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ORIGINAL ARTICLE

Effect of Amlodipine/Valsartan Versus Nebivolol/Valsartan Fixed Dose Combinations on Peripheral and Central Blood Pressure

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Abstract

Introduction Although hypertensive drugs may have the same effect on peripheral blood pressure, they vary in their effect on central blood pressure and its indices.

Aim To evaluate efficacy of fixed-dose combination of amlodipine 10 mg/valsartan 160 mg versus nebivolol 5 mg/valsartan 160 mg in grade 2 or more hypertensive patients assessed by peripheral and central blood pressure.

Methods A prospective, open label, randomized study done in the outpatient cardiology clinic at Beni-Suef University Hospital. A total of 137 patients continued the study; group I (n = 75) received Amlodipine 10 mg/Valsartan 160 mg (A/V) and group II (n = 62) received Nebivolol 5 mg/Valsartan 160 mg (N/V). Peripheral, central blood pressure and its indices were measured at baseline, after 6 and 12 weeks.

Results The two combinations reduced peripheral and central BP ($P < 0.0001$) after 6 and 12 weeks. A/V combination significantly reduces central Pulse Pressure (PP) after 6 and 12 weeks (-8.53 ± 13.80 and -10.17 ± 11.29 ($P < 0.0001$) respectively), while N/V showed its efficacy in reducing central PP after 12 weeks (-7.03 ± 13.10, $P = 0.005$). A/V combination was more effective in reducing Pulse Wave Velocity (PWV) after 6 and 12 weeks; $P < 0.0001$ vs $P = 0.004$. After 6 weeks, N/V was more effective in reducing Augmentation Index (AIx) (-6.00 ± 10.94 ($P = 0.002$) vs. -3.44 ± 9.80 ($P = 0.026$)) while after 12 weeks A/V did not show any significance ($P = 0.085$).

Conclusions Both treatment groups lowered patients' peripheral, central blood pressure after 6 and 12 week of treatment, but Amlodipine/Valsartan combination was more effective. Both treatments exerted different effects on central indices.

Keywords Combination therapy · Peripheral blood pressure · Central blood pressure · PWV · AIx

1 Introduction

Combination therapy for hypertension with separate agents or a single-pill combination (SPC) has the ability to lower blood pressure in a short period of time and obtain target blood pressure, so it is recommended to start with in patients with grade 2 or more hypertension [1–3]. There were many recommended combination therapies in hypertension guidelines, among them the combination of Calcium Channel Blocker (CCB) or Beta Blocker (BB) with Angiotensin II Receptor Blocker (ARB) [2]. It is proven that anti-hypertensive therapy is effective in controlling patients' peripheral blood pressure and protecting them from target organ damage. Central blood pressure and arterial stiffness are independent predictors of target organ damage as they better represent the load imposed on the coronaries and cerebral arteries and thus having a strong relationship to prognosis and vascular damage [4, 5]. Therefore, both peripheral and central blood pressure should be considered when choosing blood-pressure-lowering medicines. So reducing both central and peripheral BP will be the optimal choice. Not all antihypertensive drugs affect aortic stiffness and central hemodynamics in a similar way. Combining an ARB with a CCB has the potential to reduce aortic stiffness

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and improving central hemodynamics (synergy at the vascular level) [6]. In comparison with other BBs, Nebivolol, one of the third generation cardio selective vasodilating beta blockers, has a great effect on arterial stiffness [7].

2 Patients and Methods

This was a prospective, randomized, open-label study conducted in the outpatient clinic of the cardiology department at Beni-Suef University Hospital during the period from October 2016 to January 2018. A total of 160 patients (age range from 25 to 84 years) were randomized in 1:1 basis into two groups. Group I (A/V) (n = 80) received a combination of Amlodipine 10 mg plus Valsartan 160 mg "single pill combination" once daily, group II (N/V) (n = 80) received Nebivolol 5 mg plus Valsartan 160 mg "one tablet for each" once daily for a 12-week period. During the study twenty-three patients were excluded 10 patients stopped their medication, 6 patients changed their medication, and 7 patients refused to continue the study. 137 patients completed the study; 75 patients from group I and 62 patients from group II. Demographic data and laboratory tests were done at the randomization. Peripheral and Central blood pressure was measured three times: at randomization, after 6 weeks and 12 weeks.

2.1 Patients

We enrolled patients with essential hypertension diagnosed with Grade 2 or more hypertension (defined as either systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100) "According to 2018 European Society of Hypertension (ESH) guidelines for the management of arterial hypertension" and a seated pulse rate of ≥ 55 bpm [8]. Patients were uncontrolled on their hypertension treatment; not achieving peripheral blood pressure goal (BP < 140/90 mm Hg) or having uncontrolled central blood pressure, were included in the study. Participants with secondary hypertension, women of childbearing period not using effective contraception "having a chance to be pregnant" and lactating women, Second- or third-degree heart block or sick sinus syndrome, Atrial fibrillation, Ischemic heart disease or heart failure and known hypersensitivity or contraindications to Valsartan, Amlodipine or Nebivolol were excluded from the study.

2.2 Blood Pressure Measurements

2.2.1 Peripheral Blood Pressure

A standardized manual sphygmomanometer was used for peripheral BP measurements with the appropriate cuff size to the patient's arm circumference. Three consecutive measurements of peripheral BP were measured by the doctor himself in the clinic with the patient seated for 5 min "discard the first reading and take average of the last 2 readings". Mean Arterial Pressure was calculated as MAP = [(2 × diastolic) + systolic]/3.

2.2.2 Central Blood Pressure and its Indices

Brachial Cuff-Based Method was used in this study using (Mobil-O-Graph, I.E.M. Stolberg, Germany) with its analysis software Hypertension Management Software Client–Server (HMS-CS 4.3), is a computerized tool for the assessment of a range of central arterial indices non-invasively. It is approved by The European Society of Cardiology (ESC) and Food and Drug Administration (FDA) [9]. All patients were requested to rest in a quiet room for at least 5 min before the measurement. They were examined in the sitting position without any movement or talking with proper cuffs wrapped around their non-dominant left arm. Data transferred directly via Bluetooth wireless technology after completion of the measurement. The ARCSolver algorithm calculates central BP on the basis of the brachial pulse wave. It provides equivalent performance to that of the SphygmoCor device and also for Central BP and its estimates that measured invasively [10].

Data were analyzed using the software, Statistical Package for Social Science (SPSS Inc. Released 2009, PASW Statistics for Windows, version 18.0: SPSS Inc., Chicago, Illinois, USA). Frequency distribution as percentage and descriptive statistics in the form of mean and standard deviation were calculated. Chi square, t-test, and correlations were done whenever needed and p values of less than 0.05 were considered significant.

3 Results

3.1 Baseline Characteristics of Both Groups

Both groups were well matched regarding baseline characteristics as summarized in Table 1. There were some patients in the study uncontrolled on their hypertension medication, 33 patients (44.0%) in group I and 35 patients (56.5%) in group II, without a statistically significant difference between two groups (P = 0.255). Left ventricular hypertrophy (LVH) has been detected by echocardiography in 14 patients (18.7%) from group I and 7 patients (11.3%) from group II (P = 0.170).

3.2 Efficacy

3.2.1 Peripheral Blood Pressure from Baseline to 6 and 12 weeks of Treatment

Both groups reduced pSBP, pDBP and MAP effectively from baseline to 6 and 12 weeks of treatment, but group

Table 1 Baseline demographic characters and risk factors

Variable	A/V "Group I" (n = 75)	N/V "Group II" (n = 62)	P value*
Age mean ± SD	55.44 ± 11.15	57.52 ± 10.24	0.263
Male gender	25(33.3%)	19(30.6%)	0.441
Weight (kg)	87.67 ± 15.45	84.54 ± 11.91	0.214
Height (cm)	166.50 ± 9.23	163.88 ± 6.60	0.075
BMI (kg/cm^2)	31.65 ± 6.46	31.58 ± 4.99	0.948
Smoking %			
Non-Smoker	64(85.3%)	59(95.2%)	0.081
Ex-Smoker	6(8.0%)	3(4.8%)	
Smoker	5(6.7%)	0(0%)	
Comorbidities			
Diabetes	19(25.7%)	18(30.5%)	0.335
Oral anti diabetic	14 (18.7%)	12 (19.4%)	0.994
Insulin	5 (6.7%)	4 (6.5%)	
Dyslipidemia	28 (37.3%)	31 (50.0%)	0.071
Kidney function			
Serum creatinine (mg/dl)	1.12 ± 0.75	0.99 ± .39	0.335
Blood urea	36.65 ± 14.74	35.56 ± 11.09	0.710
LVH by echocardiography	14 (18.7%)	7 (11.3%)	0.170

BMI Body Mass Index, *LVH* left ventricular hypertrophy

*p value is ≤ 0.05 is significant

I (A/V) was more effective than group II (N/V). The mean reductions in pSBP and pDBP after 6 weeks were (− 39.49 ± 17.32 mmHg and − 17.43 ± 11.54 mmHg in group I vs − 31.26 ± 13.57 mmHg and − 15.28 ± 10.79 mmHg in group II).

Also, after 12 weeks the mean reduction in pSBP and pDBP was (− 40.87 ± 17.05 mmHg and − 16.31 ± 11.77 mmHg in group I vs − 34.31 ± 16.47 mmHg and − 15.16 ± 11.32 mmHg in group II). The mean reduction in MAP was more in group I than group II after 6 and 12 weeks (Table 2).

3.2.2 Central Blood Pressure and its Indices from Baseline to 6 and 12 Weeks of Treatment

The mean reduction change in cSBP and cDBP after 6 weeks was more in group I than in group II; (− 19.83 ± 14.42 and − 12.81 ± 10.84 mmHg versus − 15.69 ± 12.53 and − 7.27 ± 8.93 mmHg respectively). Only 71 patients have completed central blood pressure 12 week follow up; (n = 39) in group I and (n = 32) in group II as shown in Fig. 1. After 12 weeks the mean change in cSBP in group I was − 19.48 ± 13.35 mmHg versus − 19.50 ± 15.50 mmHg in group II and cDBP was − 12.17 ± 9.69 in group I versus − 10.84 ± 13.14 mmHg in group II. Group I (A/V) showed a high statistical significant difference in reducing central PP after 6 weeks by reduction about − 8.53 ± 13.80 (P < 0.0001) however, group II showed no statistical significant difference in reducing central PP (P = 0.304). Unlike visit 2 "after 6 weeks", group II significantly lowered central PP after 12 weeks of treatment by − 7.03 ± 13.10 (P = 0.005) but group II continued with the same efficacy; P < 0.0001 as shown in Fig. 1.

Table 2 Comparing the efficacy of both groups in reducing peripheral blood pressure after 6 and 12 weeks of treatment

Variable	A/V "Group I" Mean change ± SD		N/V "Group II" Mean change ± SD		P value
	After 6 weeks (n = 75)	After 12 weeks (n = 46)	After 6 weeks (n = 62)	After 12 weeks (n = 37)	
pSBP	− 39.49 ± 17.32	− 40.87 ± 17.05	− 31.26 ± 13.57	− 34.31 ± 16.47	< 0.0001*
pDBP	− 17.43 ± 11.54	− 16.31 ± 11.77	− 15.28 ± 10.79	− 15.16 ± 11.32	< 0.0001*
MAP	− 24.78 ± 11.55	− 24.50 ± 11.74	− 20.60 ± 9.57	− 21.54 ± 11.15	< 0.0001*

pSBP peripheral systolic blood pressure, *pDBP* peripheral diastolic blood pressure, *MAP* mean arterial pressure

*P value is ≤ 0.05 is significant

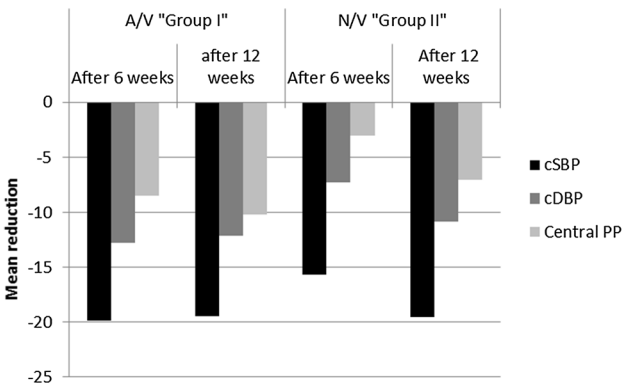

Fig. 1 Bar chart showing the mean reduction of central SBP, central DBP and central PP after 6 and 12 weeks from baseline (group I versus group II). *cSBP* central Systolic Blood Pressure, *cDBP* central Diastolic Blood Pressure, *PP* Pulse Pressure

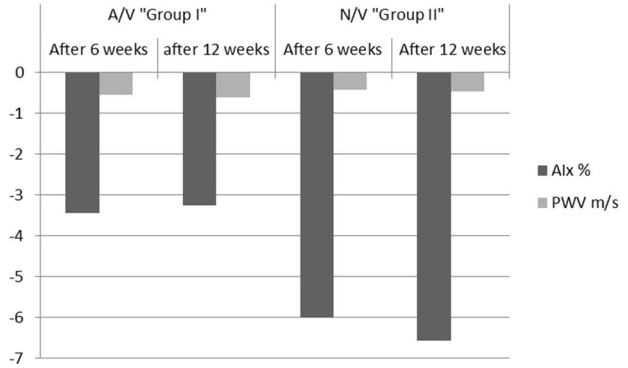

Fig. 2 The mean reduction in Augmentation Index and PWV in A/V "group I" versus N/V "group II" after 6 and 12 weeks. *AIx* Augmentation Index, *PWV* pulse wave velocity

There was no significance difference in reducing HR in both groups after 6 weeks, however group II showed some numerical reduction in HR [from 72.94 ± 11.81 bpm to 69.47 ± 12.10 bpm (P = 0.058)] compared with [81.37 ± 14.24 bpm to 81.49 ± 15.88 bpm (P = 0.957)] in group I. Also, after 12 weeks there was no statistical significant difference between both groups in reducing HR [− 0.05 ± 12.65 bpm in group I (P = 0.980) vs. − 2.25 ± 10.95 bpm in group II (P = 0.254)].

Regarding Arterial stiffness markers; Augmentation Index (AIx) and Pulse Wave Velocity (PWV), both treatment schemes significantly reduced them after 6 weeks of treatment as shown in Fig. 2. Group II (N/V) showed more efficacy in reducing AIx than group I (A/V); − 6.00 ± 10.94 (P = 0.002) versus − 3.44 ± 9.80 (P = 0.026). However, after 12 weeks group II significantly lowered AIx by a mean difference − 6.56 ± 12.64% (P = 0.006) while group I didn't show any significance (P = 0.085). Both groups showed a highly statistical significant difference in reducing PWV, the degree from strongest to weakest in reducing PWV were group I (A/V) and group II (N/V) [− 0.54 ± 0.78 m/s (P < 0.0001) versus − 0.43 ± 0.86 m/s (P = 0.004)] after 6 weeks and [− 0.60 ± 0.50 m/s (P < 0.0001) versus − 0.47 ± 0.86 m/s (P = 0.004)] after 12 weeks.

There was no statistical significant difference between both groups after 6 weeks in reported adverse effects (P = 0.091). Moderate lower limb (LL) edema and dizziness reported by patients in group I only; n = 6 (8.0%) and n = 1 (1.3%). Mild LL edema, headache and shortness of breath each reported by the same number of patients in group II only; n = 1 (1.6%). After completion of 12 weeks, two patients (3.2%) from group II (N/V) still not controlled. Only one patient (1.3%) from group I (A/V) reported some signs of hypotension without significance difference between both groups (p = 0.196).

The number of patients in whom LVH was detected remained the same after the 12 weeks follow up [14 patients (18.7%) from group I and 7 patients (11.3%) from group II (P = 0.170)]. Also, There was no statistical significance difference between both groups after 12 weeks as regard serum creatinine and blood urea; (P = 0.928) and (P = 0.634) respectively. Serum creatinine was 1.00 ± 0.21 mg/dl in A/V group and 1.00 ± 0.32 mg/dl in N/V group, and blood urea was 35.28 ± 13.72 mg/dl in A/V group and 33.94 ± 9.99 mg/dl in N/V group. Two patients having a high serum creatinine were randomly assigned to nebivolol/valsartan group, and after the 12 weeks of treatment their serum creatinine improved from (2.24 mg/dl) to (1.69 mg/dl) and from (2.66 mg/dl) to (2.4 mg/dl).

4 Discussion

There were many studies used to investigate the effect of Amlodipine/Valsartan on peripheral BP, central BP and comparing it with different drug combinations. However, there is no study used to compare the effect of amlodipine/valsartan versus nebivolol/valsartan combinations on central BP and its indices. The main findings were that both treatment groups lowered patients' peripheral, central BP and mean arterial pressure effectively after 6 and 12 weeks of treatment, but A/V was more effective. A/V reduced central PP after 6 weeks of treatment, but N/V didn't show any effect after the same duration. After 12 weeks, both treatments reduced central PP but A/V was superior to N/V. Both treatments reduced AIx after 6 weeks of treatment, although after 12 weeks A/V did not show any effect. Also, they reduced PWV but A/V was more effective than N/V.

In the present study, both treatment lower peripheral BP after 6 weeks and 12 weeks of follow up as seen in Table 2. But the mean change in reducing peripheral BP is

more in A/V than in N/V. The results in the present study are comparable with the previous studies of Timothy et al. [11] and Philipp et al. [12] that confirmed the efficacy of Amlodipine/Valsartan combination in reducing peripheral BP. Also, in 2013 Kizilirmak et al. [13] in a Systematic Review and Meta-Analysis of 11 studies confirmed the same results.

It is generally believed that combining a BB with a Renin–Angiotensin–Aldosterone System (RAAS) blocker is not ideal as it exerts little additional BP reduction compared with monotherapy with either agent alone. In contrast, two short-term randomized control trials showed a significant BP reduction with nebivolol as add-on therapy "to ACE inhibitors or ARBs" at 12 weeks or as a combination with lisinopril [14, 15]. Also, Ishak et al. [16] used to compare nebivolol as a BB + valsartan as a RAAS inhibitor with multiple types of CCBs including Amlodipine + RAAS inhibitor "valsartan" support our results that the two drug combinations were comparable in reducing peripheral BP and that combining a particular BB "vasodilatory BB" and a RAAS inhibitor produce effective BP reduction [17].

The anti-hypertensive drugs vary in their ability to decrease central blood pressure despite having the same effect on peripheral BP [4]. The strong heart study recommended central blood pressure as treatment targets in future trials [5]. Both treatment combinations are effective in reducing central SBP and central DBP. After 6 weeks, A/V is more effective than N/V in reducing mean central SBP and central PBP. The two combinations reduce mean central SBP after 12 weeks to nearly the same extent but A/V remain more effective regarding reducing mean central PBP. In the CAFE study [4], amlodipine ± perindopril-based treatment was more effective than atenolol ± thiazide-based treatment at lowering central systolic and diastolic blood pressures. Ruilope et al. [18] in a multi-center study demonstrated that combination of olmesartan/amlodipine was superior to perindopril/amlodipine in reducing cSBP and that support our results that adding ARBS contributes to much higher efficacy. Nebivolol use seems to be associated with a significant reduction of central BP in stage I hypertension [19]. Short and long-term studies showed the high efficacy of nebivolol in reducing central blood pressure compared to other b-blockers [20, 21].

Central PP may be a determinant of clinical outcomes more than brachial PP [5]. The two treatment groups in the present study exerted different effects on central PP, but amlodipine/valsartan combination showed higher efficacy (Fig. 2). In CAFE study [4], Central PP lowered significantly with amlodipine-based therapy than atenolol-based therapy. Previous studies showed a significant effect of nebivolol compared to other BB in reducing central PP after 4 weeks on patients with essential hypertension or 5 weeks on patients with isolated hypertension compared to atenolol. Kampus et al., 2011 [21] in their study showed that nebivolol significantly reduced central PP after 1 year of treatment.

In the present study, both treatments did not lower HR significantly after 6 and 12 weeks, which may be because that HR in both groups wasn't high. Previous studies showed the same findings; Boutouyrie et al. [22] in a previous randomized controlled trial showed superior effect of the BB "atenolol" over ARBS "valsartan" in reducing HR change at Week 8 and Week 24. In the EXPLOR study [23], heart rate decreased significantly with amlodipine-atenolol more than amlodipine-valsartan, that's mainly due to the effect of atenolol. Also, Studinger et al. [24] demonstrated the low effect of nebivolol on HR compared to other BB including carvedilol.

Nebivolol/valsartan combination in the present study was superior to amlodipine/valsartan in reducing AIx after 6 weeks of treatment. Nebivolol/valsartan combination remained effective after 12 weeks, but amlodipine/valsartan combination reduced AIx numerically without any significance of treatment and that's may be because nebivolol decreases peripheral resistance through vasodilation. CCBs, in particular amlodipine, have been evaluated in the CAFE study with the ACEI perindopril, showing a significant reduction in central AIx [4]. After 8 and 24 weeks of treatment in Explore study, amlodipine/valsartan combination decreased AIx more than the amlodipine/atenolol combination [23]. A randomized, open-label clinical study in 2013 done by Studinger et al., [24] showed highest efficacy of nebivolol in reducing AIx compared to carvedilol and metoprolol, that effect was arisen from its peripheral vascular effects.

In the present study, there occurred a highly significant reduction in PWV after 6 and 12 weeks of treatment in both groups but the amlodipine/valsartan combination showed much efficacy (Fig. 2). The results in the present study agreed with meta-analysis of 15 randomized trials demonstrated that in the short-term trials, Angiotensin Receptor Blockers (ACEIs) were more effective than CCB and placebo on improving arterial stiffness. In Shi et al., 12 weeks treatment study in 2017, Valsartan alone was stronger than combining it with amlodipine in reducing PWV, and amlodipine alone showed the least effect [25]. A previous study of Kampus et al. [21] comparing nebivolol and metoprolol, which showed a reduction in PWV in nebivolol group only after 6 weeks but there was no further effect of nebivolol in reducing PWV after 1 year. Also, two short-term studies demonstrated a significant reduction in PWV after treatment with nebivolol [20, 26].

There was no statistical significant difference between both groups as regard side effects. Fogari et al. [27] in at 6 weeks randomized, open label, crossover trial agreed with the low incidence of edema in the present study, the percentage of LL edema on amlodipine 10 mg was 30% versus 7.5%

in patients taken amlodipine 10 mg/valsartan 160 mg. Minor side effects with nebivolol in our study were comparable to the results of a meta-analysis in double-blinded, placebo-controlled trials, which finds no difference in adverse effects with nebivolol as compared with placebo [28]. Also, long-term, multi center safety study of nebivolol/valsartan combination showed that it was better tolerated with minimal side effects [17].

Due to short-term follow up, the number of patients having LVH did not change. That's matched with The European guidelines of hypertension recommendations in that LVH detected by echocardiography needs more than 6 months to change [8]. As regard renal fuction, there were just 2 patients in group II (N/V) their renal function improved, but from this small number we cannot get a conclusion.

4.1 Limitations

It is an open-label study. The number of patients was relatively small, resulting in the mismatch of some baseline indices. It was a rather short period study. Thus, a future study with a long period of follow up should be applied to access this therapeutic effect.

5 Conclusion

Both amlodipine/valsartan and nebivolol/valsartan can effectively control peripheral and central blood pressure, although amlodipine/valsartan remains more effective. Also, they vary in their effect on central indices. Non-invasive central blood pressure device should be more commonly used in hypertension clinics for better prediction of target organ damage. We believe that it's better to adjust both central and peripheral blood pressure at the same time.

Compliance with Ethical Standards

Ethical approval The study was approved by Faculty of Medicine - Beni-Suef University Research Ethical Committee "FM-BSU REC" and was registered (FWA00015574).

Informed consent Informed consent was obtained from each patient before participation in the trial.

Conflict of interest We declare that we have no conflict of interest.

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