ORIGINAL ARTICLE

Efficacy and Safety Compared between Chlorthalidone and Hydrochlorothiazide for Reducing Systolic and Diastolic Blood Pressure in Patients with Mild-to-Moderate Hypertension: A Randomized Clinical Trial

Rungroj Krittayaphong, MD[1], Sirichai Jamnongprasatporn, MD[1], Weranuj Roubsanthisuk, MD[2], Sirisawat Kunanon, MD[2], Chavalit Chotruangnapa, MD[2], Poom Sairat, MSc[1]

[1] Division of Cardiology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; [2] Division of Hypertension, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Objective: Hypertension is the leading cause of morbidity and mortality, and blood pressure (BP) control is shown to reduce the risk of cardiovascular events. The present study aimed to investigate the efficacy and safety of chlorthalidone and hydrochlorothiazide for reducing systolic and diastolic BP in patients with mild-to-moderate hypertension.

Materials and Methods: The present study was a randomized clinical trial. Patients 18 years or older with mild-to-moderate hypertension with or without prior antihypertensive medications were enrolled. Patients were randomly assigned to the chlorthalidone or hydrochlorothiazide group. The dose of study medication could be up-titrated at the 6-week. The primary outcomes were the reduction in systolic and diastolic BP, the rate of office BP control at 12 weeks, and the rate of adverse events.

Results: Fifty-six patients (mean age of 49.8±11.1 years) and 42.9% male, were included. Forty-three patients (76.8%) had known hypertension. Mean sitting office systolic BP (SBP) and diastolic BP (DBP) at baseline was 153.2±9.6 and 91.8±9.2 mmHg, respectively. The average daily dose of chlorthalidone and hydrochlorothiazide was 16.1±5.8 and 32.4±11.6 mg. The mean reduction in SBP in the chlorthalidone and hydrochlorothiazide groups was 28.7±12.2 and 22.8±13.7 mmHg (p=0.118), and DBP was 14.4±7.5 and 9.1±6.6 mmHg (p=0.011), respectively. The rate of office BP control was significantly greater in the chlorthalidone group at 91.7% versus 61.5% (p=0.013). There was no significant difference in the rate of adverse events between the groups.

Conclusion: Chlorthalidone was shown to be more effective than hydrochlorothiazide for office BP control. There was no difference in adverse events.

Trial registration: The trial had been registered with the Thai Clinical Trials Registry (TCTR) which complied with WHO International Clinical Trials Registry Platform dataset. The registration number was TCTR20191006002 (06/10/2019).

Keywords: Efficacy; Safety; Chlorthalidone; Hydrochlorothiazide; Reducing; Systolic and diastolic blood pressure; Patients with mild to moderate hypertension

Received 31 January 2023 | Revised 10 March 2023 | Accepted 14 March 2023

J Med Assoc Thai 2023;106(5):451-9

Website: http://www.jmatonline.com

Hypertension is the leading cause of morbidity and mortality[1]. Treatment of hypertension has been shown to reduce the risk of cardiovascular event[2]. Intensive blood pressure (BP) control had a better outcome than less intensive treatment[3,4]. The American College of Cardiology (ACC) 2017, Hypertension Guideline classify patients with office BP of 130/80 mmHg or more as hypertension[5], whereas the European Society of Cardiology (ESC) 2018, Hypertension Guideline suggest the diagnostic threshold of 140/90 mmHg[6]. Whenever treated, the target office BP should be less than 130/80 mmHg[5,6]. Choices of medication are calcium channel blockers (CCB), angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blocker (ARB), beta-blockers, and diuretics[5,6]. Systematic review and meta-analysis have shown that there were no significant differences in the effect of medications in different drug class on the cardiovascular outcomes

Correspondence to:

Krittayaphong R.

Division of Cardiology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkoknoi, Bangkok 10700, Thailand.

Phone: +66-2-4196104, **Fax**: +66-2-4127412

Email: rungroj.kri@mahidol.ac.th

How to cite this article:

Krittayaphong R, Jamnongprasatporn S, Roubsanthisuk W, Kunanon S, Chotruangnapa C, Sairat P. Efficacy and Safety Compared between Chlorthalidone and Hydrochlorothiazide for Reducing Systolic and Diastolic Blood Pressure in Patients with Mild-to-Moderate Hypertension: A Randomized Clinical Trial. J Med Assoc Thai 2023;106:451-9.

DOI: 10.35755/jmedassocthai.2023.05.13768

of patients with hypertension[7].

Diuretics have been used for the treatment of hypertension for decades[8]. The Joint National Committee (JNC) recommended hydrochlorothiazide (HCTZ) as the first line agent for the treatment of hypertension since 1977[9]. HCTZ is one of the most commonly used drugs for the treatment of hypertension. The report from the National Health and Nutrition Examination Survey indicated that the rate of HCTZ use was increased but not as much as angiotensin receptor blockers among hypertensive patients[10]. The rate of HCTZ use in Asian was not as high as in the United States and the trend was decreased[11]. Clinical trials used to support the benefit of thiazide-like diuretic were based on the study using chlorthalidone[12-15]. HCTZ had no evidence for the reduction of cardiovascular events. Despite the fact that hypertension guidelines[5,16,17] favored thiazide-like diuretic such as chlorthalidone over HCTZ for the treatment of hypertension, the prescription rate of chlorthalidone was markedly lower than HCTZ in clinical practice[18]. Besides, there were differences in the rate relation of hypertension and cardiovascular outcome of Asian and non-Asian population[19]. The associations of systolic BP (SBP) and diastolic BP (DBP) to stroke was stronger in Asian compared to non-Asians.

The primary objective of the present study was to compare the efficacy in office SBP and DBP reduction and the rate of hypertension control between chlorthalidone and HCTZ in patients with mild to moderate hypertension. The secondary objective was to compare the efficacy in home SBP and DBP reduction and the rate of adverse events between the two agents.

Materials and Methods

Study population

The authors studied male or female aged 18 years or older with mild to moderate hypertension from the out-patient clinic of internal medicine department between February 2020 and March 2021. The patients could be newly diagnosed or known hypertension with or without antihypertensive medication(s) who elevated mean sitting office SBP was 140 mmHg or more or DBP was 90 mmHg or more. The exclusion criteria were 1) mean sitting office SBP of 180 mmHg or more or DBP of 110 mmHg or more, 2) known secondary hypertension, 3) currently use of diuretics, 4) elevated alanine transferase (ALT) of two times or more than two times above upper normal limit, 4) elevated serum creatinine of 1.5 mg/dL or more, 5) current participation in drug trial within one month, 6) pregnancy or lactation or child bearing potential, 7) cannot come for follow-up, and 8) history of gout or uric acid level above 10 mg/dL. The present study was approved by the Ethical Committee of Siriraj Hospital, Mahidol University (Si. 554/2019. All patients gave written informed consents prior to participation. All methods were conducted in accordance with the principles set forth in the Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice Guidelines. The clinical trial registration number of the present study was TCTR20191006002.

Study protocol

Office BP was measured in sitting position at least five minutes after rest using validated automated upper-arm-cuff devices. The average of the three records of SBP and DBP was used in the present study.

Patients were instructed to measure their BP at home using validated automated upper-arm-cuff devices. The measurement schedule was two days before study drug initiation and two days before each study visit. In each day, the measurement was performed twice in the morning and twice before going to bed, both after five minutes rest and one minute interval between each measurement. The average values were used in analyses.

Patients were randomized into two groups as parallel groups design with 1:1 ratio, by the computer generation of randomization number (NQuery Advisor 6.01 program, Statistical Solutions Ltd., Cork, Ireland) for chlorthalidone and HCTZ with the block of four strategy. A research assistant generated the random allocation sequence. A study nurse enrolled participants and assigned participants to the interventions. The study nurse who measured BP and the physician who examined the patients were blinded to the randomization group. Starting dose of chlorthalidone and HCTZ was 12.5 and 25 mg/day, respectively. Patients were followed-up at six and 12 weeks. If the BP was not at the target of lower than 140/90 mmHg at six weeks, the study drugs were up titrated to chlorthalidone 25 mg/day or HCTZ 50 mg/day, respectively. Study protocol is shown in Figure 1. Any possible adverse events were recorded during the follow-up visits. In case of adverse events, physician judged whether the study drugs needed to be discontinued.

Metabolic profiles, liver and renal function, electrolyte and uric acid were tested at baseline and at

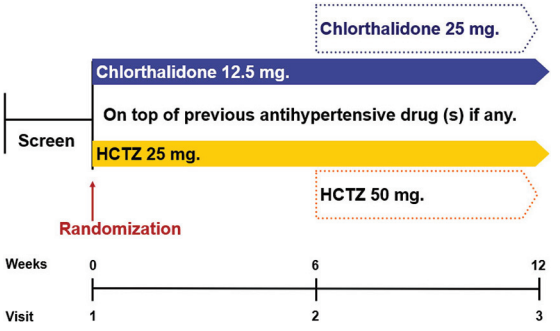

Figure 1. A horizontal flow diagram of the study enrollment, intervention randomization, and follow-up protocol.

HCTZ=hydrochlorothiazide

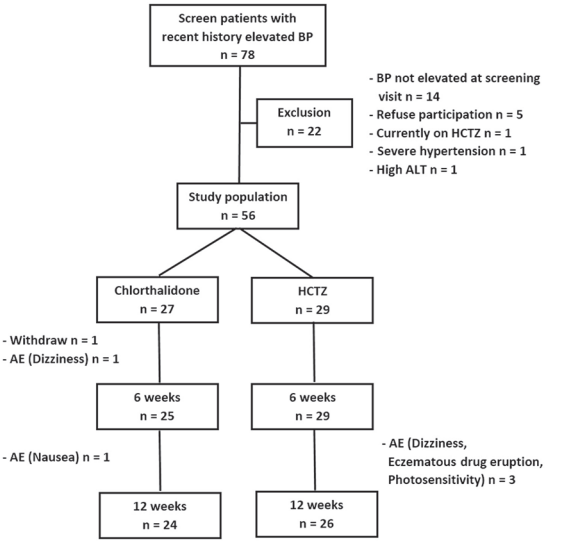

Figure 2. The flow of patients in this study.

BP=blood pressure; HCTZ=hydrochlorothiazide; ALT=alanine aminotransferase; AE=adverse events

12 weeks. The following parameters were collected, fasting plasma glucose, total cholesterol, triglyceride, high density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol, alanine aminotransferase (ALT), serum creatinine, sodium, potassium, and uric acid levels.

Outcomes

Primary outcomes of the study were 1) the reduction in systolic and diastolic BP and the rate of patients who had office BP under control defined as less than 140/90 mmHg at 12 weeks and 2) rate of adverse effect, the changes in laboratory findings.

Statistical analysis

Continuous data were described as mean ± standard deviation (SD) and compared by the student t-test for the unpaired data. Categorical variables were described as count (percentages) and compared by the chi-square test. All data were recorded in the web-based system. The required data were validated by double entry of the data. The primary outcome on difference of rate of BP control between chlorthalidone and HCTZ was analyzed by the chi-square test. The reduction in office SBP and DBP from baseline between the two groups was compared by the student t-test for the unpaired data. The comparison of BP data at baseline, six weeks, and 12 weeks were performed by repeated measure ANOVA with within group and between group p-value. A p-value of less than 0.05 was considered statistically significant. A sample size of 24 should give power of 0.80 to detect a difference in mean change of 5 mm Hg or more in SBP between the two treatments at the 0.05 significance level, assuming a standard deviation for mean SBP change of 6 mm Hg. Oversample was planned by 10% thus, at least 27 patients were required in case dropouts occurred. The trial ended after achieving target samples.

Results

Study population

The authors studied 56 patients. There were 24 male (42.9%) and 32 female (57.1%) with the average age of 49.8±11.1 years. Twenty-seven patients were randomized to chlorthalidone, and 29 patients were randomized to HCTZ. Forty-three patients (76.8%) were known to have hypertension. Mean sitting office SBP and DBP at baseline were 153.2±9.6 and 91.8±9.2 mmHg, respectively. Baseline characteristics are shown in Table 1. Thirty-eight patients (67.9%) failed to achieve target BP with at least antihypertensive agent including beta-blocker, diuretic, angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and non-dihydropyridine CCB. There were no significant differences in baseline characteristics between patients with chlorthalidone and HCTZ. Figure 2 shows the flow of study population.

Efficacy data

Average dose of chlorthalidone and HCTZ was 16.1±5.8 and 32.4±11.6 mg/day, respectively. Twenty-four patients (88.9%) with chlorthalidone could tolerate the study drug at the last visit, compared to 26 patients (89.7%) who could tolerate HCTZ, (p=0.926). Data on BP at baseline, six, and 12 weeks

Table 1. Baseline characteristics of all study subjects and compared between the chlorthalidone and HCTZ groups

Characteristics	All (n=56)	Chlorthalidone (n=27)	HCTZ (n=29)	p-value
Male; n (%)	24 (42.9)	14 (51.9)	10 (34.5)	0.189
Age (years); mean±SD	49.8±11.1	50.8±11.6	49.0±10.6	0.545
Height (cm); mean±SD	163.2±9.4	165.0±10.0	161.5±8.7	0.174
Weight (kg); mean±SD	76.1±16.9	76.5±17.4	75.7±16.7	0.874
Body mass index (kg/m^2); mean±SD	28.4±5.0	27.8±4.3	28.9±5.6	0.394
Newly diagnosed hypertension; n (%)	13 (23.2)	4 (14.8)	9 (31.0)	0.151
Known hypertension; n (%)	43 (76.8)	23 (85.2)	20 (69.0)	0.151
Use of antihypertensive agent; n (%)	38 (67.9)	20 (74.1)	18 (62.1)	0.336
1 agent	19 (33.9)	12 (44.4)	7 (24.1)	0.109
2 agents	14 (25.0)	7 (25.9)	7 (24.1)	0.877
3 agents	4 (7.1)	1 (3.7)	3 (10.3)	0.335
4 agents	1 (1.8)	0 (0.0)	1 (3.4)	0.330
Class of antihypertensive agents; n (%)				
ACE inhibitor	14 (25.0)	8 (29.6)	6 (20.7)	0.440
ARB	14 (25.0)	6 (22.2)	8 (27.6)	0.643
Beta blocker	9 (16.1)	4 (14.8)	5 (17.2)	0.805
Hydralazine	1 (1.8)	0 (0.0)	1 (3.4)	0.330
Calcium channel blocker	25 (44.6)	11 (40.7)	14 (48.3)	0.571
Current smoker; n (%)	3 (5.4)	2 (7.4)	1 (3.4)	0.605
Diabetes mellitus; n (%)	14 (25.0)	6 (22.2)	8 (27.6)	0.643
Hypercholesterolemia; n (%)	24 (42.9)	10 (37.0)	14 (48.3)	0.396

HCTZ=hydrochlorothiazide; ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; SD=standard deviation

A p-value <0.05 indicates statistical significance

are shown in Figure 3. Patients in both groups had a significant reduction in office SBP and DBP at six weeks (p<0.001 for both chlorthalidone and HCTZ), and 12 weeks (p<0.001 for both chlorthalidone and HCTZ) after treatment compared to baseline. Office SBP and DBP at 12 weeks was significantly lower in chlorthalidone compared to HCTZ (Figure 3). The reduction in office SBP in chlorthalidone group had a trend in favor of chlorthalidone and the reduction in office DBP was significantly greater in chlorthalidone compared to HCTZ (Figure 4A). The rate of BP control as defined by office SBP of less than 140 mmHg and DBP of less than 90 mmHg was greater for chlorthalidone group compared to HCTZ group at 91.7% versus 61.5% (p=0.013) (Figure 4B).

Baseline home BP was not significant different between the two groups (p=0.900 for SBP and p=0.421 for DBP) (Figure 5). There was significant reduction in home BP in both groups at six weeks (p<0.001 for chlorthalidone and p=0.001 for HCTZ for SBP and p<0.001 both groups for DBP), and at 12 weeks (p<0.001 for SBP and DBP for chlorthalidone and p=0.011 for SBP and DBP for HCTZ). The chlorthalidone group had significantly lower home DBP at 12 weeks (p=0.048).

Safety data

Two patients (8.0%) in the chlorthalidone group including one with dizziness and one with nausea and two (6.9%) in the HCTZ group including one with eczema and one with photosensitivity had adverse events (p=0.877). Adverse effects causing drug discontinuation occurred in one patient in the chlorthalidone group and two patients in the HCTZ group. Table 2 shows laboratory results at baseline, 12 weeks, and change of 12 weeks compared to baseline for both groups. There were no significant differences in the laboratory findings between the two groups.

Discussion

The present study was a randomized clinical study. The authors compared the effect of chlorthalidone and HCTZ on the control rate of hypertension in patients with mild to moderate hypertension with or without prior treatment. The results demonstrated that chlorthalidone had a better control rate of BP compared to HCTZ. Both agents are effective in reducing in SBP and DBP at six weeks. Chlorthalidone had a better efficacy in DBP reduction compared to HCTZ and had a trend toward a better reduction in SBP as well.

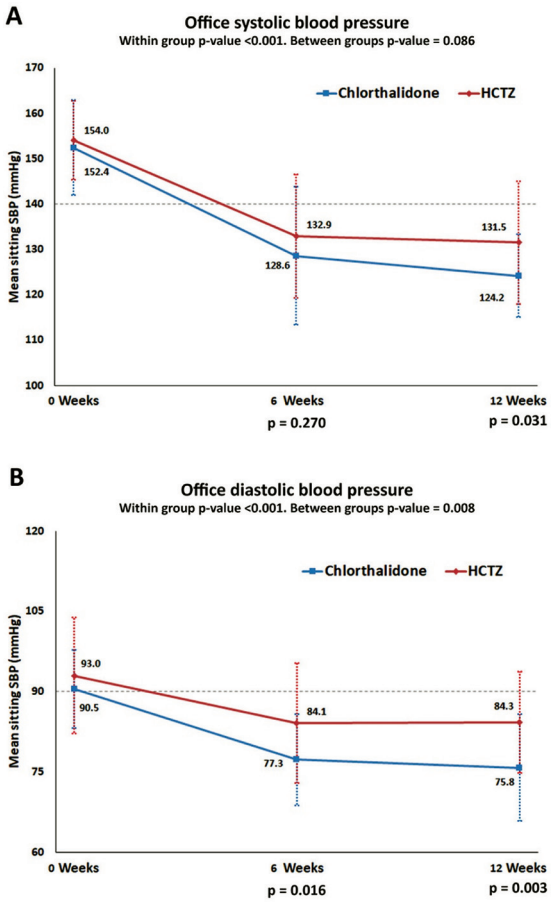

Figure 3. Office systolic blood pressure (A) and diastolic blood pressure (B) at baseline, 6 weeks, and 12 weeks compared between the chlorthalidone and HCTZ groups.

SBP=systolic blood pressure; DBP=diastolic blood pressure; HCTZ=hydrochlorothiazide

Error bars indicate standard deviation

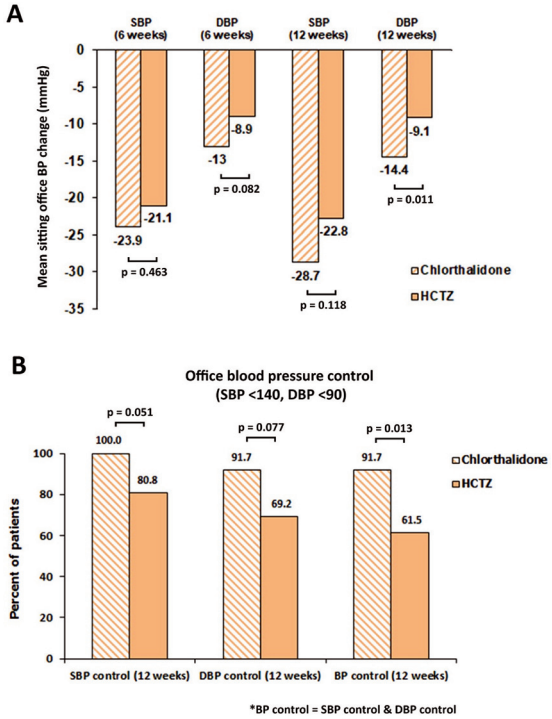

Figure 4. Reduction in mean office SBP and DBP at 6 weeks and 12 weeks compared between the chlorthalidone and HCTZ groups (A). Rate of office SBP control, DBP control, and BP control at 12 weeks compared between the chlorthalidone and HCTZ groups (B).

SBP=systolic blood pressure; DBP=diastolic blood pressure; HCTZ=hydrochlorothiazide; BP=blood pressure

Several clinical trials used to support the benefit of thiazide-like diuretic were based on the study using chlortalidone such as the Hypertension Detection and Follow-up Program (HDFP)[12], Multiple Risk Factor Intervention Trial (MRFIT)[13], Systolic Hypertension in the Elderly Program (SHEP)[14], and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[15]. The ALLHAT study concluded that chlorthalidone was more effective than amlodipine and lisinopril in the reduction of SBP[15]. HCTZ had no evidence for the reduction of cardiovascular events. Meta-analysis and systematic review have demonstrated that chlorthalidone was more effective than HCTZ in the reduction of BP[20] and cardiovascular events[21]. A recent meta-analysis also confirmed that chlorthalidone is superior to HCTZ in terms of BP reduction with a similar safety profile[22]. Hypertension guidelines such as the National Clinical Guideline Centre (NICE)[16], the ACC[5], and the Canadian guideline[17] encouraged the use of thiazide-like diuretic such as chlorthalidone over HCTZ for the treatment of hypertension due to the existence of evidence-based data from the previous clinical trials[12-15]. The results of the present study demonstrated that chlorthalidone had a better BP control compared to HCTZ, which supported results of the previous data[20,22]. Regarding the extent of SBP reduction, a previous meta-analysis showed that chlorthalidone and HCTZ had a SBP reduction on the average of 26 and 17 mmHg, respectively[20]. The SBP reduction in the present study was 28.7 and 22.8 mmHg for chlorthalidone and HCTZ groups.

Both HCTZ and chlorthalidone have an adverse effect on electrolyte imbalance and may increase uric acid level[13]. Results from meta-analysis demonstrated that the occurrence of hypokalemia or hyperuricemia was not different between chlorthalidone and HCTZ[20,22]. The mean reduction of serum potassium

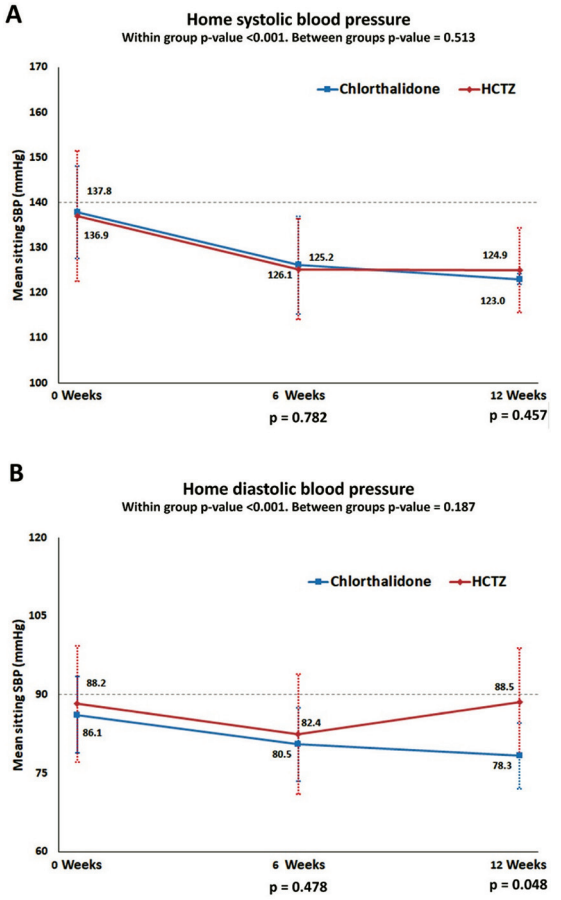

Figure 5. Home systolic blood pressure (A) and diastolic blood pressure (B) at baseline, 6 weeks, and 12 weeks compared between the chlorthalidone and HCTZ groups.

SBP=systolic blood pressure; DBP=diastolic blood pressure; HCTZ=hydrochlorothiazide

Error bars indicate standard deviation

was 0.45 and 0.36 mEq/L for chlorthalidone and HCTZ, respectively[20], which was not statistically significant. The result of the present study showed that serum potassium decreases by 0.3 and 0.2 mEq/L in chlortalidone and HCTZ, respectively, (p=0.825). Likewise, the increase in serum uric acid level was 1.3 and 1.2 mg/dL for chlortalidone and HCTZ groups, respectively (p=0.930).

Despite the similar structure, chlorthalidone and HCTZ had quite dissimilar pharmacokinetic profiles[23]. Chlorthalidone is a thiazide like diuretic that has a longer half-life than HCTZ[24]. It has been shown to have beneficial effect on the endothelial function and oxidative stress[25] and decrease platelet aggregation[26]. Despite a previous study that showed a better lipid and sugar profile in chlorthalidone group as compared to HCTZ group[13], this finding cannot be demonstrated in the present study. Moreover, chlorthalidone has been shown to be able to restore nighttime BP dip better than HCTZ[27]. Nighttime BP related to cardiovascular event more than daytime BP[28]. Most importantly, chlorthalidone, but not HCTZ, has been shown to have impact on cardiovascular outcomes in clinical studies[12-15].

Despite a better efficacy and better profiles of chlorthalidone compared to HCTZ, the rate of chlorthalidone use remains low[18]. The use may be even lower in developing countries, many of which are in Asia[29]. The limited use of antihypertensive medications in developing countries may be related to the national essential medication listing policy[29]. Not only the high-cost medication, but also the policy emphasizes the limited items of medication in the similar class. Chlorthalidone and HCTZ have been considered as medication in a similar class, therefore, most countries have a more widely use of HCTZ, and chlorthalidone is not considered in the national essential medication list. The World Health Organization (WHO) provides guidelines for national essential drug list[30,31] and chlorthalidone has been recommended together with HCTZ as diuretics for the treatment of hypertension[29]. Overall, among 53 countries, HCTZ was in the national essential medication list in 89% and chlorthalidone was in the list of only 11%[29].

Limitation

The present study had limitations. First the study medication was not blinded. However, this should not affect the results of the study. Second, the present study aimed at the BP control by definition of office SBP of less than 140 and DBP of less than 90 mmHg. Recent guidelines recommended that target office BP should be less than 130/80 mmHg[5,6]. In the present study, if using the definition of office BP control at less than 130/80 mmHg, the rate of office BP control would be 45.8% and 19.2% for chlorthalidone and HCTZ (p=0.044), respectively. The applicability of the results of the present study is based on the population who fitted in the selection criteria of the study population.

Conclusion

Chlorthalidone has been shown to be more effective than HCTZ for BP control in patients with mild-to-moderate hypertension. Additionally, no significant difference in adverse events was observed between the groups.

Table 2. Laboratory data at baseline, at 12 weeks, and the difference between baseline and 12 weeks among all patients and compared between the chlorthalidone and HCTZ groups

Data	All; mean±SD	Chlorthalidone; mean±SD	HCTZ; mean±SD	p-value
Baseline	(n=56)	(n=27)	(n=29)	
Fasting plasma glucose (mg/dL)	107.7±44.6	105.2±37.1	110.1±51.1	0.684
Total cholesterol (mg/dL)	189.3±35.0	190.2±38.5	188.5±32.1	0.858
Triglyceride (mg/dL)	159.1±119.8	163.9±113.1	154.6±127.5	0.774
HDL-cholesterol (mg/dL)	54.1±15.7	50.6±14.1	57.4±6.6	0.107
LDL-cholesterol (mg/dL)	105.5±28.6	108.2±29.9	103.01±27.75	0.506
ALT (U/L)	28.41±17.67	27.56±16.97	29.2±18.6	0.730
Creatinine (mg/dL)	0.8±0.2	0.8±1.9	0.8±0.2	0.460
Uric acid (mg/dL)	5.8±1.5	5.7±1.2	5.8±1.7	0.744
Sodium (mEq/L)	139.8±2.0	140.0±1.9	139.6±2.2	0.448
Potassium (mEq/L)	4.0±0.4	4.0±0.4	3.9±0.3	0.251
12-week follow-up	(n=50)	(n=24)	(n=26)	
Fasting plasma glucose (mg/dL)	122.2±58.1	123.7±56.6	120.8±60.4	0.860
Total cholesterol (mg/dL)	186.8±33.9	188.7±34.5	185.0±33.9	0.710
Triglyceride (mg/dL)	174.4±98.8	177.4±99.2	171.6±100.2	0.838
HDL-cholesterol (mg/dL)	51.0±13.1	48.0±11.5	53.7±14.1	0.126
LDL-cholesterol (mg/dL)	102.0±30.9	105.8±31.2	98.5±30.7	0.867
ALT (U/L)	28.0±16.7	32.3±20.2	24.1±11.6	0.091
Creatinine (mg/dL)	0.9±0.2	0.9±0.2	0.9±0.3	0.502
Uric acid (mg/dL)	7.0±1.9	6.9±1.5	7.1±2.2	0.713
Sodium (mEq/L)	139.5±2.5	139.3±2.7	139.6±2.4	0.735
Potassium (mEq/L)	3.7±0.5	3.7±0.6	3.7±0.4	0.958
Change from baseline to 12 weeks	(n=50)	(n=24)	(n=26)	
Fasting plasma glucose (mg/dL)	16.1±23.0	17.7±27.9	14.6±17.7	0.639
Total cholesterol (mg/dL)	−0.6±19.5	2.6±18.6	−3.6±20.2	0.268
Triglyceride (mg/dL)	14.9±92.4	14.7±59.5	15.1±116.1	0.988
HDL-cholesterol (mg/dL)	−2.0±6.8	−1.0±5.8	−2.9±7.6	0.332
LDL-cholesterol (mg/dL)	−2.8±18.5	−0.2±18.6	−5.3±18.5	0.332
ALT (U/L)	−0.3±13.2	3.4±12.3	−3.7±13.2	0.055
Creatinine (mg/dL)	0.1±0.1	0.1±0.1	0.10±0.09	0.906
Uric acid (mg/dL)	1.3±1.1	1.3±1.0	1.2±1.1	0.930
Sodium (mEq/L)	−0.4±2.6	−0.7±2.8	−0.1±2.5	0.429
Potassium (mEq/L)	−0.3±0.5	−0.3±0.5	−0.2±0.5	0.825

HCTZ=hydrochlorothiazide; HDL=high-density lipoprotein; LDL=low-density lipoprotein; ALT=alanine aminotransferase; SD=standard deviation

A p-value <0.05 indicates statistical significance

What is already known on this topic?

Diuretic is one of the medications recommended for the treatment of hypertension. Choice of diuretics may be HCTZ or thiazide-like diuretics such as chlorthalidone.

What this study adds?

Chlorthalidone had a better reduction of diastolic BP and a better BP control at 12 weeks compared to HCTZ.

Funding disclosure

This study was funded by an unrestricted grant from the Berlin Pharmaceutical Industry Company Limited. The funding source had no influence in any aspect of this study or the decision of the authors to submit this manuscript for publication.

Conflicts of interest

The authors declare conflict of interest.

References

1. Zhou D, Xi B, Zhao M, Wang L, Veeranki SP. Uncontrolled hypertension increases risk of all-cause and cardiovascular disease mortality in US adults: the NHANES III Linked Mortality Study. Sci Rep

2018;8:9418.
2. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension. 1. Overview, meta-analyses, and meta-regression analyses of randomized trials. J Hypertens 2014;32:2285-95.
3. Xie X, Atkins E, Lv J, Bennett A, Neal B, Ninomiya T, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet 2016;387:435-43.
4. Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103-16.
5. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;71:e127-248.
6. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;39:3021-104.
7. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016;387:957-67.
8. Krakoff LR. Diuretics for hypertension. Circulation 2005;112:e127-9.
9. Report of the joint national committee on detection, evaluation, and treatment of high blood pressure. A cooperative study. JAMA 1977;237:255-61.
10. Gu Q, Burt VL, Dillon CF, Yoon S. Trends in antihypertensive medication use and blood pressure control among United States adults with hypertension: the National Health And Nutrition Examination Survey, 2001 to 2010. Circulation 2012;126:2105-14.
11. Jung M, Choo E, Lee S. Comprehensive trends and patterns of antihypertensive prescriptions using a nationwide claims database in Korea. Clin Epidemiol 2020;12:963-75.
12. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the hypertension detection and follow-up program. III. Reduction in stroke incidence among persons with high blood pressure. JAMA 1982;247:633-8.
13. Dorsch MP, Gillespie BW, Erickson SR, Bleske BE, Weder AB. Chlorthalidone reduces cardiovascular events compared with hydrochlorothiazide: a retrospective cohort analysis. Hypertension 2011;57:689-94.
14. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991;265:3255-64.
15. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. JAMA 2002;288:2981-97.
16. National Clinical Guideline Centre. National Institute for Health and Clinical Excellence: Guidance. Hypertension: The clinical management of primary hypertension in adults: Update of clinical guidelines 18 and 34. London: Royal College of Physicians (UK); 2011.
17. Leung AA, Daskalopoulou SS, Dasgupta K, McBrien K, Butalia S, Zarnke KB, et al. Hypertension Canada's 2017 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults. Can J Cardiol 2017;33:557-76.
18. McNally RJ, Morselli F, Farukh B, Chowienczyk PJ, Faconti L. A review of the prescribing trend of thiazide-type and thiazide-like diuretics in hypertension: A UK perspective. Br J Clin Pharmacol 2019;85:2707-13.
19. Eastwood SV, Tillin T, Chaturvedi N, Hughes AD. Ethnic differences in associations between blood pressure and stroke in South Asian and European Men. Hypertension 2015;66:481-8.
20. Ernst ME, Carter BL, Zheng S, Grimm RH Jr. Meta-analysis of dose-response characteristics of hydrochlorothiazide and chlorthalidone: effects on systolic blood pressure and potassium. Am J Hypertens 2010;23:440-6.
21. Roush GC, Holford TR, Guddati AK. Chlorthalidone compared with hydrochlorothiazide in reducing cardiovascular events: systematic review and network meta-analyses. Hypertension 2012;59:1110-7.
22. Dineva S, Uzunova K, Pavlova V, Filipova E, Kalinov K, Vekov T. Comparative efficacy and safety of chlorthalidone and hydrochlorothiazide-meta-analysis. J Hum Hypertens 2019;33:766-74.
23. Kurtz TW. Chlorthalidone: don't call it "thiazide-like" anymore. Hypertension 2010;56:335-7.
24. Sica DA. Chlorthalidone - a renaissance in use? Expert Opin Pharmacother 2009;10:2037-9.
25. Dell'Omo G, Penno G, Del Prato S, Pedrinelli R. Chlorthalidone improves endothelial-mediated vascular responses in hypertension complicated by nondiabetic metabolic syndrome. J Cardiovasc Pharmacol Ther 2005;10:265-72.
26. Woodman R, Brown C, Lockette W. Chlorthalidone decreases platelet aggregation and vascular permeability and promotes angiogenesis. Hypertension 2010;56:463-70.
27. Ernst ME, Carter BL, Goerdt CJ, Steffensmeier JJ, Phillips BB, Zimmerman MB, et al. Comparative antihypertensive effects of hydrochlorothiazide

and chlorthalidone on ambulatory and office blood pressure. Hypertension 2006;47:352-8.
28. Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, et al. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. Hypertension 2005;46:156-61.
29. Husain MJ, Datta BK, Kostova D, Joseph KT, Asma S, Richter P, et al. Access to cardiovascular disease and hypertension medicines in developing countries: An analysis of essential medicine lists, price, availability, and affordability. J Am Heart Assoc 2020;9:e015302.
30. Laing R, Waning B, Gray A, Ford N, t Hoen E. 25 years of the WHO essential medicines lists: progress and challenges. Lancet 2003;361:1723-9.
31. Ewen M, Zweekhorst M, Regeer B, Laing R. Baseline assessment of WHO's target for both availability and affordability of essential medicines to treat non-communicable diseases. PLoS One 2017;12:e0171284.