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A Comparative Study of Efficacy & Safety of Aliskiren as an Add On Therapy to Olmesartan Versus Olmesartan Monotherapy in Patients with Hypertension

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ABSTRACT: The aim of the study was to compare the efficacy and safety of aliskiren as an add-on therapy to olmesartan versus olmesartan monotherapy in patients with hypertension. **Material and methods:** This was a prospective, randomized, comparative, open label, parallel study done on 50 patients who were divided into two groups of 25 patients each and were randomly allocated with the help of computer generated random numbers to receive treatment either with combination therapy of aliskiren 150mg plus olmesartan 40mg once daily (Group 1) or olmesartan 40mg monotherapy once daily (Group 2) for 8 weeks. Efficacy assessment was done for mean systolic and diastolic blood pressure in sitting, standing and recumbent posture, changes in QRS amplitude in ECG, blood urea, serum creatinine, 24hr proteinuria. The patients were followed-up at 0, 2, 4 and 8 weeks. Safety assessment was also done by observing for the side effects due to study medications. **Results:** There was statistically significant reduction in mean blood pressure in all the postures in both the groups, with an average fall by 28/14 mmHg in olmesartan and aliskiren combination therapy and by 23/11 mmHg in olmesartan monotherapy. Reduction in QRS amplitude (0.72 mm) was statistically significant in combination group as compared to monotherapy group. At the end of 8 weeks, both group1 and group 2 showed statistically significant reduction in 24hr-proteinuria levels (0.06 Vs 0.056 gm/24 hrs, $p<0.05$) respectively. **Conclusion:** Aliskiren as an add-on therapy to olmesartan compared to olmesartan monotherapy had better efficacy in BP reduction, anti-proteinuric effect. Combination therapy was equally safe as olmesartan monotherapy.

KEYWORDS: Hypertension; Systolic Blood Pressure; Diastolic Blood Pressure; Aliskiren; Olmesartan.

INTRODUCTION

Hypertension is defined as repeatedly elevated blood pressure exceeding 140 over 90 mmHg—a systolic pressure above 140 mmHg and a diastolic pressure over 90 mmHg. Presently hypertension is recognized as one of the most important risk factors accounting for nearly 50% in the development of cardiovascular diseases worldwide. It is the 4th major contributor of death in developed countries and 7th in

developing countries.[1] It is the leading cause of death in the U.S. accounting for 1 in every 2.8 deaths.[2] In India, the prevalence of hypertension is 59.9 and 69.9 per 1000 in males and females respectively in the urban population, and 35.5 and 35.9 per 1000 males and females respectively in the rural population.[3]

Most of cases of hypertension cannot be adequately controlled by monotherapy but have to be managed by combination therapy. Benefits of controlling blood pressure is that there is reduction in the incidence of stroke by 35-40%, myocardial infarction by 20-25%, and heart failure by more than 50%.[4] Effective BP control can be achieved in most patients but majority may require two or more antihypertensive drugs. A goal of BP less than 140/90 mmHg is appropriate for general prevention of cardiovascular disease[5] and a BP of less than 130/80 mmHg is recommended in patients with coronary artery disease (CAD), chronic kidney disease (CKD), stable and unstable angina and cerebrovascular disease.[6] It is important to prescribe lifestyle modifications like dietary control, weight loss, smoking cessation, reduced alcohol intake, regular exercise along with antihypertensive therapy for adequate BP control.

The Joint National Committee for Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) and 2010 Institute for Clinical Systems Improvement (ICSI) guideline on diagnosis and treatment of hypertension recommend thiazide diuretics as preferred initial agents in the absence of compelling indications. Compelling indications include heart failure, ischemic heart disease, chronic kidney disease, recurrent stroke, diabetes, high coronary disease risk, drug intolerability and contraindications.[7] In such conditions, other class of drugs should be initiated like angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), beta-blockers as effective alternatives. It is estimated that only 53% of patients receiving the treatment for hypertension achieve BP control either with monotherapy or combination therapy with various drug classes.[6] Hence, drugs with better efficacy and safety are required.

Olmesartan medoxomil is the latest angiotensin II receptor blocker approved by US-FDA for use in hypertension due to its potential advantages like once daily dosing, absence of significant adverse reactions, cost-effectiveness. This drug works by inhibiting angiotensin II, a potent vasoconstrictor and an important etiologic factor contributing to cardiovascular and renal disease. ARBs have been approved as effective alternatives for ACEI intolerant patients for treatment of hypertension.[8] A randomized trial, the ORIENT (Olmesartan Reducing Incidence of End stage Renal Disease in Diabetic Nephropathy Trial) study had shown that Olmesartan significantly decreased blood pressure, proteinuria and rate of change of reciprocal serum creatinine, in comparison to placebo in patients who received concomitant ACEI therapy. Its efficacy and safety has been demonstrated by various clinical studies like Williams study, Oparil study and ROADMAP study. These studies have shown that olmesartan monotherapy or combination therapy produced better reduction in BP compared to various other drugs.[8]

Aliskiren is an orally active direct renin inhibitor (DRI). Renin cleaves angiotensinogen to Ang I which is then converted to Ang II by ACE. Ang II is a powerful vasoconstrictor and leads to the release of catecholamines from the adrenal medulla and prejunctional nerve endings. It also promotes aldosterone secretion and sodium reabsorption. Aliskiren decreases the plasma renin activity (PRA) and inhibits the conversion of angiotensinogen to Ang I. All agents that inhibit the RAAS, including renin inhibitors, suppress the negative feedback loop, leading to compensatory rise in plasma renin levels which may render incomplete cardiorenal protection. During treatment with aliskiren, the effect of increased renin levels is blocked so that PRA, Ang I and Ang II are all reduced.[9] The combination of a DRI and an ARB or an ACE inhibitor is an effective approach for lowering blood pressure; available data indicates that such combinations favorably affect proteinuria, left ventricular mass index, and brain natriuretic peptide in patients with albuminuria, left ventricular hypertrophy, and heart failure. In this study, a comparison of efficacy and safety of aliskiren and olmesartan combination therapy with olmesartan monotherapy was made in patients with hypertension.

MATERIALS & METHODS

This was a prospective, randomized, comparative, open label, parallel study conducted by Department of Pharmacology and Medicine, Pt. B. D. Sharma PGIMS, Rohtak on 50 patients of either sex with newly diagnosed hypertension. An informed consent was obtained from all the patients who were enrolled for the study. The study protocol was approved by the PG Board of Study in Para-clinical Sciences and Institutional Review Board in PGIMS Rohtak.

The patients were divided in two groups of 25 each and were randomly allocated with the help of computer generated random numbers to receive treatment either with combination therapy of aliskiren 150mg plus olmesartan 40mg or olmesartan 40mg monotherapy once daily for a period of 8 weeks. During the study patients were not permitted to take any nonstudy antihypertensive drugs or potassium supplements. The patients were screened according to the following inclusion and exclusion criteria.

The inclusion criteria were newly diagnosed cases of mild to moderate hypertension (SBP 140-180 mmHg and DBP 90-109 mmHg), patients aged >18 yrs and those willing to give informed consent.

The exclusion criteria were any history of hypertensive encephalopathy, cerebrovascular accident, transient ischemic attack, heart failure (New York Heart Association class II-IV), coronary bypass graft surgery, percutaneous coronary intervention (PCI), unstable angina pectoris or myocardial infarction in the past 12 months, serum potassium level >5.5 mEq⁄ L, pregnant and lactating women, patient on high dose estrogen, adrenal steroids, appetite suppressants, tricyclic antidepressants, monoamine oxidase inhibitors, erythropoietin, cocaine, antipsychotic agents, oral corticosteroids, diuretics, antiarrhythmics, chronic sympathomimetic drugs (nasal decongestants, bronchodilators), nonsteroidal anti-inflammatory drugs and those who refused to give informed consent.

Patients fulfilling the above criteria were divided into two groups. One group received olmesartan 40mg and aliskiren 150mg once daily and another group received olmesartan 40mg once daily for a period of 8 weeks and the same brand of the available commercial preparations of the drugs were used. A provision was made for escape treatment for those patients who did not respond to study medications adequately.

Clinical assessment was carried out in terms of efficacy of the treatment along with safety estimation which was done at week 0, 2, 4 and 8. Primary endpoints were changes in the mean sitting, standing and recumbent systolic blood pressure (SBP), changes in the mean sitting, standing and recumbent diastolic blood pressure (DBP), and changes in the QRS amplitude in electrocardiogram. Secondary endpoints were measurement of blood urea, serum creatinine, and 24hr-Proteinuria. Safety assessment was done by observing side effects of anti-hypertensive therapy and doing relevant investigations.

The primary objective was to compare the clinical efficacy of two study regimens. Quantitative variables were given as Mean±SEM. Intragroup analysis was done using repeated measures ANOVA for parametric data and Friedman's test for non-parametric data. Intergroup analysis was done using unpaired't' test for parametric data and Mann whitney U test for non-parametric data. Categorical data like gender, incidence of adverse events in both the groups was analyzed using Chi-square test. A p-value <0.05 was considered as statistically significant.

Table-1 Comparison of Study Population Characteristics in Both the Groups

Variables	Group 1 (n=25)	Group 2 (n=25)	'p' value
	Mean ± SEM	Mean ± SEM	
Age in years	54.28±1.27	51.04±2.06	0.19
Gender: **Male** **Female**	 18 7	 16 9	0.544
Weight (Kgs)	68.16±1.39	65.48±1.37	0.178
Diet **Vegetarian** **Non-vegetarian**	 16 9	 17 8	0.765
Alcoholics	10	8	0.556
Smokers	7	9	0.544
Diabetics	9	7	0.544
Family history of cardiovascular disease	5	3	0.44
History of drug allergy	0	0	-

Table-2 Comparison of Changes in Mean Systolic Blood Pressure in Different Postures in Both the Groups

POSTURE	GROUPS	BASELINE	2 WEEKS	4 WEEKS	8 WEEKS
SITTING	1	169.36 ± 1.21	152 ± 1.87**	143.44 ± 1.66**#	140.8 ± 1.57**
	2	165.84 ± 1.71	153.76 ± 1.69**	148.56 ± 1.47**#	143.6 ± 1.52**
STANDING	1	162.92 ± 1.55	148.16 ± 1.79**	138.88 ± 1.62**	135.52 ± 1.58**
	2	160.88 ± 1.85	149.84 ± 1.57**	142.32 ± 2.17**	138 ± 1.92**
RECUMBENT	1	161.28 ± 1.72	144.48 ± 1.91**	135.84 ± 1.61**	132.4 ± 1.55**
	2	159 ± 2.1	145.2 ± 1.95**	139.52 ± 1.87**	135.04 ± 1.88**

Group 1- Olmesartan 40mg + Aliskiren 150mg combination therapy
Group 2- Olmesartan 40mg monotherapy
*Intragroup analysis-Comparison of values at the end of week 2, 4 and 8 with baseline values, **p<0.001
#Intergroup analysis-Comparison of 4 weeks values, #p<0.05

Table-3 Comparison of Changes in Mean Diastolic Blood Pressure in Different Postures in Both the Groups

POSTURE	GROUPS	BASELINE	2 WEEKS	4 WEEKS	8 WEEKS
SITTING	**1**	96.32 ± 1.37	87.92 ± 1.2**	83.76 ± 1.13**	82.56 ± 0.83**@
	2	96.48 ± 1.36	88.16 ± 1.38**	86.4 ± 1.18**	85.52 ± 1.14**@
STANDING	**1**	98.64 ± 1.19	90.88 ± 1.2**	86.24 ± 1.16**	84.4 ± 0.86**
	2	98.48 ± 1.58	91.52 ± 1.18**	88 ± 1.08**	87.12 ± 1.09**
RECUMBENT	**1**	92.48 ± 1.26	85.04 ± 1.28**	80.32 ± 1.01**#	78.8 ± 0.78**@
	2	94.96 ± 1.03	87.84 ± 1.12**	85.04 ± 1.13**#	83.52 ± 0.82**@

Group 1- Olmesartan 40mg + Aliskiren 150mg combination therapy
Group 2- Olmesartan 40mg monotherapy
*Intragroup analysis-Comparison of values at the end of week 2, 4 and 8 with baseline values, **p<0.001
#Intergroup analysis-Comparison of 4 weeks values, #p<0.05
@Intergroup analysis- Comparison of 8 weeks values, @<0.05

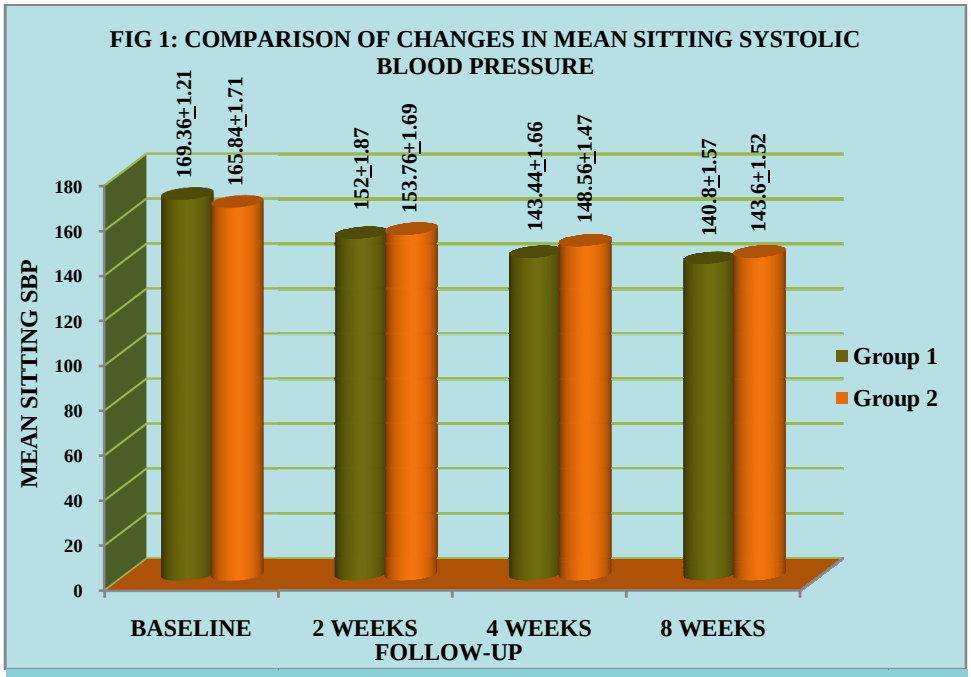
Table -4 Incidence of Adverse Drug Reactions

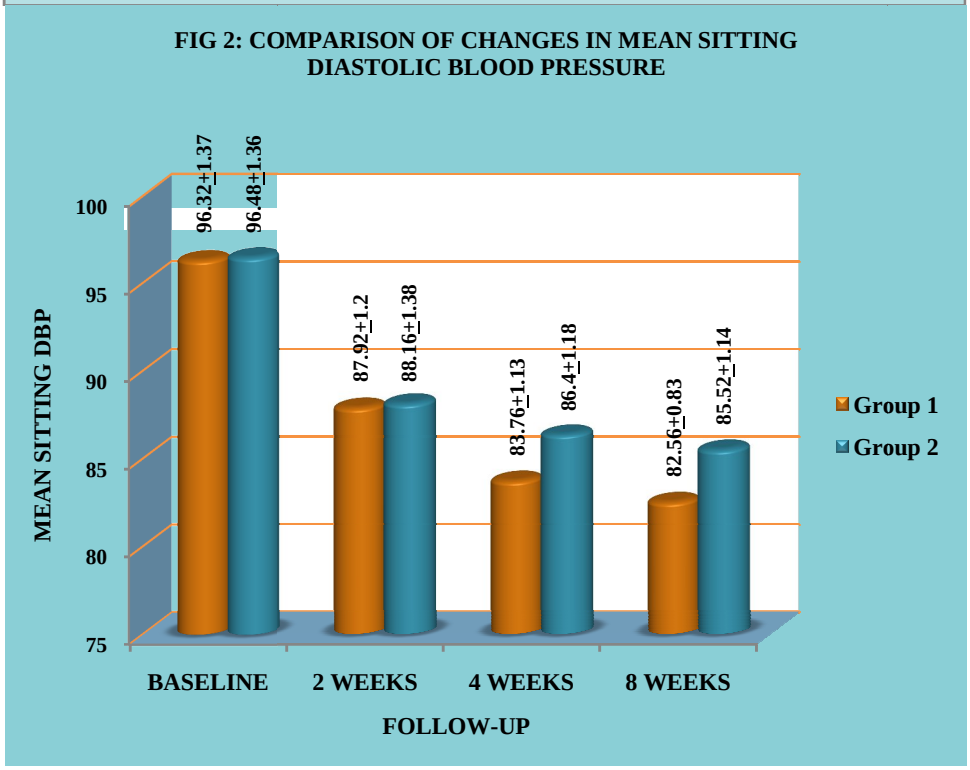
Adverse Drug Reactions (ADRs)	Group 1 n=25(%)	Group 2 n=25(%)
Dizziness	3(12%)	2(8%)
Diarrhea	2(8%)	2(8%)
Rashes	1(4%)	1(4%)
Vomiting	1(4%)	1(4%)
Headache	1(4%)	1(4%)
Abdominal pain	1(4%)	1(4%)
Malaise	1(4%)	1(4%)
Nausea	1(4%)	0
Myalgia	1(4%)	0
Pruritis	1(4%)	0
Peripheral edema	1(4%)	0
Dyspepsia	0	1(4%)
Anxiety	0	1(4%)

All values are expressed as number of patients (Percentage)
Group1: Olmesartan 40mg + Aliskiren 150mg treated patients
Group2: Olmesartan 40mg treated patients

RESULTS

A total of 73 patients with newly diagnosed hypertension were screened for this study. Out of this, 14 patients were excluded, as 9 patients did not fulfill the predefined inclusion criteria of the study and 5 were not willing to give informed consent and remaining 59 patients were randomized with the help of computer generated random numbers and were allocated to either of the two treatment groups. Of the 59 patients enrolled, 7 patients in combination therapy group and 2 patients in monotherapy group were lost to follow-up and remaining 25 patients in either group completed the treatment successfully. The baseline characteristics of the patients are tabulated in table-1. There was no statistically significant difference in the baseline characteristics in both the groups.





On intragroup comparison, both the groups (table-2,3 & fig-1,2) showed statistically highly significant reduction ($p<0.001$) in mean blood pressure (systolic as well as diastolic) in all the postures i.e. sitting, standing and recumbent over a period of 8 weeks. Reduction in mean sitting BP (SBP and DBP) in group 1 was around 29/14 mmHg whereas, in group 2 it was around 22/11 mmHg at the end of 8 weeks compared to their baseline values ($p<0.001$). Reduction in mean standing BP (SBP and DBP) in group 1 was around 28/14 mmHg whereas in group 2 it was around 23/11 mmHg at the end of 8 weeks compared to their baseline values ($p<0.001$). Reduction in mean recumbent BP (SBP and DBP) in group 1 was around 29/14 mmHg whereas, in group 2 it was around 24/11 mmHg at the end of 8 weeks compared to their baseline values ($p<0.001$).

Similarly intergroup comparison showed that combination therapy led to additional fall in systolic BP around 6-7 mmHg and diastolic BP around 2-3 mmHg. However, statistically significant difference in BP reduction in group 1 Vs group 2 was observed in: mean sitting SBP at the end of 4 weeks (25.92 Vs 17.28), mean sitting DBP at the end of 8 weeks (13.76 Vs 10.96), mean recumbent DBP at the end of 4 weeks (12.16 Vs 9.92) and 8 weeks(13.68 Vs 11.44).

The principle ECG changes associated with ventricular hypertrophy as a result of hypertensive heart disease are increase in QRS amplitude and duration. So, QRS amplitude was observed in both the groups over a period of 8 weeks. Statistically significant reduction in QRS amplitude was observed only in group 1 at the end of 8 weeks compared to its baseline value (0.72±0.28 mm, $p<0.05$). Although QRS amplitude decreased in group 2 also over a period of 8 weeks, but no statistically significant reduction was noted. However, no statistically significant difference was observed between both the groups regarding the reduction of QRS amplitude, at the end of 8 weeks.

Among secondary endpoints, 24hr-proteinuria (gm/24hrs) showed statistically significant reduction at the end of 8 weeks in both the groups compared to baseline values. The reduction observed was 0.78±0.06 to 0.72±0.05 in group 1 and 0.57±0.07 to 0.51±0.07 in group 2 (fig-3). Statistically significant reduction was observed in group 1 compared to group 2 at the end of 8 weeks (0.06 Vs 0.056, $p<0.05$).

In both the groups, there was slight increase in blood urea levels (mg/dl) over a period of 8 weeks, but this increase was not statistically significant. On comparing both the groups, there was slightly higher elevation in blood urea levels in group 1 compared to group 2 (1.12±0.44 Vs 0.84±0.55). Serum creatinine levels were also increased in both the groups over a period of 8 weeks but the rise in serum creatinine was statistically significant in group 1 at the end of 8 weeks (increased by 0.072±0.02 mg/dl, $p<0.05$) compared to baseline values. However, on comparing both the groups, there was no statistically significant difference in the increase of serum creatinine levels.

All the patients responded to the study medications, so escape treatment was not required in any of the patients of either group.

The frequency of adverse events was 11(44%) in combination group and 9(36%) in monotherapy group ($p>0.05$) as shown in table-4. Thus, no statistically significant difference was observed between the two groups regarding the incidence of adverse effects. The incidence of reported ADRs was as follows in both the groups. Vomiting, headache, abdominal pain, malaise, rashes were observed in one patient each (4%) and diarrhea in two patients each (8%) in both groups, 3 patients (12%) in group1 and 2 patients (8%) in group 2 reported dizziness. In addition, nausea, peripheral edema, myalgia and pruritis were observed by one patient each (4%) in group 1 whereas anxiety and dyspepsia were reported by one patient each (4%) in group 2. No new adverse reactions were reported in both the groups. None of the patients withdrew from the study due to ADRs. This shows that all treatments regimens were well tolerated except with minor ADRs.

Safety assessment was also done by measuring the hematological parameters (hemoglobin, total and differential count), biochemical parameters (serum uric acid, serum potassium and lipid profile). On intragroup analysis as well as intergroup analysis, it was observed that there was no statistically significant alteration in Hb levels, TLC, DLC. Both the groups- group 1 and group 2, showed a mild decrease in hemoglobin levels (0.08±0.06 gm/dl and 0.02±0.08 gm/dl) respectively, but this decrease was not statistically significant. On comparing both the groups, there was no statistically significant difference regarding the decrease in hemoglobin levels.

In both the groups, group 1 and group 2, a slight increase in serum uric levels (0.11±0.05 & 0.06±0.06) respectively was observed at the end of 8 weeks. However, it was not statistically significant. On intergroup analysis, although there was more increase in serum uric acid levels in group 1 as compared to group 2 over a period of 8 weeks, but was not statistically significant.

Both the groups were observed to be safe for the lipid profile. Moreover, both group 1 and 2 led to rather reduction in total cholesterol (11.32±1.19 & 10.32±1.22), triglycerides (4.8±1.2 & 8.3±1.2), LDL-

cholesterol (13.56±2.8 & 10.72±1.08) and VLDL-cholesterol (1.16±0.18 & 1.52±0.25) and increase in HDL-cholesterol (1.84±0.37 & 1.84±0.28) respectively and this was statistically highly significant at the end of 8 weeks compared to their baseline values. No statistically significant difference was observed in between the groups over a period of 8 weeks.

There was statistically significant increase in serum potassium levels (mEq/L) in group 1 at the end of 8 weeks compared to its baseline values (by 0.14±0.04). Although minor increase in serum potassium levels was observed in group 2 (0.076) over a period of 8 weeks compared to its baseline values, but this was not statistically significant. On intergroup analysis, although there was more increase in serum potassium levels in group 1 as compared to group 2 over a period of 8 weeks but that was not statistically significant.

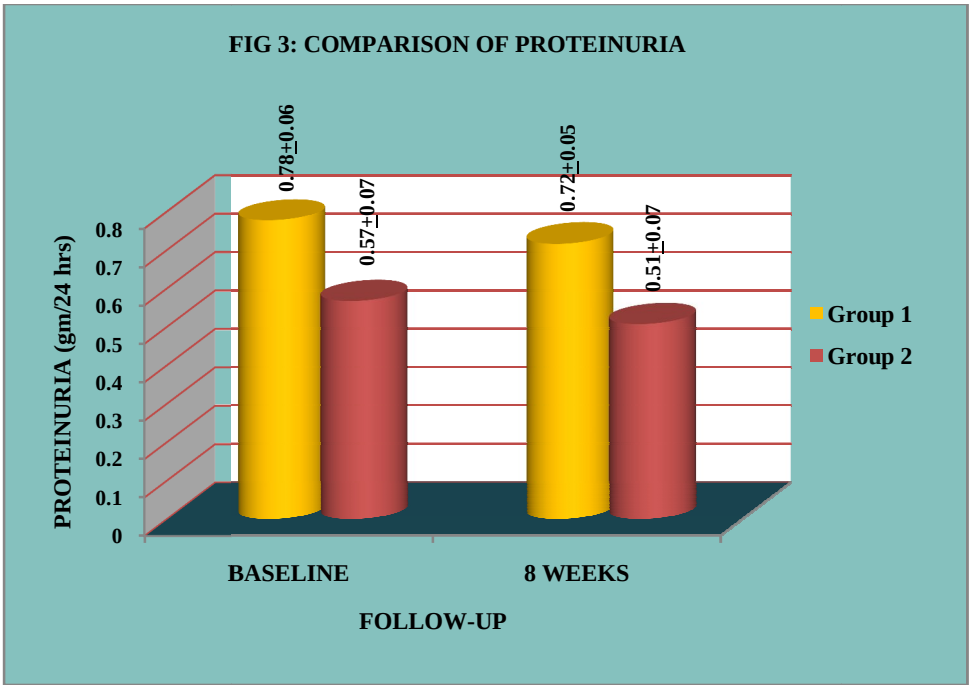
DISCUSSION

Hypertension is very well recognized as one of the most important risk factors, accounting to nearly 50% in the development of cardiovascular diseases. The most preferred antihypertensives are diuretics, calcium channel blockers, ARBs, ACEIs, ß-blockers etc.

The commonly used drugs for the treatment of hypertension are angiotensin receptor blockers (ARBs). These are used as one of the first line drugs and they target the RAAS pathway, which is one of the major contributing factors in causation of hypertension. Olmesartan ranks second in order next to candesartan in its affinity for AT1 receptors and the antagonism is unsurmountable. Aliskiren is a direct renin inhibitor. It reduces the plasma renin activity and blocks the generation of Ang II by ACE and non-ACE pathways and thus has synergistic effect when used in combination with ARBs. Studies have shown that aliskiren when used in combination with CCBs or ARBs, provides additional reduction in the BP and its better control.[9]

Some studies have compared the efficacy and safety of aliskiren as an add-on therapy to other drugs in the ARB class like valsartan, irbesartan, losartan, telmisartan.[10] But to the best of our knowledge no study has been done comparing the efficacy and safety of aliskiren as add-on therapy to olmesartan versus olmesartan monotherapy. In order to test if the supplementation of olmesartan with aliskiren would improve the outcomes of the study, we had designed an open labeled, randomized study to compare the efficacy and safety of aliskiren as an add-on therapy to olmesartan versus olmesartan monotherapy in patients with newly diagnosed hypertension.

The present study revealed that both the groups led to statistically highly significant reduction ($p<0.001$) in mean BP (SBP and DBP) in all the 3 postures i.e. sitting, standing and recumbent over a period of 8 weeks compared to baseline values.



On comparing both the groups, statistically significant difference in BP reduction in group 1 Vs group 2 was observed in: mean sitting SBP at the end of 4 weeks (25.92 Vs 17.28), mean sitting DBP at the end of 8 weeks (13.76 Vs 10.96), mean recumbent DBP at the end of 4 weeks (12.16 Vs 9.92) and 8 weeks (13.68 Vs 11.44). Even though similar study was not found, yet in a study done by Oparil et al in which aliskiren plus valsartan combination therapy, aliskiren and valsartan as monotherapies and placebo group were compared in 1797 patients, it was observed that the mean sitting SBP and DBP was reduced by 17.2/12.2 mmHg with once daily aliskiren 300mg/valsartan 320 mg, by 13/9 mmHg with aliskiren 300mg and by 12.8/9.7 mmHg with valsartan 320 mg and 4.6 with placebo after 8 weeks of treatment ($p<0.0001$ for combination versus monotherapy or placebo).[10] The findings of our study was quite similar to this study in the context that ARB when given along with direct renin inhibitor (aliskiren) gave better results than ARB alone. The reason could be because of the fact that compensatory rise in plasma renin activity which can occur with long term usage of ARBs alone, is taken care by aliskiren.

Hypertensive heart disease leads to structural and functional changes leading to left ventricular hypertrophy. Clinically, LVH is diagnosed by electrocardiography.[11] Changes in the QRS amplitude was assessed using Sokolow and Lyon index and expressed as mm (millimeter). In this study it was found that reduction in QRS amplitude was observed in both the groups over a period of 8 weeks. It was statistically significant only in group 1 at 8 weeks compared to its baseline values (0.72 ± 0.28, $p<0.05$). However, no statistically significant difference was observed when both the groups were compared at end of 8 weeks for QRS amplitude reduction. In a study done by Solomon et al, it was observed that all the 3 treatment groups i.e. aliskiren, losartan and combination group led to statistically significant reduction in the QRS amplitude compared to their baseline values. The reduction in the QRS amplitude in aliskiren, losartan and combination group was 1.2 ± 3.7, 0.9 ± 4.2 and 1.6 ± 3.9 respectively.[12] The findings of our study are quite similar to the above mentioned study. However, the reduction in QRS amplitude with combination therapy was quite less as compared to the above mentioned study (0.72 ± 0.28 Vs 1.6 ± 3.9). The reason for less reduction in QRS amplitude in our study is probably due to the reason that it was a short term study (8 weeks) whereas the above mentioned study[12] was done for a period of 36 weeks.

In our study, both the groups showed statistically significant reduction in proteinuria levels at 8 weeks compared to the baseline values. On comparing both the groups, it was observed that**,** there was statistically significant reduction in proteinuria levels in group 1 compared to group 2 (0.06 Vs 0.056, $p<0.05$) at the end of 8 weeks. Even though similar study was not available, yet in a study done by Persson et al, it was observed that aliskiren treatment reduced albuminuria by 48% compared with placebo ($p<0.001$), not significantly different from the 58% reduction with irbesartan treatment ($p<0.001$ vs. placebo). Combination treatment reduced albuminuria by 71%, more than either monotherapy ($p<0.001$ and $p<0.028$).[13] The findings of our study are quite similar to the above mentioned study that combination therapy led to more reduction in proteinuria at the end of 8 weeks as compared to monotherapy ($p<0.05$).

In our study, elevation of blood urea and serum creatinine was observed at the end of 8 weeks in both the groups. However, statistically significant elevation was seen only in serum creatinine in group 1 at the end of 8 weeks. This finding in our study can be supported by a study in which minor increase in blood urea and serum creatinine were observed in less than 7% of patients with essential hypertension treated with aliskiren alone vs. 6% on placebo.[9]

Incidence of adverse events in combination therapy was 44% whereas in monotherapy it was 36% ($p>0.05$). Thus no statistically significant difference was observed between the two groups. Although exact similar study was not available in which safety profile was observed with the similar treatment groups, however in study done by Parving et al, no difference in the overall incidence of adverse events between the aliskiren-losartan group and the placebo-losartan group (66.8% and 67.1%, respectively) was observed.[14] The incidence of adverse events was quite less in our study as compared to above mentioned study in both the groups as number of patients was less and it was a short term study for a period of 2 months.

In the present study there was a mild decrease in hemoglobin levels in group 1 and 2 (0.08 ± 0.06 and 0.02 ± 0.08) respectively, but this decrease was not statistically significant. A study quotes that small decrease in hemoglobin levels (approximately 0.08 g/dl) was observed with aliskiren monotherapy, a small decrease in hemoglobin levels was also observed with ARBs. The reason mentioned for mild reduction in hemoglobin levels in the quoted study is probably due to reduction of AngII which normally stimulates erythropoietin production by the AT1 receptors. However, no patients discontinued therapy due to anemia.[9]

Both the groups (group 1 and group 2) led to a slight increase in serum uric levels (0.11 ± 0.05 & 0.06 ± 0.06) respectively at the end of 8 weeks. In a study done by Nishida et al in which a comparative study of

effect of ARBs on serum uric acid levels was done in type 2 diabetic patients with hypertension, it was observed that losartan decreased the serum uric acid levels from baseline, while it was conversely increased in users of other ARBs; valsartan, telmisartan, candesartan and olmesartan. However, the rise was not statistically significant.[15] In our study, the findings are quite similar to the above mentioned study as olmesartan led to mild elevation in serum uric acid over a period of 8 weeks, yet it was not statistically significant.

There was more increase in serum potassium levels in group 1 as compared to group 2 over a period of 8 weeks but that was not statistically significant. Although exact similar study was not available in which serum potassium levels were observed with the similar treatment groups, yet in a study done by Oparil et al, in combination therapy(olmesartan & aliskiren), 4% patients had serum potassium levels more than 5.5 mmol/L whereas, 2% patients in valsartan monotherapy group.[10] The findings of the present study are quite similar to the above mentioned study as the combination therapy (olmesartan and aliskiren) led to more increase in serum potassium levels as compared to the monotherapy group. The reason for this effect is that both of the drugs i.e. olmesartan and aliskiren lead to decrease of the sodium reabsorption and more of potassium retention.

Both the groups were observed to be safe for the lipid profile. Moreover, both the groups rather led to reduction in total cholesterol, triglycerides, LDL-cholesterol and VLDL-cholesterol and increase in HDL-cholesterol and this was statistically highly significant at the end of 8 weeks compared to their baseline values but there was no statistically significant difference in between the two groups as far as the effect on lipid profile is concerned. Although exact similar study was not available in which serum lipid profile was observed with the similar treatment groups, yet in a study done by De Luis et al, patients treated with olmesartan had a significant decrease of total cholesterol and LDL cholesterol.[16] The findings of our study are thus in accordance to the findings of the above mentioned study in which olmesartan led to improvement of the lipid profile.

CONCLUSION

Both the treatment groups i.e. olmesartan and aliskiren combination therapy and olmesartan monotherapy were found to be safe and efficacious in patients with hypertension. On comparing the above mentioned treatment groups, better response was observed in combination therapy, as aliskiren as an add-on therapy to olmesartan produced an additional reduction in blood pressure and showed better anti-proteinuric effect compared to olmesartan monotherapy.

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