Amlodipine and Hydrochlorothiazide for Isolated Systolic Hypertension in the Thai Elderly

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ABSTRACT

Objective: 1) To compare the efficacy of two drugs, Amlodipine and hydrochlorothiazide (HCTZ), in elderly Thai patients with isolated systolic hypertension (ISH) in terms of regression of left ventricular hypertrophy (LVH) and blood pressure control. 2) To detect the short (six months) and medium (18 months) terms of clinical outcomes of major cardiovascular events, i.e., congestive heart failure (CHF), myocardial infarction (MI), cerebrovascular disorders (CVD), death and minor clinical outcomes or adverse drug effects. This is a prospective randomized control study.

Methods: From October 1997 to March 2000, 200 elderly patients with ISH, mean age of 69.3 years, were randomized into two groups, to receive either Amlodipine or HCTZ as a primary drug. Their baseline clinical data, blood chemistry, ECG, and echocardiography (ECHO) were evaluated. Regression of LVH was re-examined at six months; BP measurement was measured every 3 months for 18 months; and, clinical outcomes were followed at the end of study. Clinical end points were defined as death, myocardial infarction, and congestive heart failure.

Results: Sixty-six percent of all patients had LVH by the ECHO criteria. After six months of monotherapy, there was regression of LVH in both groups ($p < 0.01$), but no difference in the reduction of left ventricular mass index (LVMI) between the two groups ($p = 0.33$). There was a significant reduction in systolic blood pressure (BPsys) in both treatment groups ($p < 0.01$). Those who received Amlodipine had more frequent side effects and were withdrawn from the study ($p = 0.02$). The major adverse drug effect was leg edema (Amlodipine). However, more patients in the HCTZ group required additional drugs (Prazosin) in order to control BP to the desired level (39.2% vs 14.5%, $p < 0.001$). There was no statistical difference in clinical end points during follow-up. Difference of total drugs costs for one year of treatment was 8,084 Baht/patient in favor of the HCTZ regimen.

Conclusion: It is suggested that a low dose of the HCTZ regimen is more cost effective when compared with Amlodipine and should be considered as the first antihypertensive agent of choice for ISH in the Thai elderly.

Keywords: Calcium channel blocker; Diuretic; Isolated systolic hypertension; Elderly

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As the population of the elderly will increase approximately fourfold through 2030, and cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality in the elderly, this substantially results in the increase of economic and social burden which will consume most of healthcare resources. Isolated systolic hypertension (ISH) is generally defined as an elevated systolic pressure above 160 mmHg, with diastolic blood pressure less than 90 mmHg[1] is a recognized risk factor for CVD among individuals in the age group of 60 years old and above. The importance of ISH lies in the observation that it is associated with a two to fourfold increase in the risk of myocardial infarction, left ventricular hypertrophy, stroke, and cardiovascular mortality.[2-4] This observation suggests that antihypertensive treatment might be beneficial. The systolic hypertension in the elderly demonstrated the effectiveness of low dose diuretic (base chlorthalide) compared with placebo during five years in preventing major CVD events, cerebral and cardiac, in both non-insulin-treated diabetic and nondiabetic older patients with ISH.[5] So far, there is no evidence that the main benefit of hypertension treatment is contributed by a particular drug property, rather than lowering the blood pressure. However, different drug therapies provided various effectiveness in the reduction of blood pressure.[6,7] Moreover, new drugs of high cost have been more produced and widely available in Thai market. Under present economic constraint, the cost effective antihypertensive drug has prime importance in the treatment of the elderly with ISH. Therefore our study is aimed to compare the antihypertensive efficacy, safety and cost of treatment of two different classes of drugs; a risk cost drug but good efficiency and low side for Amlodipine, a calcium-channel antagonist, versus a low cost drug hydrochlorothiazide, a diuretic. Once-daily dose of each compound were used to determine their effects on trough sitting blood pressure. This study was the 8th out of 14 projects under the mega project of the Faculty of Medicine Siriraj Hospital on the Integrated Health Research Program for the Thai Elderly.

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TABLE 1. Patients characteristics according to treatment group.

	Amlodipine (n=100)	Hydrochlorothiazide (n=100)	p-value
Clinical			
Male (%)	35	29	0.36
Age, y (SD)	69.7 (6.1)	68.9 (9.4)	0.45
History of previous HT	53	62	0.20
Family history of HT	9	9	1.00
Underlying illness			
IHD	6	6	1.00
COPD	5	1	0.10
Coronary risk factors			
Diabetes	12	8	0.35
Dyslipidemia	18	13	0.33
Smoker	8	8	0.06
Ex-smoker	25	14	
Family history of CAD	2	0	0.16
Mean body mass index [kg/m^2] (SD)	23.8 (1.6)	24.3 (2.8)	0.11
Mean BP [mmHg] (SD)	178.8 (16.3)	177.1 (15.4)	0.46
Mean BP^{sys}_{dias} [mmHg] (SD)	84.7 (5.5)	83.7 (5.5)	0.30
LVH assessed (ECHO)	54	58	0.57
Mean LVMI [gm/m^2] (SD)	123.1 (40.7)	122.1 (40.9)	0.87

IHD = ischemic heart disease; BP_{sys} = systolic blood pressure; BP_{dias} = diastolic blood pressure; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index

MATERIALS AND METHODS

Patient selection

This study protocol has received an approval from the Ethics Committee on Human Rights involving Human Research of the Faculty of Medicine Siriraj Hospital. All recruited patients provided their written informed consents. Men and women were 60-80 years of age and had a well-established history of mild to moderate isolated systolic hypertension, defined as systolic blood pressure >160 mm Hg, diastolic blood pressure <90 mm Hg with adequate transthoracic projection view for Doppler-echocardiographic (ECHO) analysis. Exclusion criteria included those who had co-existing severe valvular heart disease, a poor left ventricular ejection fraction below 40%, serum creatinine >2.5 mg/dL, atrial fibrillation and any concomitant disease that would present safety hazards and concomitant medications that might interfere with the assessment of efficacy or safety (e.g. drugs known to affect blood pressure).

Study design

This prospective, randomized study was conducted from October 1997 to March 2000 at the Division of Cardiology, Department of Medicine, and at 41 sites in the communities located within a radius of 10 km around Siriraj Hospital. A community survey on 1,571 elderly and their case findings was performed during the first three months of the study. Clinical data, including coronary risk profiles, history of hypertension, and history of antihypertensive therapy were recorded. Sitting office blood pressure measures were taken by a physician using an automated oscillometric device (Press-Mate BP-8800 Series) in order to avoid measurement error. After a 5-minute rest, sitting systolic blood pressure (BPsys) and diastolic blood pressure (BPdias) were measured at two separate intervals. Those who met the inclusion criteria were appointed to our study site for a second blood pressure measurement. Blood chemistry was analyzed; a 12-lead electrocardiogram (ECG) and two-dimensional ECHO (ECHO) were performed as a baseline study. Parameters were measured at the baseline; and after an 18-month follow-up period they included left ventricular wall thickness, left ventricular cavity size, systolic and diastolic function, left ventricular ejection fraction, left ventricu lar mass (LV mass) and valvular function. All previewed anti-hypertensive agents were withdrawn for two weeks before randomization. Confirmation of ISH was made afterwards. After consent, eligible patients with ISH were randomized to one of the following once-daily monothera-py groups: 25-50 mg of hydrochlorothiazide (HCTZ) or 5-10 mg of Amlodipine. The study drugs could be titrated according to physician discretion after each visit, on week 1, 4 and every 3 months. Subgroups of patients who had left ventricular hypertrophy (LVH) detected under ECHO criteria (left ventricular mass index, LVMI) (Appendix 1) underwent another ECHO after a 6-month treatment to evaluate the regression of LVH. After the 6-month ECHO measurement, only Prazosin 1-20 mg per day could be added for those who had sitting systolic blood pressure above 160 mmHg in order to achieve optimal sitting systolic blood pressure below 140 mmHg.

Statistical methods

Sample size determination

A sample size of 85 randomized patients of each treatment group was chosen to give at least 90% power, with a type I error of 5% (two-tailed), in detecting a true difference of 3.5 mmHg between treatments with regard to the primary variable (changes from baseline in trough sitting blood pressure at month 6). We expected a 15% loss of patients during the follow-up period.

Quantitative data were analyzed by a one-way analysis of variance and qualitative data were assessed by a χ^2 test. These statistical tests were two-sided with a significance level of $\alpha = 0.05$.

Efficacy and safety measurements

The primary statistical comparison was a reduction in the left ventricular mass at the baseline and sixth month

TABLE 2. Blood chemistry levels at the baseline.

Blood chemistry	Amlodipine	Hydrochlorothiazide	p-value
	Mean (SD)		
Fasting blood sugar, mg/dL	109.9 (33.4)	118.4 (52.8)	0.19
Blood urea nitrogen, mg/dL	14.9 (4.2)	14.5 (4.2)	0.45
Creatinine, mg/dL	1.3 (1.4)	1.1 (0.5)	0.27
Uric acid, mg/dL	6.3 (4.7)	5.8 (1.9)	0.47
Sodium, mEq/L	143.6 (3.2)	143.6 (3.8)	0.94
Potassium, mEq/L	4.4 (0.5)	4.3 (0.5)	0.36
Chloride, mEq/L	106.7 (9.2)	106.6 (9.2)	0.95
Total CO_2, mEq/L	26.5 (8.9)	27.1 (8.2)	0.95
Cholesterol, mg/dL	241.2 (46.8)	248.6 (40.6)	0.25
Triglyceride, mg/dL	171.4 (121.6)	164.3 (88.2)	0.65
HDL, mg/dL	50.6 (13.6)	49.2 (12.7)	0.47

TABLE 3. Baseline echocardiographic findings according to LVMI.

Echocardiographic finding	LVH Mean (SD) (n=112)	No LVH Mean (SD)(n=88)	p-value
EF ± SD	67.6 ± 8.5	68.0 ± 7.7	0.68
LVMI, gram/m^2	146.4 (37.3)	92.3 (18.2)	0.00*
Diastolic wall thickness			
Interventricular septum (mm)	11.9 (2.4)	9.1 (1.8)	0.00*
LV internal diameter (mm)	45.1 (6.0)	42.9 (5.6)	0.01*
LV posterior wall (mm)	11.4 (2.1)	9.3 (1.5)	0.00*
Mitral inflow velocity (Doppler)			
E velocity (cm/sec)	64.3 (14.3)	68.9 (16.5)	0.04*
A velocity (cm/sec)	87.2 (19.0)	86.7(17.8)	0.87
E:A ratio	0.8 (0.6)	0.8 (0.2)	0.85
Deceleration time (sec)	228.0 (42.7)	222.1 (46.2)	0.35
Isovolumetric relaxation time (sec)	98.8 (20.1)	107.7 (23.5)	0.45

*LVMI = left ventricular mass index, LVEF = left ventricular ejection fraction, *Statistical significance*

TABLE 4. Effect of 6-month monotherapy on regression of left ventricular hypertrophy assessed by (ECHO) and cost.

LVMI	Amlodipine Mean (SD) (n=44)	Hydrochlorothiazide Mean (SD) (n=45)	p-value
Baseline	149.9 (39.9)	142.9 (29.2)	0.35
AT 6 months	128.5 (34.7)	114.9 (22.2)	0.03*
% Change at 6 months	-21.5 (35.3)	-27.9 (27.1)	0.33
Cost per case (Baht)	4413.7 (1954.9)	302.6 (419.4)	< 0.001
Number of cases with LV regression	31/44 (70%)	36/45 (80%)	0.528

TABLE 5. Blood pressure at baseline and follow-up at 6 and 18 months according to treatment groups.

	Amlodipine Mean (SD) (n=69)	Hydrochlorothiazide Mean (SD) (n=74)	p-value
BP_{sys}			
At baseline	176.9 (15.3)	175.6 (14.5)	0.59
BP_{sys} at 6 months	148.2 (13.9)	147.4 (13.4)	0.73
BP_{sys} at 18 months	145.1 (13.9)	147.8 (12.3)	0.24
BP_{dias}			
At baseline	84.2 (5.7)	83.6 (5.5)	0.56
BP_{dias} at 6 months	75.9 (6.1)	76.6 (6.3)	0.55
BP_{dias} at 18 months	74.2 (5.7)	76.1 (7.4)	0.09
Change of BP_{sys}			
At 6 months	-28.6 (17.4)	-27.8 (17.0)	0.79
At 18 months	-31.9 (15.3)	-27.8 (17.1)	0.15
Change of BP_{dias}			
At 6 months	-8.4 (7.1)	-6.9 (7.9)	0.24
At 18 months	-10.0 (6.8)	-7.5 (8.7)	0.06
BP 140-160 mmHg at 18 months	40 (58 %)	52 (70%)	0.16
BP_{sys} <140 mmHg at 18 months	23 (33%)	15 (20%)	0.092
Loss to follow up	9 (12.3%)	15 (19.5%)	0.22
Cessation of treatment	19	9	0.02*
Adverse drug effects	12	6	
Other causes	7	3	
Requirement of second additive drug (Prazosin)	10 (14.5%)	29 (39.2%)	0.001*
Reported minor S/E			
At baseline (previous drugs)	26 (40.6%)	30 (40.0%)	0.94
At 18 months (active drugs)	2 (3.1%)	4 (5.7%)	0.47

BP_{sys} = systolic blood pressure; BP_{dias} = diastolic blood pressure; S/E = side effect
**Statistical significance*

between the Amlodipine and HCTZ groups. The secondary statistical comparison was sitting systolic blood pressure at the baseline versus sixth month and the end of the study at eighteenth month. The addition of Prazosin for those without an adequate control of blood pressure was recorded. Side effects and withdrawal of treatment drugs were counted. The total cost of each treatment was compared after the 18 months of study.

End points

Death, myocardial infarction, and stroke were considered as clinical endpoints of the two-treatment drugs up to the eighteenth month.

RESULTS

Patient demographics and characteristics

Two hundred elderly patients with ISH entered the study. The majority of the patients were female (68%) who had a history of hypertension (57%) and diabetes (10%). The mean age was 69.3 years and the mean baseline systolic blood pressure was 175.9 mmHg; the mean sitting diastolic blood pressure was 83.9 mmHg The subjects were randomized (100 to Amlodipine, and 100 to hydrochlorothiazide). No statistically significant baseline differences were observed among the treatment groups (Tables 1, 2).

Left ventricular hypertrophy

All patients underwent 12-leads ECG and ECHO measurements. One hundred and twelve patients (56%) met the criteria of LVH via the left ventricular mass indexes (LVMI) corresponding to their gender (Appendix 1). Among various ECHO parameters diastolic wall thickness and mitral E-wave velocity were statistically significant indicators for LVH (Table 3).

Therapeutic response

Regression of left ventricular hypertrophy

Eighty-nine of 112 patients with left ventricular hypertrophy had completed the 6-month randomized treatment and required a second ECHO measurement. The baseline LVMI between the two treatment groups was similar without statistical significance. After six months of treatment, the mean LVMI was statistically and significantly lower in the HCTZ group (114.9+22.2 gram) than in the Amlodipine group (128.5+34.7 gram); p =0.03. Net reduction in LVMI from the baseline was higher in the HCTZ group

TABLE 6. Cost analysis calculated from cost of active drugs (in Baht) per patient per year.

Cost (Baht)	Amlodipine (n=73) Mean (SD)	Hydrochlorothiazide (n=76)	p-value
Cost of Active Drug	9047.5 (3280.7)	476.7 (130.4)	<0.001
Cost of Prazosin	123.3 (428.7)	619.9 (1071.9)	<0.001
Total Cost	9170.7 (3441.3)	1096.6 (1122.5)	<0.001

(-27.9+27.1) than Amlodipine group (-21.5+35.3) but without statistical significance (p =0.33). (Table 4) The number of cases with LV regression in Amlodipine (70%) vs. HCTZ (80%) did not show any statistically significant difference (p = 0.528). The 6-month BP with LV regression was found in 21/28 (75%) of BPsys <140 mmHg; 33/45 (73%) of BPsys 140-160 mmHg; and 13/16 (81%) of BPsys >160 mmHg; these revealed no statistical difference (p = 0.27).

Trough blood pressure

A total of 69 patients in the Amlodipine and 74 patients in the HCTZ treatment completed the study period of 18 months. At the sixth and the eighteenth month of the study period, the secondary efficacy variable was found similar between the two groups of treatment, with reductions from the baseline in trough sitting BPsys (Table 5). The mean reduction in mean sitting BPsys were 28.6 vs. 27.80 mmHg (p = 0.79). Only 23 (33%) in the Amlodipine group and 15 (23%) in the HCTZ group achieved optimal sitting BPsys control (SBP <140 mmHg); these showed no significant difference (p = 0.092). Ten (14.5%) in the Amlodipine group and 29 (39.2%) in the HCTZ group needed a second anti-hypertensive agent to control their sitting systolic blood pressure (p = 0.001).

Safety and tolerability

During the run-in period, there were reports of higher side effects from previous antihypertensive treatment before randomization, 26 (40.6%) in the Amlodipine group and 30 (40.0%) in the HCTZ group. The major side effect was an intolerable cough from the angiotensin-converting enzyme inhibitor. After the 18-month study, no statistical difference in reported minor side effects between the two treatment groups. Early discontinuation due to adverse effects occurred more often in the Amlodipine than in the HCTZ group; p = 0.02 (Table 5). It was observed that vertigo, hot flashes and leg edema were common in the Amlodipine group, at the dose of 10 mg/day. They usually occurred within the first six months of treatment. Vertigo and hot flashes resulting in cessation of treatment could occur even at a low dosage of Amlodipine, i.e., 2.5-5 mg/day; usually they occurred within one month. However, the side effects of HCTZ that resulted in the cessation of treatments were vertigo, malaise and hypokalemia.

Clinical endpoint

There were similar non-cardiovascular deaths between the two-treatment groups during the study. One patient was dead in Amlodipine group. Nineteen cases from Amlodipine group versus 9 cases from hydrochlorothiazide group were able to stop the therapy. There were 2 cases in both groups diagnosed as cancer.

Cost analysis

The total cost per case after six months of treatment was much lower in the HCTZ group than the Amlodipine group (p < 0.001). Hence, the cost of saving was 4,111 baht/case for six months (Table 4). There was a significant difference in the cost of active drugs per patient between the two treatment groups (Table 6). The principal drug cost per patient was higher in the Amlodipine group; however, the additional drug costs per patient (Prazosin) were higher in the hydrochlorothiazide group. The overall drug cost per patient per year was higher in the Amlodipine group (9,107.70 baht vs. 1,096.6 baht; p <0.001).

DISCUSSION

Blood-pressure effects of treatment

An important finding was that a substantial reduction in blood pressure could be achieved with both treatment regimens. We found no further benefit in increasing the dose of hydrochlorothiazide to control systolic blood pressure. The addition of a second drug (Prazosin) resulted in better control of systolic blood pressure in 39% of the hydrochlorothiazide group. The overall reductions in systolic blood pressures were striking, e.g., reduction was 28-32 mmHg in this study (-31.9 mmHg in Amlodipine vs. -27.8 mmHg; p = 0.15) in comparison with those reported in the Hypertension Optimal Treatment (HOT) study (26-29 mmHg).[9] However, the blood-pressure reduction observed in the two different target groups made it difficult to recognize significant differences in event rates between the two groups. Furthermore, the number of clinical events was lower due to a shorter follow-up period compared to the higher total mortality reported in the HOT study (8.3 per 1,000 patients/years).[9] There were no death, fatal or nonfatal strokes, and myocardial infarction in our study com-pared to other trials. Liu et al.[10] demonstrated that treatment of 1,000 Chinese patients for five years could prevent 55 deaths, 39 strokes or 59 major cardiovascular endpoints.

Effects of treatment on the left ventricular mass index

Although left ventricular hypertrophy (LVH) is an adaptive response to the increased load imposed on the heart in patients with hypertension, it ultimately is a major risk factor for cardiovascular disease. The prevalence of LVH assessed by (ECHO) in our study (56%) is comparable to other studies (varying from 10% to 96%), depending on factors such as the severity of hypertension, age, gender, race, caloric and salt intake, and the methodology (ECG or ECHO) used and is highly dependent on the criteria used.[4,11-13] There is no definite value defining LVMI by using LVH among Thai patients. We used different cut-point values determining LVMI according to gender as in one of Framingham studies.[11] The influences of LVH on the left ventricular function and on coronary circulation, and the occurrence of serious ventricular arrhythmias, are major mechanisms of this increased risk[14] and could be modified by LVH regression. Significant regression of LVH could be observed in both of our study drugs (-21.5% in Amlodipine vs. -27.9% in hydrochlorothiazide) and prognosis could be improved afterwards.[15] Furthermore, it has yet to be determined whether regression of LVH has a positive influence on the long-term prognosis in such patients. Morbid events will occur in a higher proportion of subjects in whom LVH progress (13-59%) rather than regresses (7-12%).[16] In our study, HCTZ seems to be more effective than Amlodipine in reducing

LVMI as demonstrated from the previous SHEP trial.[17,19] However, there is no universal agreement on the influence of diuretics on LVH in hypertension. Several major trials have shown a consistent reversal of electrocardiographic manifestations of LVH during diuretic-based therapy.[20] However, there were similar comparable results in the ability of various forms of antihypertensive therapy to reverse LVH as assessed by ECHO.[20-21] Clinical endpoints were similar in both groups. More patients in the Amlodipine group terminated the study drug (19 patients) than those in the HCTZ group (9 patients), due mainly to the adverse drug effects but without statistical significance. At six months in the treatment community whether BPsys was at least 73-80% will have LV regression which is the response.

Cost analysis

After completing the study, the cost of the two active drug treatments, including the second drug, were analyzed. The total cost of hydrochlorothiazide plus Prazosin was cheaper than Amlodipine plus Prazosin ($p < 0.001$). After twelve months of treatments, the difference of the average cost of the two groups was calculated to be 8,084 baht/case; whereas, the prevalence of hypertension in the community survey was 19%.[22] Given the size of elderly population is approximately 5.5% of the total population of 60 million, there will be 3.3 million Thai elderly with of 627,000 cases of hypertension. Initial treatment of low dose of hydrochlorothiazide would save up to 5,068.70 million baht from the annual national health budget. Under the situation of economic constraints in this country, it is very important to consider a therapy based on low dose diuretic for the treatment of the increasing number of elderly patients with isolate systolic hypertension. Furthermore, our findings confirm the data from SHEP study which has proven the effectiveness of chlorthalidone as a major active drug.[5] Therefore, thiazide should be considered the first anti-hypertensive agent prescribed for elderly Thai patients with ISH.

Study limitation

Our sample size is probably too small to demonstrate the efficacy between the two drugs. At the end of the study, there was a higher than expected number of patients who were lost to follow-up. Further study is suggested with a larger sample size and a longer clinical follow-up period. They are mandatory to demonstrate the efficacy of the two drugs.

CONCLUSION

There is a similar efficacy between Amlopidine and HCTZ found in our study. An active therapy is associated with a similar effect in the reduction of the left ventricular mass index (LVMI). At the follow-up after the end of 18 months, blood pressure control could be reached with the two active drugs. The second drug was required more frequently in the thiazide group than in the Amlodipine group for effective blood pressure control as illustrated in similar studies. Only 20% of the patients treated with hydrochlorothiazide, and 33% of those treated with Amlodipine reached a target systolic blood pressure below 140 mmHg during the study. A second drug was needed to obtain a better control of blood pressure. We concluded that when Amlodipine is compared with HCTZ, the latter is a cost effective drug and should be considered initial treatment for ISH, both in reducing the LVH and providing relatively more effective control of blood pressure in elderly patients with financial difficulties.

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Appendix 1. Penn-Convention Measurement

Prolate ellipsoid configuration of left ventricle contour Long to short axis left ventricular length = 2:1	
LV mass	= 1.04 [(IVSTd + LVIDd + PWTd)^3 - (LVIDd)^3] - 13.6
LVMI	= LV mass / (body surface area)
IVSTd	= interventricular septal thickness (diastole), cm
LVIDd	= left ventricular internal diameter (diastole), cm
PWTd	= posterior wall thickness (diastole), cm
LV mass	= gram
Body surface area	= meter^2
LVMI	= gram/meter^2
LVH is defined as LVMI >131 gm/M^2 (male) or >100 gm/M^2 (female).	

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บทคัดย่อ

แอมโลดิปินและไฮโดรคลอโรไธอะไซด์ ในการรักษาความดันโลหิตสูงในผู้ป่วยสูงวัย ในชุมชน

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วัตถุประสงค์: ความชุกของความดันโลหิตสูงซิสโตลิก (Isolated systolic hypertension, ISH) พบได้บ่อยกว่า 20% ของผู้สูงอายุ และเป็นสาเหตุของกล้ามเนื้อหัวใจหนา, หัวใจโต ซึ่งเป็นปัจจัยบ่งชี้ที่สำคัญในการทำนายว่าผู้ป่วยมีโอกาสเกิดภาวะแทรกซ้อนทางระบบหัวใจและการไหลเวียนโลหิตมากกว่าบุคคลทั่วไป การรักษาด้วยยาลดความดันโลหิตสามารถลดภาวะกล้ามเนื้อหัวใจหนาและหัวใจโต ลดอัตราการเกิดอัมพาตและหัวใจล้มเหลว ในปัจจุบันมียาลดความดันโลหิตหลายชนิดซึ่งแตกต่างกันในแง่ประสิทธิภาพ, ผลข้างเคียง, และราคา เพื่อเปรียบเทียบประสิทธิภาพของยาลดความดันโลหิตระหว่างยาต้านแคลเซียม Amlodipine ซึ่งมีประสิทธิภาพดี, ผลข้างเคียงต่ำ, แต่มีราคาแพง และยาขับปัสสาวะ ได้แก่ Hydrochlorothiazide (HCTZ) ซึ่งมีราคาถูกกว่ามากในการลดมวลกล้ามเนื้อหัวใจ, ความดันโลหิต ภาวะแทรกซ้อนที่เกิดกับระบบหัวใจและหลอดเลือด และผลข้างเคียงของยา

วิธีการ: เป็นการศึกษาแบบสุ่ม ระหว่างเดือนตุลาคม 2540 - เดือนมีนาคม 2543 ผู้ป่วยสูงอายุ (60-80 ปี) ที่มีความดันโลหิตซิสโตลิกสูง > 160 และความดันโลหิตไดแอสโตลิก <90 มม.ปรอท จำนวน 200 ราย อายุเฉลี่ย 69.31 ปี, เป็นเพศชาย 32%, มีประวัติความดันโลหิตสูง (57%), เป็นเบาหวาน (10%) ได้คัดเลือกผู้ป่วยแบบสุ่มเป็น 2 กลุ่ม กลุ่มที่ 1 ได้รับยา Amlodipine และ กลุ่มที่ 2 ได้รับยา HCTZ

ผลการศึกษา: เมื่อติดตามผลการรักษานาน 18 เดือน พบว่าประสิทธิภาพในการลดความดันโลหิตของยาทั้ง 2 ไม่แตกต่างกัน แต่กลุ่มที่ได้รับยา HCTZ มีจำนวนที่ต้องให้ยาเสริมได้แก่ Prazosin บ่อยกว่า เพื่อควบคุมความดันโลหิตให้อยู่ในเกณฑ์ปกติ (39.2% vs. 14.6%, $p < 0.01$) ไม่พบกล้ามเนื้อหัวใจตาย, หรืออัมพาต มีผู้ป่วยเป็นมะเร็ง 4 ราย (กลุ่มละ 2 ราย) ผู้ป่วย 1 รายเสียชีวิตจากมะเร็ง ผู้ป่วย 112 ราย (56%) ที่พบมีกล้ามเนื้อหัวใจหนาถูกคัดเลือกแบบสุ่มเป็น 2 กลุ่มเช่นกัน กลุ่มที่ 1 ได้รับยา Amlodipine และ กลุ่มที่ 2 ได้รับยา HCTZ นาน 6 เดือน เปรียบเทียบผลการตรวจคลื่นเสียงสะท้อนหัวใจผ่านผนังทรวงอกก่อนและหลังการรักษาที่ 6 เดือน 89 ราย พบว่ามวลกล้ามเนื้อหัวใจลดลงในผู้ป่วยทั้ง 2 กลุ่มอย่างมีนัยสำคัญทางสถิติ ($p < 0.01$) แต่ไม่พบความแตกต่างในการลดของมวลกล้ามเนื้อหัวใจระหว่างกลุ่ม ($p = 0.33$) ส่วนต่างของค่ายาทั้งหมดในการรักษากลุ่ม HCTZ ถูกกว่า Amlodipine 8,084 บาท/ราย/ปี

สรุป: คณะผู้วิจัยเชื่อว่า HCTZ ขนาดต่ำเป็นยาลดความดันโลหิตสูงแบบซิสโตลิก ที่มีประสิทธิภาพคุ้มค่ามาก ควรได้รับการพิจารณาใช้เป็นยาอันดับแรกในการรักษาโรคนี้ในผู้สูงอายุไทย