued neurological deficit and corresponding positive lesions on DWI. The causes of ischemic stroke were determined using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [13]. All patients with the main endpoints underwent brain CT scan to exclude intracranial hemorrhage.

Intracranial or extracranial hemorrhagic events were monitored due to safety concerns. Other safety outcomes were those known to be associated with the trial medications. Clopidogrel-specific safety outcomes were the incidence of thrombotic thrombocytopenic purpura and granulocytopenia, and atorvastatin-specific safety outcomes were mainly muscle pain and myositis.

2.3. Statistical analysis

Differences in baseline factors (sex, age, vascular risk factors, stroke subtypes) between groups were compared using the χ^2 test. Changes in NIHSS scores were examined using analysis of covariance, adjusted for baseline scores.

3. Results

Between September 2010 and October 2012, 690 patients were randomly assigned to the two groups. Forty-three of these patients were subsequently excluded from the study because they refused participation, had an adverse event, or met at least one exclusion criterion (Fig. 1). A total of 321 patients in the dual therapy group and 326 patients in the monotherapy group completed the treatment.

Table 1 shows the patients' baseline demographic characteristics. Baseline characteristics were similar between the groups. Mean time to randomization was 22.35 hours after stroke or TIA onset in the dual therapy group and 24.59 hours after onset in the monotherapy group. According to the TOAST classification system, the principal causes of stroke were small vessel occlusion (dual therapy, 45.79%; monotherapy, 46.63%) and large artery atherosclerosis (dual therapy, 31.46%; monotherapy, 31.9%). The most prevalent risk factors in both groups were hypertension, smoking, and diabetes mellitus. Nearly one-third of patients had experienced previous ischemic stroke or TIA (dual therapy, 32.4%; monotherapy, 35.89%).

During the 2 week treatment period, deterioration of stroke occurred in nine patients in the dual therapy group and 19 patients in the monotherapy group (Table 2). Stroke occurred after TIA in one patient in the dual therapy group and three patients in the monotherapy group. NIHSS scores on admission (not including patients with TIA) were similar in the two groups (Table 3). Both antiplatelet therapeutic approaches produced an obvious decrease in NIHSS scores after 2 weeks of treatment ($p < 0.001$, Table 3). Excluding patients with stroke deterioration, mean NIHSS scores at 2 weeks after admission were 0.84 and 0.98 in the dual therapy and monotherapy groups, respectively, representing decreases of 77.24% and 70.48%, respectively.

Similar numbers of adverse events occurred in the two groups (Table 4). No severe intracranial hemorrhage or severe systemic bleeding event occurred. Two patients in the dual therapy group and one in the monotherapy group showed minor hemorrhagic transformation (presenting as slight capillary hemorrhage). Six patients in the dual therapy group and two patients in the monotherapy group had minor systemic bleeding events (Table 4).

4. Discussion

In this study, we compared the efficacy of aspirin plus clopidogrel versus aspirin alone in preventing or reducing the recurrence or deterioration of acute ischemic stroke. The results showed that early dual antiplatelet treatment reduced early neurological deterioration of acute ischemic stroke compared with antiplatelet monotherapy. These results imply that dual antiplatelet therapy is superior to monotherapy in the early treatment of acute ischemic stroke.

Antiplatelet treatment is an important therapeutic strategy for acute ischemic stroke because thrombolysis cannot be used widely due its strict indications. Many studies of antiplatelet therapy have focused on its role in the secondary prevention of ischemic stroke