



Adequacy of Olmesartan monotherapy versus cotherapy in patients with essential hypertension

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ABSTRACT

Olmesartan is a class of an angiotensin II receptor blocker drugs used for the treatment of hypertension. The aim of this crossover clinical study is to evaluate the safety and effectiveness of Olmesartan monotherapy compared to Olmesartan plus amlodipine co-therapy in patients with essential hypertension. An entire of eighty-three patients (45 males, 38 females) their age ranging (45-55) years with essential hypertension enrolled from Al Yarmouk hospital /Iraq for this study. After reaching the point of inclusion criteria, they treated with Olmesartan medoxomil 20 mg daily for a period of two months, then after two weeks of wash off, they treated with Olmesartan 20 mg daily plus amlodipine 10 mg daily for another two months. Blood pressure (systolic and diastolic) and clinical laboratory tests that include fasting blood levels of glucose, insulin, lipid profile, adiponectin, leptin, cystatin c and creatinine were obtained and studied at baseline (prior treatment), after two months of Olmesartan monotherapy and after two months of Olmesartan co-therapy. The statistical analyses of the data in patients using Olmesartan co-therapy versus Olmesartan mono therapy showed more effectiveness in decreasing blood pressure, better in reducing the blood levels of glucose, insulin, total cholesterol, triglyceride, and leptin, superior in elevating the values of insulin sensitivity index and in elevating the blood levels of adiponectin. Concisely, the addition of amlodipine to Olmesartan treatment ameliorated insulin sensitivity and adiponectin level and attenuated the leptin level.



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INTRODUCTION

Olmesartan medoxomil (Benicar) is a class of an angiotensin-II receptor blocker (ARB) that used for the management of hypertension as alone or in com-

ination with other drugs (Mason, 2011). Amlodipine is a calcium channel blocker drug used for decreasing blood pressure by its effect as a vasodilator of peripheral arteries on smooth muscles of blood vessels (Derosa and Maffioli, 2011). Olmesartan, like other drugs belong to angiotensin-II receptor blocker (ARB) act by inhibiting the binding of angiotensin-II to its receptor, angiotensin type 1 (AT₁) receptors, in vascular smooth muscles and thereafter inhibiting its vasoconstrictor effect causing lowering in blood pressure (Agata *et al.*, 2006).

Olmesartan medoxomil (C₂₉ H₃₀ N₆ O₆) was inactive ester form drug that after oral intake absorbed quickly through the alimentary channel and converted in the liver to its active form (RNH-6270) (Aulakh *et al.*, 2007). It is excreted in urine as unchanged (small amount) or as conjugated form after metabolized in the liver. Thus, patients with

renal disease may need for modulating their dose of Olmesartan (Lu *et al.*, 2014). Many drugs used for the treatment of hypertension as monotherapy or cotherapy. The goal of combination is to regulate the blood pressure and to lower for the far extent the cardiovascular adverse incidents (Turnbull *et al.*, 2003).

Numerous studies found that the optimum level of blood pressure needed to reach with treatment for hypertensive patients with no specific organ defect was 140/90 mmHg, and for hypertensive patients with other organ defects like diabetes, kidney or heart defect was 130/80mmHg (European Society of Hypertension, 2003).

The use of combine therapy in the treatment of hypertension was either to lesser the blood pressure more efficiently or to reduce the unfavorable effects of either drug. For Instance, the use of valsartan or telmesartan with amlodipine (dihydropyridine) was found to be more effective in lessening blood pressure in reducing edema and unfavorable effect of amlodipine and in minimizing the atrophy of left ventricle (Fogari *et al.*, 2012a).

The ambition of this cross over clinical study is to evaluate and scrutinize the impact of the addition of amlodipine on Olmesartan treatment as compare to Olmesartan alone by using many biochemical markers in patients with essential hypertension.

MATERIALS AND METHODS

Study design and location

This randomized, crossover clinical study conducted at al Yarmouk hospital/in Iraq. An entire of eighty-three patients (45 males and 38 females) aged range 45-55 years of either sex, with stage I essential hypertension, which defined as systolic blood pressure (SBP) ranging 140 -160 mmHg and diastolic blood pressure (DBP) ranging 90 -100 mmHg.

Patients selection

All participants examined through collecting medical histories, vital signs, measuring blood pressure and electrocardiogram. After that patients with ineligible criteria will be excluded, such as secondary hypertension, abnormality in liver function or kidney function, impaired cardiovascular conditions and patients with known sensitivity to drugs such as angiotensin-II receptor blocker or calcium antagonists.

All eligible patients will put in a washout period for 2 weeks from taking any drug and will provide written informed consent to partake in this study. The study protocol coincides to the ethical guidelines of the

Declaration of Helsinki and approved by the institution's ethics committee.

Thereafter the patients will be allocated on Olmesartan medoxomil (Benicar) tablet (20 mg daily) for two months period. At the ends of the first two months period, the patients put on the washout period for two weeks, then the patients allocated on Olmesartan medoxomil tablet (20 mg daily) plus amlodipine besylate (Acino) tablet 10 mg daily for another two months period. During the periods of the study, all patients were examined weekly for evaluating the adverse outcome and drug sufferance.

Data collection and laboratory measurements

After 12-hr. Overnight fasting, venous blood samples were taken for all patients between 8 - 9 am at baseline (prior treatment, after two months of monotherapy and after two months of cotherapy). Commercially available Kits were purchased to measure the biochemical parameters by following the manufacturer's instructions for each kit and all the samples were examined in duplicate.

Fasting blood glucose levels were assayed by glucose-oxidase method (HUMAN-Germany), blood levels of Cystatin C, adiponectin, insulin and leptin were measured by using enzyme-linked immunosorbent assay (ELISA) method (CUSABIO). Blood levels of total cholesterol, high-density lipoprotein-cholesterol, triglyceride (AGAPE-Switzerland) and creatinine (HUMAN-Germany) were estimated by using Photometric Colorimetric method.

Quantitative Insulin-Sensitivity Check Index (QUICKI), an index of insulin sensitivity (Katz *et al.*, 2000), is calculated as follows (insulin expressed in $\mu\text{U/ml}$ and glucose expressed in mg/dl): $\text{QUICKI} = 1/[\log(\text{insulin}) + \log(\text{glucose})]$

Statistical analyses

Data stratified as mean \pm SD (standard deviation) with a 95% confidence interval (CI). Contrasting of continuous variables was analyzed by using Student's *t*-test. All tests for statistical significance were two-tailed and *P* values of <0.05 were taken as an edge point for statistical significance. All statistical analyses accomplished by using series SPSS version 18 and Microsoft Excel.

RESULTS AND DISCUSSION

(Table 1) displayed the details of demographic characteristics, biochemical data, and statistical analyses of the selected variables in the studied patients. Notably, a high significant suppression in the blood

Table 1: Alterations of blood pressure and clinical bioassays for the studied patients

Variables	Baseline (prior treatment)	Olmesartan monotherapy (2 months)	Olmesartan plus Amlodipine cotherapy (2 months)
Number	83	83	83
Gender (Male/Female)	(45,38)	(45,38)	(45,38)
Age (year)	50 ± 5	50 ± 5	50 ± 5
SBP (mmHg)	148±17	140±16 ***	136±15 *** c
DBP (mmHg)	98±8	90±7 ***	85±6 ***c
Glucose (mg/dL)	88±5	85±5.2 ***	84±6.2 ***
Insulin (μU/mL)	10±3	9.2±2.8	8.6±3.2 *
Quicki	0.342±0.02	0.348±0.02	0.351±0.025 *
Total cholesterol (mg/dL)	189±16	182±16.2 *	180±18.3 **
HDL-C (mg/dL)	48±5	47.5±5	46.8±6
Triglyceride (mg/dL)	164±22	157±22.7 *	154±23 **
Creatinine (mg/dL)	0.96±0.4	0.95±0.3	0.97±0.3
Cystatin C (mg/dL)	0.76±0.03	0.75±0.03	0.755±0.03
Adiponectin (μg/mL)	3.8±0.3	4.3±0.35 ***	4.6 ±0.43 ***c
Leptin (ng/mL)	6.3±0.8	5.3±0.82 ***	5.2±0.91 ***

Data presented as mean ± SD for continuous variable, (*) significant difference $P < 0.05$ vs. baseline, (**) high significant difference $P < 0.005$ vs. baseline, (***) high significant difference $P < 0.001$ vs. baseline, (C) high significant difference $P < 0.001$ vs. monotherapy. Abbreviation :SBP :Systolic blood pressure, DBP : Diastolic blood pressure, Quicki : Quantitative insulin-sensitivity check index, HDL-C : High-density lipoprotein cholesterol.

pressure (systolic and diastolic) ascertained after two months of treatment with Olmesartan alone or with Olmesartan plus amlodipine co-therapy when compared to the baseline mean values (Table 1). However, the percentage of suppression of blood pressure (systolic and diastolic) after two months of treatment were more with Olmesartan co-therapy than with Olmesartan monotherapy (Figure 1).

Analyses of fasting plasma glucose level revealed a high significant decrease ($P < 0.001$) after two months of treatment with Olmesartan alone or with Olmesartan plus amlodipine therapy as compared with the baseline mean level. Whereas the percentage of suppression of fasting plasma insulin level after two months treatment was more with Olmesartan plus amlodipine co-therapy than with Olmesartan monotherapy (Figure 1).

Even though both treatment approaches increased insulin sensitivity index (Quicki) as compared to the baseline mean value, but Olmesartan plus amlodipine co-treatment was more effective in increasing Quicki value than Olmesartan mono treatment (Table 1).

As shown, the mean plasma levels of total cholesterol, triglyceride and leptin were considerably lower after two months treatments, but they are more significantly lower in concomitant adminis-

tration of Olmesartan plus amlodipine than in the administration of Olmesartan alone, as illustrated in (Figure 1) and (Table 1).

Conversely, in contrast to prior treatments, although the mean plasma level of adiponectin was appreciably higher in patients on Olmesartan alone and in patients on co-therapy of Olmesartan plus amlodipine. But the percentage of elevation of adiponectin plasma level was more superior with the intake of Olmesartan plus amlodipine than with intake of Olmesartan alone as elucidated in (Figure 1) and (Table 1).

There were unnoteworthy alterations in mean plasma levels of cystatin c, creatinine, and high-density lipoprotein cholesterol after two months of treatment with Olmesartan alone or with Olmesartan plus amlodipine cotherapy as compared with their baseline mean levels.

(Figure 2) charted the momentous power analysis for the minimum detectable effect of amlodipine (10 mg daily) addition to Olmesartan treatment (20 mg daily) on blood pressure (systolic and diastolic) and on plasma levels of adiponectin.

There were 80% eventuality that addition of amlodipine 10 mg daily to Olmesartan treatment 20 mg daily causes a decrease of 6.04 mmHg (4.31%) in mean value of systolic blood pressure, a decrease

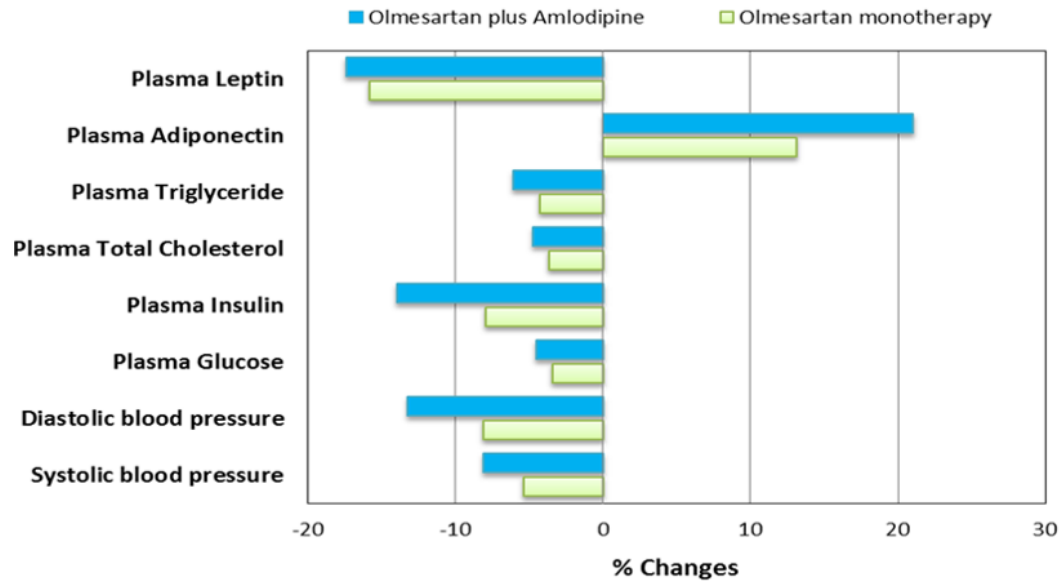


Figure 1: Prominent percentage changes in mean values of blood pressure and of selected bioassays for the studied patients

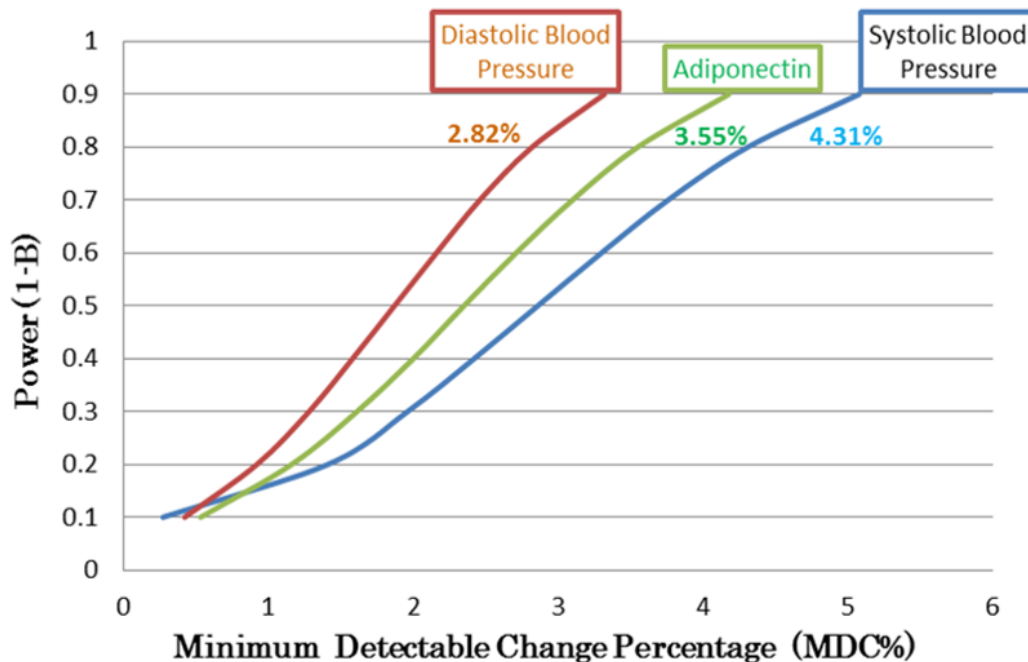


Figure 2: Power analysis for the minimum detectable effect percentage of Amlodipine 10 mg addition to Olmesartan 20 mg daily for two months treatment period

of 2.54 mmHg (2.82%) in mean value of diastolic blood pressure, and an increase of 0.153 $\mu\text{g}/\text{mL}$ (3.55%) in mean plasma level of adiponectin.

Although Olmesartan drug has a potent effect on reducing blood pressure as compared to other drugs, belong to angiotensin II receptor blocker (Zaiken *et al.*, 2013), but cotherapy of Olmesartan with amlodipine found to be more effectively decrease blood pressure as demonstrated in this study and previously reported study (Chrysant *et al.*, 2008).

Many study found that the drugs related to either angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), or calcium channel blockers not accompanied with the increased menace of diabetes. Unlike other drugs (β -blocker or diuretic), that increased menace of diabetes (Taylor *et al.*, 2006).

Regarding the effect of both drugs on the sensitivity of insulin, the observation of this study noticed that both monotherapy of Olmesartan and cotherapy with amlodipine amended the sensitivity of insulin,

but more amendments occurred with cotherapy of Olmesartan and amlodipine.

Contrarily, other study found that the sensitivity of insulin amended with monotherapy of losartan (angiotensin II receptor blocker) rather than monotherapy of amlodipine (Fogari *et al.*, 2012b). Therefore, the concomitant taking of Olmesartan and amlodipine enhanced insulin sensitivity better than taking amlodipine lonely.

The prolonged activation of AT1 receptor by angiotensin II causing increase in superoxide anion production, oxidative disturbance, and abnormal function of vascular endothelium (Pueyo *et al.*, 2000; Masuda *et al.*, 2012). Consequently, the using of an ACE inhibitor or ARB will decrease the generation of oxidative anion and decreasing the level of oxidase enzyme, an angiotensin II-dependent enzyme, leading to more conservation of endothelium (Nickenig and Harrison, 2002). As well, Olmesartan modulate the movement and function of endothelial progenitor cells in carotid arteriosclerosis patients (Gong *et al.*, 2015).

Additionally, cross-talk signaling pathways that connect the angiotensin II receptor signaling pathway with the insulin receptor signaling pathway and may relate to insulin resistance can interrupt with the intake of angiotensin II receptor blockers. Hence, amelioration of endothelium function may lead to amelioration of insulin sensitivity (Han *et al.*, 2007a).

The measurement of lipid assay in this study informed a significant lessening in triglyceride level with Olmesartan monotherapy and with Olmesartan plus amlodipine cotherapy and this result was inconsistent with the result achieved by (Nishida *et al.*, 2011).

The current study showed insignificant alteration in mean serum levels of HDL-Cholesterol in patients with Olmesartan monotherapy and in patients with Olmesartan plus amlodipine cotherapy as compared with the baseline mean.

Contrarily, other study found that the level of HDL-Cholesterol was more significantly elevated in patients on Amlodipine monotherapy. The elevated level of ATP-binding cassette transporter A1 and apo-A1 that occur with the using of calcium channel blockers drugs (Amlodipine, Verapamil) lead to enhance HDL formation (Koh *et al.*, 2010). Adiponectin is an adipocyte producing protein that enhances and imitates the effect of insulin on vascular tissues (Han *et al.*, 2007b).

In this study, Olmesartan monotherapy and Olmesartan plus amlodipine cotherapy highly signifi-

cantly increased blood level of adiponectin when compared with the baseline mean. The elevated blood level of adiponectin may reflect the amelioration of endothelial performance and insulin susceptibility.

Angiotensin II enhances leptin production from adipocyte, thus the inhibition of the Angiotensin II receptor will lead to decrease in leptin production (Skurk *et al.*, 2005). This may explain the reason of the high significant decrease of blood leptin levels, in this study, in patients with Olmesartan monotherapy and patients with Olmesartan plus amlodipine cotherapy when compared with the baseline mean. The increased level of leptin with the increased level of angiotensin II may associate with the inflammation of the blood vessels, disturbance in oxidative status and overgrowth of vascular smooth muscle, as well; these factors may enhance the risk of cardiovascular diseases (Koh *et al.*, 2008).

CONCLUSIONS

The clinical observations of this study offer a valuable role of Olmesartan and amlodipine co-therapy, in addition, to lessen blood pressure, in ameliorate insulin sensitivity and adiponectin production, and in attenuate leptin production.

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