Hypertensive Patients Using Thiazide Diuretics as Primary Stroke Prevention Make Better Functional Outcome after Ischemic Stroke

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Background: Thiazides have been used for the control of blood pressure and primary prevention of ischemic stroke. No previous studies have assessed the influence of thiazides on functional prognosis after ischemic stroke. *Methods:* Demographics, prestroke conditions, poststroke National Institutes of Health Stroke Scale score, and clinical and laboratory parameters were prospectively registered in 216 Taiwanese patients. One hundred forty patients who completed follow-up 3 months after experiencing ischemic stroke were assessed with the modified Rankin scale as functional prognoses. *Results:* Twenty-one patients used thiazide to control hypertension before experiencing ischemic stroke. No differences of stroke subtypes and comorbidities before stroke were observed between the 2 groups. The emergency department National Institutes of Health Stroke Scale was lesser among thiazide users (4 [2-7] versus 6 [4-16], *P* = .02). Among 140 patients who completed follow-up in 90 days, thiazide users had more favorable functional status (modified Rankin scale ≤2: 42.4% versus 26.9%, *P* = .02, odds ratio 3.34, 95%, confidence interval .130-.862). *Conclusion:* Hypertensive patients treated with thiazides long term had a lesser severity of stroke and better functional outcomes after ischemic stroke. **Key Words:** Thiazide-diuretics—ischemic stroke—hypertension—functional prognosis—stroke in evolution—stroke primary prevention.
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Introduction

Ischemic stroke is one of the major causes of death worldwide. Epidemiologic studies have revealed that arterial hypertension is the most likely risk factor for stroke.[1,2] Approximately 54% of stroke and 47% of ischemic heart disease cases worldwide are attributable to high blood pressure.[1] The risk of hypertension in ischemic stroke patients, however, can be reversed with antihypertensive drug treatment, especially in elderly patients who have isolated systolic hypertension.[3,4]

Thiazide diuretics have been a mainstay of essential hypertension therapy. A recent Cochrane review of 19 randomized controlled trials demonstrated that thiazide diuretics reduced overall mortality and risk of stroke.[5] In the Systolic Hypertension in the Elderly Program, chlorthalidone caused a 36% reduction in the incidence of stroke.[3] Without contraindication, thiazide diuretics may serve as a first-line antihypertensive medication for primary stroke prevention.[6]

Only a small amount of medical literature has been published about the prognosis of long-term thiazide users after acute ischemic stroke. We performed this prospective observational study to evaluate the severity and

functional outcome after ischemic stroke in patients who used thiazides to control hypertension.

Methods and Materials

Study Design

This was a prospective observational study of consecutive patients admitted to the Chia-Yi Chang Gung Memorial Hospital, a stroke referral center, in the period from between October 2007 and June 2010. All patients with a measurable National Institutes of Health Stroke Scale (NIHSS) score were recruited to participate. In addition, patients transferred from other hospitals also were eligible for enrollment. Patients were excluded if they had a previous acute ischemic stroke, unknown drug history, recorded time >12 hours between the onset of neurologic symptoms and presentation to the emergency department (ED), evidence of hemorrhagic stroke assessed by brain computed tomography (CT), fibrinolytic therapy requirement, diagnosed transient ischemic attack, or lack of ischemic stroke diagnosis on discharge. The study protocol was approved by the Chang Gung Memorial Hospital institutional review board. Written informed consent was obtained from all approached patients.

Diagnostic Studies

Data were collected from the ED participants via a standardized data collection form, including age, sex, arterial blood pressure on ED admission and every 8 hours for the first 3 days, admission blood glucose, complete blood count, blood urea nitrogen, creatine, blood urea nitrogen/creatine ratio, triglycerides, and total cholesterol. All patients received brain CT scans within 6 hours of ED admission. A radiologist from the stroke team interpreted the CT findings. Previous medication histories also were reviewed.

Clinical Assessment

Stroke severity was assessed via the NIHSS and performed by physicians trained in NIHSS assessment. This assessment was carried out immediately after a patient's ED admission and every 24 hours within the first 3 days during hospitalization. NIHSS of ED and 24 hours after admission were compared to see whether there was early improvement clinically. Stroke in evolution (SIE) was diagnosed in those patients who experienced worsening neurologic condition as indicated by an increase of 4 or more points on the NIHSS within 72 hours after stroke onset. Stroke subtype using TOAST classification was made before discharge after surveyed possible cause of stroke. Neurologists evaluated patient functional independent status with modified Rankin scale (mRS) 3 months after stroke. A good functional outcome was defined as mRS ≤2.[7]

Statistical Analysis

Patients were divided into 2 groups according to use or nonuse of thiazides. The differences between the 2 groups were analyzed using the chi-square (χ^2) test for categorical variables; they were expressed as frequencies and percentages. Continuous data were analyzed with independent two sample *t* tests for continuous variables expressed as a mean ± SD. NIHSS was analyzed with the Mann-Whitney *U* test and presented via median (interquartile range). Variables that were associated with a prognosis of stroke, including age, sex, stroke subtype (lacunar or nonlacunar), risk of cardiac embolism (atrial fibrillation or congestive heart failure), use or nonuse of thiazide, SIE, and glucose level on admission, were used in multivariate analysis.[8] All statistical assessments were 2-sided, and differences with *P*-values < .05 were considered statistically significant. Statistical analyses were performed using SPSS 17.0 statistical software (SPSS Institute, Chicago, IL).

Results

There were 216 patients who met the enrolled criteria and agreed to join this study. Only 140 patient completed follow-up in 90 days. Patients were divided into 2 groups according to their thiazide use for controlling blood pressure. Twenty-one patients used thiazides. The mean age of 140 patients was 70.1 ± 10.3 years of age with a range between 46 and 96 years of age. Table 1 summarizes both the demographic and clinical characteristics of 21 thiazide users and 119 thiazide nonusers. There were no differences found between the 2 groups in multiple variables, including associated underlying disease, age, and sex, as well as clinical features, including blood pressure measurements, heart rate, blood glucose levels, and triglyceride levels.

Table 2 compares initial NIHSS at ED, better NIHSS when followed 24 hours after admission, SIE within 72 hours, favorable outcome as mRS ≤2 90 days after stroke, and stroke subtypes using the TOAST (ie, Trial of Org 10172 in Acute Stroke Treatment) classification. There was no difference in stroke subtypes between the 2 groups. The ED NIHSS was lower among thiazide users (4 [2-7] versus 6 [4-16], *P* = .02). There also was more neurologic improvement at 24 hours after admission and less SIE within 72 hours in thiazide users, although not statistically significant.

There was a statistically significant increase in favorable function outcome among thiazide users as seen by the mRS followed at 90 days later (mRS ≤2: 42.4% versus 26.9%, *P* = .02, odds ratio [OR] 3.34, 95%, confidence interval [95% CI] .130-.862).

Table 3 shows the result of multivariate logistic regression of variables that may influence functional outcome of stroke patients, including age, sex, use or nonuse of thiazides, glucose levels on admission, SIE ≥4, the presence