Effects of Hydrochlorothiazide on Oxidative Stress and Pulse Pressure in Hypertensive Patients with Chronic Stroke: The EMINENT Study

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Abstract

Objective Thiazide diuretics are reported to have antioxidant effects and reduce pulse pressure (PP). The aim of this study was to elucidate whether hydrochlorothiazide additionally exerts such effects in stroke patients under treatment with losartan.

Methods This study was an open-label, randomized, multicenter study. Patients with a history of chronic stroke and treatment with angiotensin receptor blockers or angiotensin-converting enzyme inhibitors for essential hypertension were enrolled. Fifty-five hypertensive patients were randomly assigned to two groups: those further treated with hydrochlorothiazide and those further treated with non-diuretic antihypertensive drugs.

Results Both groups showed a significant decrease in PP over six months (hydrochlorothiazide group: 67 ± 12 mmHg to 58 ± 12 , $p < 0.001$; non-diuretic group: 72 ± 12 to 61 ± 12 , $p < 0.001$), although no significant differences were observed between the two groups. The malondialdehyde-modified low-density lipoprotein levels did not change significantly after treatment in either group.

Conclusion In this study, hydrochlorothiazide treatment did not provide any additional benefits over non-diuretic antihypertensive drugs in terms of antioxidant effects or reducing PP.

Key words: angiotensin receptor blocker, stroke, thiazide, oxidative stress, pulse pressure

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Introduction

Thiazide diuretics have been shown to reduce cardiovascular events in clinical trials (1, 2). In addition to their blood pressure-lowering actions, the antioxidant effects of these agents may have a beneficial impact on the incidence of cardiovascular events (3, 4). Furthermore, thiazide diuretics

have been reported to reduce pulse pressure (PP) (5, 6), which may also help to prevent cardiovascular diseases. Based on these findings, thiazide diuretics are useful for preventing cardiovascular events in hypertensive patients who suffer from stroke. However, the prescription of diuretics is less prevalent in such patients in Japan due to concerns regarding the adverse metabolic effects of these drugs.

Angiotensin receptor blockers (ARBs) may have favorable

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pleomorphic effects in patients with stroke, including vasodilation of the cerebral arteries, anti-inflammatory effects and improvements in insulin resistance (7, 8). Therefore, ARBs are currently used in a large number of Japanese hypertensive patients with stroke as antihypertensive agents. The concomitant use of a thiazide diuretic with an ARB is beneficial for reducing blood pressure (BP) (9, 10), as thiazide diuretics have complementary actions to ARBs (9). However, it remains unclear whether diuretics show more potent antioxidant effects or achieve a more significant reduction in PP compared with other non-diuretic antihypertensive drugs when administered in addition to ARBs.

In order to evaluate the antioxidant and PP-reducing effects of thiazide diuretics, we performed an open-label, randomized, multicenter study, the Effects of sodium Management on the PP and oxidative stress IN hypertensive patients with chronic stroke (EMINENT) study. The aim of this study was to elucidate whether thiazide, administered in combination with an ARB, exerts more prominent antioxidant effects or more remarkably reduces PP without adverse effects in patients with a previous history of stroke.

Materials and Methods

Study subjects

This study was conducted at four hospitals participating in the EMINENT study group: Kyushu University Hospital, National Hospital Organization Fukuoka Higashi Medical Center, Seiai Rehabilitation Hospital and Imazu Red Cross Hospital. Patients who satisfied the following criteria were prospectively enrolled: an age between 20 and 75 years, a history of previous stroke occurring more than three months before registration and treatment with ARBs or angiotensin-converting enzyme inhibitors (ACEIs) for essential hypertension. The exclusion criteria were as follows: congestive heart failure (New York Heart Association class 2 or higher), a serum creatinine level of >2.0 mg/dL, a HbA1c level of $>8.0\%$, an alanine aminotransferase (ALT) level more than three times the normal upper limit, cardiovascular diseases, including stroke or myocardial infarction, diagnosed within three months before registration and current treatment with diuretics. Each institutional ethics committee approved the study protocol. Written informed consent was obtained from all subjects prior to enrollment.

Study protocol

The present study was conducted in accordance with the principles of the Declaration of Helsinki. This open-label, randomized, multicenter study consisted of a two-month screening period and subsequent six-month treatment period. At the beginning of the screening period, the prescribed ARB or ACEI was changed to treatment with 50 mg/day of losartan. At least two BP measurements were obtained over two months during the screening period. Patients whose baseline BP measurements remained over 140/90 mmHg af-

ter the screening period were randomly assigned to two groups: those in whom losartan was changed to a combination of fixed-dose losartan (50 mg) and hydrochlorothiazide (HCTZ, 12.5 mg) (diuretic group), and those in whom an antihypertensive drug other than an ARB, ACEI or diuretic was additionally administered (non-diuretic group). All antihypertensive drugs were allowed, except for ARBs, ACEIs and diuretics, when the BP exceeded 140/90 mmHg. The subjects' clinical symptoms, sitting BP, pulse rate and serum parameters, including the levels of potassium, uric acid, lipids, creatinine, glucose, HbA1c, high-sensitivity C-reactive protein (hs-CRP) and malondialdehyde-modified low-density lipoprotein (MDA-LDL), were evaluated three times, i.e., during the screening period and at the beginning and end of the treatment period.

Sixty-four patients were enrolled in this study. Among them, six patients refused to participate and two patients were excluded because their BP values declined to under 140/90 mmHg during the screening period. The remaining 56 patients were randomized to the two groups: 29 patients were assigned to the diuretic group and 27 patients were assigned to the non-diuretic group. We were unable to provide follow-up for one patient in the diuretic group because he did not return to the hospital. Ultimately, 55 patients (28 in the diuretic group and 27 in the non-diuretic group) were included in the analysis (Figure).

Statistical analysis

All data are expressed as the mean $\pm$ SD. The statistical analyses were performed using Student's *t*-test for continuous parameters and the chi-square test for categorical variables. Statistical significance was assumed for values of $p < 0.05$. The hs-CRP levels were changed to logarithmic values because they were not normally distributed.

Results

The baseline characteristics of the study population were summarized in Table 1. There were no significant differences in age, sex or the incidence of diabetes or dyslipidemia between the two groups. The systolic blood pressure (SBP), diastolic blood pressure (DBP), PP and heart rate values obtained after randomization were also not significantly different between the groups. Calcium antagonists were prescribed more often after randomization in the non-diuretic group.

The laboratory data at six months were not significantly different from those observed at baseline, except for the uric acid and HbA1c levels, both of which significantly increased at six months, although they did not exceed the upper normal limit in the diuretic group (Table 2). Meanwhile, the SBP values in the both groups and the DBP values in the diuretic group significantly decreased, whereas the DBP values in the non-diuretic group did not, from baseline to six months after randomization. The changes in the SBP and DBP values were not significantly different between the two

Figure. Trial profile**Table 1.** Baseline Characteristics in the Diuretic and Non-diuretic Groups

	Diuretic group n=28	Non-diuretic group n=27	p
Age, y	64±10	63±8	0.922
Male	23 (82%)	17 (63%)	0.196
Diabetes mellitus	4 (14%)	9 (33%)	0.179
Dyslipidemia	9 (32%)	13 (48%)	0.349
Antihypertensives with losartan after randomization			
Calcium antagonists	18 (64%)	25 (93%)	0.027
β-blockers	4 (14%)	1 (4%)	0.370
αβ-blockers	1 (4%)	3 (11%)	0.577
α-blockers	1 (4%)	4 (15%)	0.327
BMI, kg/m ²	25.5±4.7	24.2±3.2	0.240
SBP, mmHg	147±8	148±7	0.653
DBP, mmHg	80±9	75±12	0.077
Heart rate, /min	73±11	74±11	0.773
PP, mmHg	67±12	72±12	0.094
Hematocrit, %	42.7±5.1	41.0±3.3	0.163
Sodium, mEq/L	141±2	141±2	0.931
Potassium, mEq/L	4.0±0.4	4.2±0.3	0.065
Chloride, mEq/L	104±2	103±2	0.433
Uric acid, mg/dL	5.3±1.2	4.9±1.2	0.243
Creatinine, mg/dL	0.7±0.2	0.7±0.2	0.447
HbA1c, %	5.4±0.8	5.6±1.0	0.339
MDA-LDL, U/L	108±34	109±37	0.890
hs-CRP, μg/dL	1,629±2,679	943±907	0.213

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, PP: pulse pressure. HbA1c: hemoglobin A1c. MDA-LDL: malondialdehyde-modified low-density lipoprotein, hs-CRP: high-sensitivity C-reactive protein

groups. The PP also significantly decreased after randomization in both groups; however, the changes were not significantly different between the two groups. The expression of the oxidative stress marker, MDA-LDL, and the levels of hs-CRP were not significantly different at six months compared with those observed at baseline (Table 2).

In order to exclude the effects of differences in the rate of

calcium antagonist use between the two groups, we compared the PP and MDA-LDL values only in the patients who received calcium antagonists. Consequently, the mean PP in the diuretic group was 65±14 mmHg at baseline and 58±14 mmHg at six months ($p=0.161$, vs. 0 m), while that in the non-diuretic group was 71±12 mmHg at baseline and 60±11 mmHg at six months ($p=0.002$, vs. 0 m; $p=0.268$, diuretic vs. non-diuretic group in terms of the changes in the values from 0 to 6 m). In contrast, the MDA-LDL values at six months remained unchanged compared with those observed at baseline in both groups: the MDA-LDL values in the diuretic group and the non-diuretic group were 103±35 U/L and 111±38 U/L at baseline, respectively, and 118±54 U/L ($p=0.327$, vs. 0 m) and 107±38 U/L ($p=0.728$, vs. 0 m; $p=0.143$, diuretic vs. non-diuretic group in terms of the changes in the values from 0 to 6 m) at six months, respectively.

Discussion

In the present study, the addition of HCTZ to losartan did not result in any further evident antioxidant effects and the degree of PP reduction obtained with diuretics was not prominent compared with that achieved with non-diuretic antihypertensive drugs.

Pivotal clinical trials of antihypertensive treatment have shown that thiazide diuretics induce significant reductions in the risk of cardiovascular events (1, 2). Previous studies have also suggested that thiazide diuretics have antioxidant effects, which may contribute to the beneficial effects of these drugs noted in patients with cardiovascular disease (11, 12). Although we hypothesized that HCTZ has more potent antioxidant effects than other non-diuretic anti-

Table 2. Changes in Blood Pressure, Heart Rate and Serum Parameters after Treatment with Diuretic or Non-diuretic Antihypertensive Drugs

	Diuretic group			Non-diuretic group			
	0 m	6 m	p*	0 m	6 m	p*	p [†]
SBP, mmHg	147±8	133±12	<0.001	148±7	134±10	<0.001	0.911
DBP, mmHg	80±9	75±10	0.015	75±11	73±8	0.157	0.265
Heart rate, /min	73±11	72±10	0.791	74±11	74±10	0.886	0.886
PP, mmHg	67±12	58±12	<0.001	72±12	61±12	<0.001	0.452
Hematocrit, %	42.7±5.1	42.1±5.4	0.330	41.0±3.3	40.9±3.3	0.843	0.583
Sodium, mEq/L	141±2	140±4	0.563	141±2	140±2	0.217	0.985
Potassium, mEq/L	4.0±0.4	4.0±0.3	0.594	4.2±0.3	4.1±0.3	0.181	0.416
Chloride, mEq/L	104±2	102±4	0.042	103±2	104±2	0.656	0.056
Uric acid, mg/dL	5.3±1.2	6.0±1.0	<0.001	4.9±1.2	4.8±1.3	0.503	<0.001
Creatinine, mg/dL	0.7±0.2	0.8±0.2	0.211	0.7±0.2	0.7±0.2	0.505	0.590
HbA1c, %	5.4±0.8	5.6±0.7	0.008	5.6±1.0	5.7±0.9	0.205	0.421
MDA-LDL, U/L	108±34	117±54	0.259	109±37	105±39	0.596	0.237
Log hs-CRP, µg/dL	2.87±0.51	2.95±0.49	0.272	2.81±0.38	2.87±0.42	0.475	0.852

SBP: systolic blood pressure, DBP: diastolic blood pressure, PP: pulse pressure, HbA1c: hemoglobin A1c, MDA-LDL: malondialdehyde-modified low-density lipoprotein, hs-CRP: high-sensitivity C-reactive protein. The values of hs-CRP were transformed into logarithmic values.

p*: 0 vs. 6 m, p[†]: Diuretic vs. Non-diuretic group in change of each values from 0 to 6 m.

hypertensive drugs, the superiority of HCTZ in terms of its antioxidant effects was not evident in this study. One possible reason for this finding is that the antioxidant effects of different thiazide diuretics might not be the same. For example, chlorthalidone and indapamide have been shown to have more potent antioxidant effects than other thiazides (11, 12). Another report showed that HCTZ does not significantly decrease the erythrocyte MDA concentrations in hypertensive patients (13). Another reason may be that antihypertensive drugs, such as ARBs, calcium antagonists, β -blockers and α -blockers, themselves have an antioxidant effect (14-17) that possibly obscures the antioxidant effects of thiazide diuretics. Since the rate of calcium antagonist use differed between the two groups in the current study, we additionally performed a sensitivity analysis of the patients who received calcium antagonists. However, the results remained unchanged, indicating that the different rate of calcium antagonist use did not affect the outcomes. Based on these findings, the antioxidant effects of HCTZ may be minor.

The PP is a strong independent predictor of cardiovascular risk in hypertensive patients. A previous report demonstrated that HCTZ reduces the PP values more significantly than captopril, atenolol, clonidine, diltiazem or prazosin after one year of treatment (6). Considering these data, HCTZ is expected to reduce the PP more potently than non-diuretic antihypertensive drugs. In the present study, both the HCTZ and non-diuretic groups showed a decrease in PP after treatment; however, no significant differences were observed between the two groups. The mechanism of PP reduction is thought to involve the normalization of arterial stiffness and wall thickness (18). A longer observation period may be needed to detect morphological changes in the vessel wall with subsequent reductions in PP, as previous studies have mostly observed such effects after one year (5, 6).

Previous reports have also shown that combination treatment with losartan/HCTZ safely and steadily reduces the BP (19-21) and improves the quality of life in patients with

uncontrolled hypertension (21). Furthermore, in patients with symptomatic internal carotid artery or middle cerebral artery steno-occlusive disease, this drug regimen also safely lowers the BP without worsening the cerebral hemodynamics (22). In the current study, no adverse events were observed over six months of treatment in the losartan/HCTZ group. A longer follow-up period may be needed in order to assess the safety of losartan/HCTZ in chronic stroke patients.

The present study is associated with some limitations. First, the sample size was small. Patient recruitment was likely stopped before the number of enrolled patients reached a sufficient sample size. Although it was difficult to estimate the mean and standard deviation of the PP and MDL-LDL before the start of the study, the required sample size is expected to be at least twice the size of that used in the present study in order to detect differences in PP and MDA-LDL with 80% statistical power and a level of significance of 5%. Therefore, the possibility of a type I or II error cannot be excluded. Furthermore, other confounding factors that may alter the degree of oxidative stress, such as smoking and vitamin supplementation, were not evaluated, and we measured only the level of MDL-LDL as an oxidative stress marker. Although the MDL-LDL level is a commonly used and reliable marker, there are many useful oxidative stress markers. The use of measurements of other oxidative stress markers, such as 8-iso-prostaglandin F2 α (8-iso-PGF2 α), 8-hydroxy-2'-deoxyguanosine (8-OHdG) and thiobarbituric acid reactive substances (TBARS), and adjustment for possible confounding factors related to oxidative stress would have strengthened our conclusions. Since the present study provided preliminary results based on data for a limited number of patients, further studies with larger sample sizes are thus needed to clarify the additional effects of losartan/HCTZ beyond the blood pressure-lowering actions of these drugs.

Author's disclosure of potential Conflicts of Interest (COI).

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