EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 11
Issue: 8
1-10
Year: 2024

ASSESSING THE MAGNITUDE OF BLOOD PRESSURE REDUCTION IN NEWLY DIAGNOSED PATIENTS TREATED WITH PERINDOPRIL OR AMLODIPINE MONOTHERAPY AT VARIOUS DOSAGES – A RETROSPECTIVE, MULTICENTER OBSERVATIONAL STUDY

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Article Received on 31/05/2024 **Article Revised on 21/06/2024** **Article Accepted on 11/07/2024**

ABSTRACT
Hypertension is a well-established modifiable risk factor for the spectrum of cardiovascular diseases. What is being missing from available clinical practice guidelines in managing hypertension is the absence of the data on magnitude of reduction (%) or mean BP reduction potential of individual antihypertensive agent. The main objective of this study was to identify the magnitude of BP reduction of the two most common antihypertensive agents (perindopril and amlodipine) at various dosages used in the public primary care clinics in Malaysia. A significant reduction of mean SBP was observed after three months of treatment with perindopril 4mg OD. Mean SBP was reduced significantly by 5.47% (95% CI: 4.15-12.15, $p < 0.001$). However, there was no statistically significant reduction in mean DBP ($p = 0.368$). Amlodipine 5mg OD reduced both mean SBP and DBP significantly. Mean SBP was reduced by 8.48% after 3 months of treatments ($p < 0.001$) while mean DBP was reduced by 4.65% ($p < 0.001$). Amlodipine 10mg OD reduced mean SBP and DBP significantly. Mean SBP was reduced significantly by 9.04% ($p < 0.001$). Mean DBP was reduced significantly by 7.22% ($p = 0.001$). Mean BP reduction by perindopril 4mg OD in study population was 5.47%/1.23%. Amlodipine 5mg OD, and 10mg OD reduced mean BP in study population by, 8.48%/4.65%, and 9.04%/7.22% respectively. The result of this study shall provide the mean BP reduction of both commonly used antihypertensive agents.

KEYWORDS: Hypertension, perindopril, amlodipine, magnitude of BP reduction, Malaysia.

INTRODUCTION
Ischaemic heart disease and stroke are the top two leading causes of death globally, contributing to 16% and 11% of the world's total deaths respectively in 2019, outnumbering communicable diseases like lower respiratory infections, neonatal conditions and diarrhoea.[1] Hypertension is a well-established modifiable risk factor for the spectrum of cardiovascular diseases. Uncontrolled blood pressure is associated with stroke, myocardial infarction, heart failure, peripheral arterial disease and renal failure.[2,3] Hardy et al. (2015)[4] reported that about 33% of all-cause mortality and coronary heart disease mortality were associated with uncontrolled BP, especially elevated systolic blood pressure (SBP).

The choice of antihypertensive agents should be individualised and guided by the global cardiovascular risk. Monotherapy with low dose is recommended for patients with stage one hypertension, which includes the most common antihypertensive agents like angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta blockers (BBs), calcium channel blockers (CCBs) and diuretics.[5]

What is being missing from available clinical practice guidelines in managing hypertension is the absence of the data on magnitude of reduction (%) or mean BP reduction potential of each antihypertensive agent. Clinical practice guidelines on hypertension management have been introduced and established for many years, yet

the population data on the extent of BP reduction by each antihypertensive agent remained unreported. In contrary, the average haemoglobin A1c (HbA1c) reductions of oral antidiabetic agents are often reported in diabetic clinical practice guidelines. In example, metformin or sulphonylurea is reported to be able to reduce HbA1c by up to 1.5% renders them becoming the first line agent among other antidiabetic agents for patients with no contraindication.[6,7] Similarly, lipid lowering effects of all lipid modifying drug classes are explicitly indicated in guidelines in managing hyperlipaemia. In fact, the HMG-CoA (3-Hydroxy-3-Methyl-Glutaryl-Coezyme A) reductase inhibitors or statins are categorized into various potencies based on their ability in reducing low density lipoprotein- Cholesterol (LDL-C).[8] This information is useful and crucial in assisting physicians in initiating the correct medications at correct dosages, tailoring to the patient's condition and demographic data.

AIMS OF STUDY

The main objective of this study was to identify the magnitude of BP reduction of the two most common antihypertensive agents (perindopril and amlodipine) at various dosages used in the public primary care clinics in Malaysia. The potential mean BP reduction of both perindopril and amlodipine generated from this research shall be able to provide a useful guidance for physicians to recommend the appropriate antihypertensive agent and dose.

Method

This was a multicentre, retrospective and observational study that identify the magnitude of the BP reduction of perindopril and amlodipine from 1st January 2017 to 30th of September 2019. The study was conducted at six primary public health clinics at Northern Region of Malaysia. Amlodipine and perindopril were identified and selected for analysis in this study as these 2 agents are the most commonly used antihypertensives for newly diagnosed hypertension at primary public clinics (government funded primary care clinics) in Malaysia.

The inclusion criteria included patients with newly diagnosed primary hypertension and were new users of perindopril or amlodipine monotherapy and attended the follow-up visit to primary health clinics within 3 months of duration from January 2017 to September 2019; patients who were taking the perindopril or amlodipine with the same dose daily without any self-adjustment; and patients with age range of 18 years old or older. Meanwhile the exclusion criteria included patient with cardiac, respiratory, diabetes, kidney and liver failure; patient with severe hypertension (SBP ≥ 180 and/ or DBP ≥ 110 mm Hg) at the baseline visit; patients with secondary hypertension (caused by atherosclerosis, renal artery stenosis, renal failure, hypothyroidism and etc); pregnant women and women who breastfeed; patients who defaulted follow-up after the initial diagnosis or during the 3 months after perindopril or amlodipine monotherapy being initiated; data that had dose adjustment (increased or decreased dose) or added with other antihypertensive agents; data that discontinued the perindopril or amlodipine treatment due to side effects of the medications during the 3 months; and concurrent use of other hypertensives agents, including BBs, diuretics, alpha-blockers.

This study only enrolled patients who had taken their antihypertensive agent for at least 3 months between the January 2017 to September 2019. Therefore, patients that were newly diagnosed with primary hypertension from 1st of October 2019 till 31st December of 2020 were excluded due to the possibility of reduced frequency of clinic follow-up visits in line with the restriction movement during MCO on March 2020.

The sample size required in this study was calculated according to Raosoft software. A total of 574 patients were newly diagnosed with essential hypertension from all six primary health clinics in 2019, according to the hypertension registry in each clinic. The population of essential hypertension was set at 574 patients. The confidence level of the study was set at 95% with the margin of error of 5% and 50% respond distribution rate. The minimum sample size for the study was 231 patients. An additional of 15% sample size was added for dropout or missing data, hence the total sample size required for the study was 277 (Raosoft, 2004).[9]

In this study, data were analyzed using Statistical Package for the Social Sciences (SPSS®) version 27.0 software. All continuous baseline and demographic data were being assessed by independent sample t-test as long as parametric assumptions were met. Otherwise, Mann-Whitney test was used for continuous data that is not normally distributed. For outcome measurement of continuous data, independent sample t-test (if parametric assumptions were met) or Mann-Whitney test (for non-parametric assumption) were used to explore the mean BP reduction (or mean percentage) for both perindopril and amlodipine. The comparison of mean BP reduction between the baseline visits and the follow-up visits was performed using paired-samples t-test in case condition for normal distribution was provided, whereas the Wilcoxon signed-rank test was used in the case the condition for normal distribution was not provided. All variables assumed to be not statistically significant difference if $p > 0.05$. Two-tailed tests were used for all subsequent analyses.

RESULTS AND DISCUSSION

Table 1: Demographic and baseline characteristics of study population (n = 277)

		Health Clinics					
	Clinic A	**Clinic B**	**Clinic C**	**Clinic D**	**Clinic E**	**Clinic F**	**Total**
Clinic	(n = 61)	(n =36)	(n = 33)	(n = 43)	(n =47)	(n = 57)	(n = 277)
Mean age in years (± SD)	52.91 ± 7.83	55.68 ± 8.93	53.00 ± 8.14	57.06 ± 6.15	50.56 ± 9.92	53.28 ± 6.76	53.73 ± 8.25
Mean weight in kg (± SD)	74.28 ± 18.07	68.15 ± 14.47	75.37 ± 18.37	71.60 ± 15.38	72.92 ± 15.27	71.37 ± 11.70	72.30 ± 15.71
Age groups, N (%)*							
< 60 years old	43 (70.50)	18 (50.00)	27 (81.82)	25 (58.14)	33 (70.21)	17 (29.82)	193 (69.70)
≥ 60 years old	18 (29.50)	18 (50.00)	6 (18.18)	18 (41.86)	14 (29.79)	40 (70.18)	84 (30.30)
Genders, N* (%)							
Male	35 (57.38)	19 (52.78)	14 (42.42)	17 (39.53)	23 (48.94)	14 (24.56)	119 (43.00)
Female	26 (42.62)	17 (47.22)	19 (57.58)	26 (60.47)	24 (51.06)	43 (75.44)	158 (57.00)
Ethnicity, N (%)*							
Malay	33 (54.10)	8 (22.22)	23 (69.70)	21 (48.84)	33 (70.21)	37 (64.91)	158 (57.00)
Chinese	18 (29.51)	23 (63.89)	4 (12.12)	16 (37.21)	11 (23.41)	11 (19.30)	86 (31.00)
Indian	10 (16.39)	5 (13.89)	6 (18.18)	6 (13.95)	3 (6.38)	9 (15.79)	33 (12.00)
Age of newly diagnosed hypertension (Years; mean) †	49.71 ± 7.88	52.11 ± 9.05	49.85 ± 8.21	53.89 ± 6.05	47.31 ± 9.89	50.19 ± 6.87	50.49 ± 8.28
SBP (mm Hg) †	150.11 ± 8.78	149.00 ± 8.58	155.74 ± 10.21	152.40 ± 8.85	153.71 ± 9.44	154.60 ± 9.42	152.64 ± 9.45
DBP (mm Hg) †	84.62 ± 8.48	83.34 ± 8.44	90.46 ± 9.38	85.79 ± 9.13	91.56 ± 9.43	89.57 ± 7.71	87.63 ± 9.25
Type of antihypertensive, N (%)*							
ACEI	24 (39.34)	14 (38.89)	4 (12.12)	12 (27.91)	15 (31.91)	15 (26.32)	78 (28.20)
CCB	37 (60.66)	22 (61.11)	29 (87.88)	31 (72.09)	32 (68.09)	42 (73.68)	199 (71.80)

*All categorical data were presented in number (percentage), n (%).

† Normally distributed data were presented in mean ± standard deviation.

A total of 277 subjects were recruited from six public primary health clinics at northern region of Malaysia. Characteristics of the overall patients were summarized at table 1 (Demographic data of studied population).

The mean age of patients recruited in this study was 53.73 ± 8.25 years old. The youngest patients were 21 years old while the oldest patient being studied was 72 years old. This study observed more females than males, comprising of 158 females (57.00%) and 119 males (43.00%). Majority of the patients were younger than 60 years old (69.70%). Mean age of males were 53.32 ± 9.73 years old while for females were 54.03 ± 6.95 years old. The mean age difference between male and female patients was not statistically significant (95% CI: -2.78 to 1.36) with the independent samples t-test (p = 0.498).

Majority of the patients in this study were Malays with 158 (57.00%), followed by 86 Chinese (31.00%) and 33 Indians (12.00%). The mean age of Malays, Chinese and Indians were 52.40 ± 8.34 years old, 55.95 ± 8.13 years old and 54.27 ± 6.92 years old respectively. There was a statistically significant difference in mean age across different races as determined by one-way analysis of variance (F (2, 274) = 5.414, p = 0.005). Post-hoc comparisons using the Tukey's Honest Significant Difference (HSD) test indicated that the mean age for Malays (M = 52.40, SD = 8.34) was significantly different from Chinese (M = 55.95, SD = 8.13), while Indians (M = 54.27, SD = 6.92) did not differ significantly from either Malays or Chinese. The mean age (years) of newly diagnosed of hypertension in overall hypertensive patients was 50.49 ± 8.28 years old. The baseline means SBP and DBP were 152.64 ± 9.45 mm Hg and 87.63 ± 9.25 mm Hg respectively. Majority of patients were started with amlodipine (71.80%) than perindopril (28.20%).

Table 2: Demographic of patients initiated with perindopril.

Characteristic	Perindopril	
	2 mg (n = 24)	4 mg (n = 54)
Age (years; mean ± SD)	51.00 ± 10.71	53.96 ± 7.45
Age when patient newly diagnosed with hypertension (Years; mean ± SD) Mean SBP (mean ± SD) Mean DBP (mean ± SD)	47.71 ± 10.83 149.96 ± 7.02 86.96 ± 11.83	50.78 ± 7.51 149.09 ± 7.66 85.93 ± 8.06
Age Group*		
< 60 years old, n (%) ≥ 60 years old, n (%)	18 (75.00) 6 (25.00)	38 (70.37) 16 (29.63)
Gender*		
Males, n (%)	14 (58.33)	24 (44.44)
Females, n (%)	10 (41.67)	30 (55.56)
Ethnicity *		
Malays, n (%)	14 (58.34)	34 (62.96)
Chinese, n (%)	8 (33.33)	16 (29.63)
Indians, n (%)	2 (8.33)	4 (7.41)

* All categorical data were presented in number (percentage), n (%).

Characteristics	Amlodipine			
	2.5 mg (n = 23)	5 mg (n = 122)	7.5 mg (n = 17)	10 mg (n = 37)
Age (years; mean ± SD) Age when patient newly diagnosed with hypertension	52.91 ± 10.42	53.79 ± 7.42	57.12 ± 5.53	53.89 ± 9.56
(Years; mean ± SD)	49.61 ± 10.59	50.58 ± 7.42	53.71 ± 5.46	50.65 ± 9.51
Mean SBP (mean ± SD)	154.04 ± 8.78	152.89 ± 9.26	162.59 ± 10.03	155.81 ± 10.09
Mean DBP (mean ± SD)	85.32 ± 9.02	88.34 ± 8.70	91.18 ± 10.55	87.97 ± 10.05
Age Group*				
< 60 years old, n (%) ≥ 60 years old, n (%)	14 (60.87) 9 (39.13)	91 (74.59) 31 (25.41)	10 (58.82) 7 (41.18)	22 (59.46) 15 (40.54)
Gender*				
Males, n (%)	9 (39.13)	44 (36.07)	8 (47.06)	20 (54.05)
Females, n (%)	14 (60.87)	78 (63.93)	9 (52.94)	17 (45.95)
Ethnicity*				
Malays, n (%)	9 (39.13)	81 (66.39)	5 (29.41)	15 (40.54)
Chinese, n (%)	9 (39.13)	28 (22.95)	7 (41.18)	18 (48.65)
Indians, n (%)	5 (21.74)	13 (10.66)	5 (29.41)	4 (10.81)

* All categorical data were presented in number (percentage), n (%).

Demographic Characteristic of Patients Initiated with Perindopril

A total of 24 patients were started with perindopril 2mg OD. Majority of the patients were males (58.33%). Malay patients constitute a great proportion in this group (58.34%), followed by Chinese patients (33.33%) and 8.33% of Indian patients. Majority of the patients (75.00%) were less than 60 years old. The mean age of patients in this group were 51.00 ± 10.71 years old but the mean age of newly diagnosed of hypertension were 47.71 ± 10.83 years old.

A total of 54 patients were started with perindopril 4mg OD. More female patients (55.56%) were initiated as compared to the male counterparts. Majority of the patients were Malays (62.96%) and minority were Indians (7.41%). A total of 70.37% of patients were younger than 60 years old. The mean age of patients in this group were 53.96 ± 7.45 years old and hypertension were newly diagnosed at the mean age of 50.78 ± 7.51 years old.

Demographic Characteristic of Patients Initiated with Amlodipine

A total of 23 patients were started with amlodipine 2.5mg OD. More female patients (60.87%) were initiated as compared to male counterparts. Majority of the patients were Malays and Chinese (39.13% respectively) and were aged less than 60 years old (60.87%). The mean age of patients in this group were 52.91 ± 10.42 years old while the mean age of newly diagnosed hypertension were 49.61 ± 10.59 years old.

A total of 122 patients were started with amlodipine 5mg OD. More female patients (63.93%) than male patients in this group. A total of 66.39% of the patients were Malays. Majority of the patients (74.59%) were aged less than 60 years old. The mean age of patients in this group

were 53.79 ± 7.42 years old while the mean age of newly diagnosed hypertension were 50.58 ± 7.42 years old.

Less patients (17 patients) were started with amlodipine 7.5mg OD. More female patients (52.94%) than male patients in this group. Chinese were the majority patients (41.18%) in this group as compared to Indians and Malays (29.41% respectively). A total of 58.82% of patients were aged less than 60 years old. The mean age of patients in this group were 57.12 ± 5.53 years old while the mean age of newly diagnosed hypertension were 53.71 ± 5.46 years old.

A total of 37 patients were started with amlodipine 10mg OD. More male patients (54.05%) than female patients in this group. Chinese were the majority patients (48.65%) in this group as compared to Malays (40.54%) and Indians (10.81%). Most of the patients (59.46%) were aged less than 60 years old. The mean age of patients in this group were 53.89 ± 9.56 years old while the mean age of newly diagnosed hypertension were 50.65 ± 9.51 years old.

Table 4: Magnitude of BP Reduction for Perindopril at Various Dosages.

Dose/ day	2mg	# P-value	4mg	# P-value
SBP reduction, mmHg	-9.71	0.002	-8.15	< 0.001
% of SBP reduction*	-6.48		-5.47	
DBP reduction, mmHg	+0.67	0.756	-1.06	0.368
% of DBP reduction*	+0.77		-1.23	

* is calculated by [(baseline BP – BP at follow-up)/ baseline BP] x 100%
# is based on paired t test
SBP: Systolic Blood Pressure
DBP: Diastolic Blood Pressure

Table 5: Magnitude of BP Reduction for Amlodipine at Various Dosages.

Dose/ day	2.5 mg	# P-value	5mg	# P-value	7.5mg	# P-value	10mg	# P-value
SBP reduction, mmHg	-6.83	0.051	-12.95	< 0.001	-18.06	< 0.001	-14.08	< 0.001
% of SBP reduction*	-4.55		-8.48		-11.11		-9.04	
DBP reduction, mmHg	-1.74	0.291	-4.11	< 0.001	-3.18	0.197	-6.35	0.001
% of DBP reduction*	-2.04		-4.65		-3.48		-7.22	

* is calculated by [(baseline BP – BP at follow-up)/ baseline BP] x 100%
# is based on paired t test
SBP: Systolic Blood Pressure
DBP: Diastolic Blood Pressure

Magnitude of BP reduction in patients treated with perindopril at various dosages

Changes in mean SBP after a follow-up visit with perindopril 2mg and 4mg OD are demonstrated in table 4. The mean SBP at follow-up visit was significantly reduced by 9.71 ± 13.36 mm Hg (p = 0.002), which represented a mean reduction of 6.48% (95% CI: 4.07-15.35). The effect on DBP was not encouraging as it raised from 86.96 ± 11.83 mm Hg to 87.63 ± 11.09 mm Hg with perindopril 2mg treatment (p = 0.756).

A significant reduction of mean SBP was observed after three months of treatment with perindopril 4mg OD (refer to table 4). Mean SBP was reduced significantly by 8.15 ± 14.66 mm Hg (95% CI: 4.15-12.15, p < 0.001), which represented a reduction of 5.47%. However, there was no statistically significant reduction in mean DBP, which was 1.06 ± 8.55 mm Hg (95% CI: -1.28-3.39, p = 0.368, 1.23%).

Magnitude of BP reduction in patients treated with amlodipine at various dosages

There was no statistically significant SBP (p = 0.051) and DBP (p = 0.291) reduction after three months of 2.5mg per day of amlodipine. Mean SBP was reduced by 6.83 ± 15.84 mm Hg after 3 months of treatments, which represented a reduction of 4.55% (95% CI: -0.02-13.67). Mean DBP was reduced by 1.74 ± 7.71 mm Hg, which represented a reduction of 2.04% (95% CI: -1.60-5.07) (refer to table 5).

Amlodipine 5mg OD reduced both mean SBP (p < 0.001) and DBP (p < 0.001) significantly. Mean SBP was reduced by 12.95 ± 13.31 mm Hg after 3 months of treatments, which represented a reduction of 8.48% (95% CI: 10.57-15.34), while mean DBP was reduced by 4.11 ± 10.90 mm Hg, which represented a reduction of 4.65% (95% CI: 2.16-6.07) (refer to table 5).

A significant reduction of mean SBP was observed in the first three months of treatment with amlodipine 7.5mg OD. Mean SBP was reduced significantly by 18.06 ± 10.52 mm Hg (95% CI: 12.65-23.47, p < 0.001), which represents reduction of 11.11%. However, there was no statistically significant reduction in mean DBP (95% CI: -1.83-8.18, p = 0.197), which reduced by 3.18 ± 9.73 mm Hg (3.48%) (refer to table 5).

Amlodipine 10mg OD reduced mean SBP and DBP significantly. Mean SBP was reduced significantly by

14.08 ± 15.30 mm Hg (95% CI: 8.98-19.18, p < 0.001), which represents reduction of 9.04%. Mean DBP was reduced by 6.35 ± 11.15 mm Hg significantly (95% CI: 2.63-10.07, p = 0.001), which represent reduction of 7.22% (refer to table 5).

DISCUSSION

Majority of the patients in this study (69.7%) who were diagnosed hypertension were below age of 60 years old. This is comparable to the prevalence of hypertension was reported by Teh et al. (2020)[10] that about 61.6% of hypertensive patients were below age of 65 years old from 40 primary public health clinics in Malaysia. The rising of hypertension at younger age was reported to be attributed to the urbanization, sedentary lifestyles and unhealthy eating habits resulting from consumption of high calorie, salty and fatty food.[11,12] The prevalence of hypertension below age of the 60 years old in our study were higher than the prevalence of hypertension among middle-age adults (45%) in China[13] and 55% among Koreans aged 30 years or older[14], highlighting the need for Malaysia to adopt preventive measure towards young or middle aged hypertensive patients in national hypertension strategy.

Our study reported that Malays (57%) being the most newly diagnosed with hypertension, followed by Chinese (31%) and Indian (12%). Similar prevalence of hypertension trend is also being observed in Singapore where Malays and Chinese had the higher prevalence of hypertension of 37.5% and 36.1% respectively as compared to the Indians (29.5%) during the year of 2019 to 2020.[15] Comparable ethnicity distribution was seen in a cross sectional study by Teh et al. (2020)[10] where Malays were the majority (66%), then Chinese (23.1%), Indians (9.4%) and others (1.5%).

Our study showed that amlodipine was prescribed more (71.8%) than perindopril (28.2%) in primary health clinics in the Northern region of Malaysia. Similar prescribing pattern was also adopted in 40 primary public health clinics in Malaysia[10], in which CCBs (77.2%) was the most commonly prescribed antihypertensive as compared to ACEIs (54.8%), BBs (29.8%), diuretics (23.4%), ARBs (5.8%) and alpha blockers (4.6%). The high usage of both perindopril and amlodipine in Malaysia shows that the prescribing practice of physicians was in line with the recommendation of CPG as both perindopril and amlodipine are the first line antihypertensive agents for essential hypertension.[16] Our finding is also in par with the conclusion from Malaysian Statistics on Medicines report in which CCBs (especially amlodipine) and ACEIs (especially perindopril) were the most utilized antihypertensive drugs in both public or private clinics in Malaysia from 2015 to 2016 (Malaysia Statistic on Medicines, 2016)[17], mostly due to readily availability of the generic products in the primary health clinic.[10]

Three month's follow-up data was used in this study to investigate the mean BP changes of perindopril and amlodipine. This is parallel with the recommendation of follow-up visits after initiation of an antihypertensive agent from several guidelines based on level three evidence. 2018 ESC/ESH guidelines for the management of arterial hypertension suggests to review patients within the first two months, however it depends on the severity of hypertension, patient's comorbidities and the urgency to achieve BP control.[18] Duration of follow-up of 3 months to 6 months is recommended by 2020 International Society of Hypertension Global Hypertension Practice Guidelines.[19] Similarly, Malaysia's CPG hypertension guidelines also recommends follow-up intervals based on global cardiovascular risk, pre-treatment levels and type of antihypertensive agents being used. An interval of 3 months to 6 months are recommended once the target BP is achieved.[16]

The data from 3 months follow-up visits are being used in this study is based on the several reasons. Firstly, one of the reasons was regarding the steady-state plasma concentration of both perindopril and amlodipine. During repeated administration of perindopril OD, perindoprilat accumulates around 1.5 to two folds and reaches steady-state plasma levels in 3 to 6 days[20,21], meanwhile amlodipine reaches steady-state plasma concentration after 7-8 days of continuous OD administration.[22-24] In addition, a meta-analysis analysed the 18 trials that recruited 4168 patients that were taking antihypertensive monotherapy estimated the maximum effect of antihypertensive therapy can be anticipated between the first and second weeks after administration.[25] Taylor et al. (1998)[26] elaborated a minimum time for amlodipine to achieve its full antihypertensive effect is at least 4 to 8 weeks at a constant dose. Similarly, Hu et al. (2017)[27] also revealed that maximum BP lowering effects can be observed at 4 weeks to 8 weeks after initiation of treatment with no effects from the half-life of antihypertensive agents. Hence 3 months of antihypertensive treatment used in this study should be able to provide the clear picture of sustained BP reduction effects of both antihypertensive agents.

In our study, perindopril 2mg and 4mg OD did not reduce mean DBP significantly. However, perindopril 2mg OD reduced mean SBP significantly in a comparable magnitude with 4mg OD, with the formal reduced mean SBP by 9.71 mm Hg and 8.15 mm Hg by latter. This finding is differed from the result reported in a randomized double-blind study, in which they studied the dose-effect relationship of perindopril in 40 patients with essential hypertension were administrated with either placebo or perindopril 2mg, or 4mg, or 8mg OD for a month after a two-weeks placebo run-in period.[28]

In the study of Luccioni et al. (1988), perindopril 8mg OD was associated with the highest BP reduction of 17/12 mm Hg, followed by perindopril 4mg OD (10/6.5

mm Hg) and perindopril 2mg OD has resulted in the least mean BP reduction (8/5 mm Hg). There was statistically significant difference in mean BP reduction by perindopril 8mg OD and 2mg OD and placebo, which justified the dose-effect relationship of perindopril. Another dose-effect relationship of perindopril was also shown in an open-label, multicentre and observation trial in Canada where additional mean BP reduction of 10.1/5.3 mm Hg were observed when perindopril 4mg OD was up-titrated to perindopril 8mg OD.[29] Nevertheless, our findings did not show the dose-effect relationship of perindopril due to the varied baseline characteristics of individuals and exclusion of patients who underwent dose titration.

Amlodipine reduced BP dose-dependently, in which magnitude of BP reduction by 5mg OD was 2-folds of that by 2.5mg OD. Mean SBP reduced by amlodipine 7.5mg OD and 10mg OD were also approximately 3-folds of the magnitude of SBP reduction by 2.5mg OD, while both amlodipine 7.5mg OD and 10mg OD reduced mean DBP approximately 2 to 3-folds of the magnitude of DBP reduced by 2.5mg OD. Our result was assumed to be comparable with the result from a multicenter, open-label, randomized, and parallel-group comparison study conducted in Japan.[30] Amlodipine has demonstrated a dose-dependent antihypertensive effects, which higher dose of amlodipine 10mg OD decreased BP to a greater extent than amlodipine 5mg OD in the study of Uno et al. (2008).[30]

In our study, amlodipine 2.5mg OD did not reduce mean SBP (6.83 mm Hg, $p = 0.051$) and mean DBP (1.74 mm Hg, $p = 0.291$) significantly after 3 months. But the p-value of mean SBP of 0.051 is almost close to statistically significance, and there is possibility of mean SBP dropping to $p < 0.05$ if more data of patients are added. Hence it is possible to interpret that amlodipine 2.5mg OD is in fact might be able to reduce mean SBP significantly. This finding is similar to the statement from a multicentre, open-label, randomized, parallel trial in China that examined the low dose (2.5mg OD) versus high dose (5mg OD) of amlodipine in 523 subjects with mild and moderate hypertension.[31] Low dose of amlodipine 2.5mg OD was effective to reduce mean BP by 20.60/12.70 mm Hg after 8 weeks. Efficacy of low dose of amlodipine 2.5mg OD was also demonstrated in a randomized, double-blind, parallel-group, placebo-controlled comparison trial in US. The BP was reduced significantly as compared to the baseline by approximately 12/6 mm Hg after 2 months treatment.[32]

Efficacy of low dose of amlodipine within shorter duration also being testified in another multicentre, double-blind, randomized, parallel study, which amlodipine 2.5mg OD reduced mean BP significantly by 11.40/10.30 mm Hg within one month.[33] Amlodipine 2.5mg OD was also being reported to be as effective as 5mg OD in an 8-week, open-labelled phase IV clinical trials in Turkey.[34] Amlodipine 2.5mg OD reduced mean SBP significantly in both treatment naïve patients (13.90 mm Hg) and patients who previously being treated with antihypertensive monotherapy (1.80 mm Hg) after 4 weeks. Mean DBP was reported to be reduced significantly, however only one set of the result of DBP was published without indicating whether it was reduced by amlodipine 2.5mg or 5mg OD. Hence, all of these findings clarified that low dose of amlodipine did not delay the goal-attaining time, but might be helpful to achieve BP control in certain group of patients, especially patients with marginal increase of BP to prevent hypotension and for elderly for its low incidence of adverse effects. In fact, the usual adult dosage of amlodipine for hypertension is 2.5mg to 5mg OD in Japan.[35]

Amlodipine 5mg OD in our study reduced mean BP significantly (12.95/ 4.11 mm Hg). This result is consistent with several studies despite the magnitude of BP reduction is varied. An 8-week, randomized, double-blind, phase II, multicentre study in Korea reported higher mean BP reduction (15.48/11.69 mm Hg) by amlodipine 5mg OD after 8 weeks treatment as compared to our study.[36] Another phase 2, multicentre, randomized, double-blind clinical trial in the same country also demonstrated comparable mean BP reduction by 17/11 mm Hg with the similar duration of treatment.[37]

Another phase 3, multicentre, collaborative, double-blind, parallel-group study in Japan also reported the similar result. Patients were administered with amlodipine 5mg OD during the 8 weeks screening period, then being randomly receiving either amlodipine 5mg or 10mg OD during the double-blind period of 8 weeks. The mean BP reduction by amlodipine 5mg OD was 7/2.70 mm Hg after 8 weeks treatment.[35] All these results testified amlodipine 5mg has provided a sufficient and effective antihypertensive effect for hypertensive patients.

Amlodipine 10mg OD in the study of Fujiwara et al. (2009)[35] also reduced mean BP significantly after 8 weeks. The magnitude of BP reduction in their study (13.70/6.80 mm Hg) was comparable to the finding from our study (14.08/6.35 mm Hg). The study of Fujiwara et al. (2009)[35] also verified that the high dose amlodipine 10mg OD is as safe as amlodipine 5mg OD, when they observed the similar incidence of adverse effects between amlodipine 5mg and 10mg groups. The incidence of peripheral oedema was low (about 4%) and the transient increased of pulse rate were mild and do not need medical treatment, proved that high dose of amlodipine has good tolerability and efficacy profile.

In comparison, the study of Park et al. (2012)[36] and Sohn et al. (2017)[37] reported a higher BP reduction by 23.62/16.43 mm Hg and 25.70/14.70 mm Hg respectively with high dose of amlodipine 10mg OD after 8 weeks. Again, the huge differences in magnitude

of BP reduction could partly be explained by the compliance to the drug regimen. Only patients with compliance level ≥ 80% were included in both studies, and the compliance level in Sohn et al. (2017)[37] was even higher, ranging from 92.5% to 96.7%. However, the compliance level was not able to be reassess in our study due to unavailability of the particular information in patient's medical record file or book. Of note, the prevalence of non-compliance toward antihypertensive treatment was observed in all Malaysian studies, example 51.30% in General Hospital of Penang, Malaysia[38], 46.6% in primary health clinic in Selangor[39] and 25% in Hospital Serdang, Malaysia[40], hence it is believed that non-compliance toward their hypertensive treatment that might cause the big discrepancies in our finding. The magnitude of BP reduction in our study, although not as impressively high as those studies, are nevertheless more reflective of the real-world practice.

CONCLUSION

Mean BP reduction by perindopril 2mg OD and 4mg OD in study population were 9.71/+0.67 mm Hg (6.48%/+0.77%) and 8.15/1.06 mm Hg (5.47%/1.23%) respectively. Amlodipine 2.5mg OD, 5mg OD, 7.5mg OD and 10mg OD reduced mean BP in study population by 6.83/1.74 mm Hg (4.55%/2.04%), 12.95/4.11 mm Hg (8.48%/4.65%), 18.06/3.18 mm Hg (11.11%/3.48%) and 14.08/6.35 mm Hg (9.04%/7.22%) respectively.

The result of this study shall provide the mean BP reduction of both commonly used antihypertensive agents, which enable the future researchers to evaluate a large cohort of Malaysians for antihypertensive effect of perindopril and amlodipine.

The results of this study also might serve as a reference for researchers to evaluate and compare the magnitude of BP reduction of Malaysians with other patients from Asian countries in future, although this study did not enrol significant number of Asian patients for adequate subgroup analysis. Some information like the sample size calculation will certainly be useful for future full-scale and prospective study. Hence this study is vital for the improvement for the quality and efficiency of future studies.

ACKNOWLEDGEMENT

The authors would like to acknowledge the Director General of Health, Ministry of Health Malaysia for allowing to conduct this study and to publish the research finding.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

All the authors have made a significant contribution to this manuscript, have seen and approved the final manuscript, and have agreed to its submission to the "European Journal of Biomedical and Pharmaceutical Sciences"

No financial disclosure

Conflict of Interest: All the authors have no conflict of interest in connection with the paper.

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