ORIGINAL ARTICLE

EFFICACY OF FIX DOSE COMBINATION (ATORVASTATIN AND AMLODIPINE) IN TREATMENT OF UNCONTROLLED HYPERTENSION AND DYSLIPIDEMIA

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Background: The fixed-dose combination containing the antihypertensive agent amlodipine and the statin, atorvastatin, is the first combination of its kind designed to treat two risk factors for cardiovascular disease (CVD), i.e., hypertension and dyslipidemia. In this study, blood pressure and lipid lowering effects of combination of amlodipine and atorvastatin were evaluated in uncontrolled hypertensive patients. **Methods:** Thirty patients both male and female in the age group 35–60 years attending the Hypertensive Clinic of PMRC FJMC suffering from uncontrolled hypertension were selected. Baseline blood pressure was checked after half hour rest in sitting and standing position using mercury sphygmomanometer. Blood sample was collected from all patients after overnight fasting for assessment of serum cholesterol, triglycerides, LDL and HDL cholesterol levels. They were prescribed with fixed dose combination of 5 mg amlodipine and 10 mg atorvastatin. Patients were followed for their blood pressure measurement after every 4 weeks up to 12 weeks. At the end of 12 weeks their fasting blood sample was taken again for determination of serum cholesterol, triglyceride, LDL and HDL cholesterol levels. **Results**: Systolic blood pressure after 4, 8 and 12 weeks was significantly lower at all intervals from baseline. When systolic blood pressure after 8 and 12 weeks was compared with 4 weeks, the effect was again significant (p=0.024, p=0.002 respectively).There was no significant reduction seen in 8 versus 12 weeks (p=0.493). Diastolic blood pressure at 4, 8 and 12 weeks was significantly lower from baseline. Diastolic blood pressure after 4 and 8 weeks when compared with 8 and 12 weeks was not significantly low (p=0.99 and 0.91 respectively). Lipid profile of the patients was significantly reduced from baseline after twelve weeks of fixed dose combination of treatment (p<0.000). **Conclusion:** Combination therapy proved to be effective in controlling hypertension and dyslipidemia than single pill. It also improved patient's compliance. It is suggested that polypill should be prescribed instead of multiple drugs.

Keywords: combination therapy, atorvastatin, amlodipine, uncontrolled hypertension, dyslipidemia

INTRODUCTION

Hypertension and dyslipidemia are two most commonly co-occurring cardiovascular risk factors. Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide accounting for in excess of 930,000 deaths.[1] It is a multi-factorial disease, emphasis is to treat overall cardiovascular risk, rather than single risk factors in isolation.[2] The third National Health and Nutrition Examination Survey (NHANES) estimated that more than 64% of patients with hypertension also have dyslipidemia; conversely, approximately 47% of patients with dyslipidemia have hypertension.[3]

Burden of major vascular risk factors, i.e., hypertension, diabetes mellitus, smoking, dyslipidemia and obesity is enormous in Pakistan and revealed that 39% of the people aged 18 years or above have hypertension, dyslipidemia and history of active smoking.[4] Among these only 40% of hypertensive patients had controlled blood pressure.[4]

Antihypertensive and lipid-lowering medications substantially reduce the risk of CAD, stroke, and death in patients with cardiovascular risk factors.[5–7] Therefore prompt and 'aggressive' control of blood pressure (BP) and cholesterol is needed in patients with hypertension alone and for patients with additional cardiovascular risk factors including dyslipidemia and diabetes.[6,8,9] Recent trials indicated that patients with hypertension and concomitant multiple cardiovascular risk factors can benefit from lipid-lowering therapy regardless of their baseline lipid levels.[6]

The fixed-dose combination containing the antihypertensive agent amlodipine and the statin, atorvastatin, is the first combination of its kind designed to treat two risk factors for cardiovascular disease (CVD). The pharmacokinetic and pharmaco-dynamic properties of amlodipine and atorvastatin make them well suited for combination in a single pill to manage cardiovascular risk.[10] The half-lives of both agents facilitate once-daily dosing, and both can be administered at any time of day with or without food.[11] Neither drug has any adverse effects on the other's efficacy or tolerability.[12–14]

In this study hypertensive patients whose blood pressure was not controlled despite of using various antihypertensive medications were prescribed combination 5/10 or 10/10 (amlodipine and atorvastatin)

to determine the effect in lowering the blood pressure and lipid levels.

MATERIAL AND METHODS

This cross-sectional analytical study was conducted by PMRC Research Centre Fatima Jinnah Medical College in collaboration with Feroz Sons Laboratories Pvt. Ltd. Non-probable convenient sampling was done. Thirty patients, male and female in the age group 35–60 years attending the Hypertensive Clinic of PMRC FJMC suffering from uncontrolled hypertension were selected. Written informed consent was obtained from all patients. Baseline BP was checked in sitting and standing position after half an hour rest using mercury sphygmomanometer. Blood samples were collected from all patients after an overnight fasting for assessment of serum cholesterol, triglycerides, LDL and HDL cholesterol levels. Any antihypertensive medicines already in use were stopped and fixed dose combination of 5 mg amlodipine and 10 mg atorvastatin was prescribed; dosage was titrated to 10/10 for the patients who were not controlled. Patients were followed for their blood pressure measurement after every 4 weeks up to 12 weeks. At the end of 12 weeks their fasting blood sample was taken again for determination of serum cholesterol, triglyceride, LDL and HDL cholesterol levels. Data was analysed using SPSS-15.

RESULTS

Thirty hypertensive patients, 18 females and 12 males, of mean age 54.4±8.2 were included in this study. Most of the patients (26, 86.6%) were diabetic, had history of hypertension of 5.5±4.9 years. Lipid profile of the patients was significantly reduced from baseline after 12 weeks of fixed dose combination of treatment (p<0.000, Table-1).

Table-1: Serum lipid profile of the patients before and after fixed dose combination treatment

Lipid parameter	Baseline	After 12 wks	*t*	*p*
Cholesterol	247.93±46.50	193.67±41.61	7.57	0.000
Triglycerides	205.93±46.61	169.23±48.08	4.95	0.000
HDL cholesterol	37.46±4.53	35.65±4.63	3.54	0.001
LDL cholesterol	169.29±42.78	124.17±40.33	6.55	0.000

Systolic BP at baseline was compared with systolic BP after 4, 8 and 12 weeks, it was significantly lowered from baseline. The systolic BP was significantly different at different times, details given in Table-2 and 4. When systolic blood pressure after 8 and 12 weeks reading was compared with 4 weeks, the effect was again significant (p=0.024 and 0.002 respectively). There was no significant reduction between 8 and 12 weeks (p=0.493). Significant mean difference in reduction of systolic BP from baseline after 4, 8 and 12 weeks were seen, i.e., 13.00 mmHg, 18.33 mmHg and 21.33 mmHg (p=0.000 and 0.024 respectively). Mean difference in reduction of systolic BP from baseline was more when compared with mean difference at 8 and 12 weeks with 4 week's reading.

Table-2: Systolic BP observed at different time intervals before and after the fixed dose combination treatment

Systolic BP(I)	Systolic BP(J)	Mean Difference (I-J)	Std. Error	*p*
Baseline	After 4 wks	13.00*	2.043	0.000
	After 8 wks	18.33*	2.449	0.000
	After 12 wks	21.33*	2.866	0.000
At 4 weeks	After 8 wks	5.33*	1.711	0.024
	After 12 wks	8.33*	2.039	0.002
At 8 weeks	After 12 wks	3.00	1.804	0.493

*The mean difference is significant at 0.05 level.

Diastolic BP at baseline compared with Diastolic BP at 4, 8 and 12 weeks was significantly lower than baseline. Diastolic BP was significantly different at different times, details given in Table-3 and Table-4. A mean difference of diastolic BP from baseline after 4, 8 and 12 weeks was 7.33 mm, 7.00 mm, and 8.33 mm with p-values of 0.007, 0.025 and 0.001 respectively. But diastolic BP after 4 and 8 weeks when compared with 8 and 12 week was not significantly low (p-value 0.99 and 0.91 respectively).

Table-3: Diastolic BP at different time intervals before and after fixed dose combination treatment

Diastolic BP (I)	Diastolic BP (J)	Mean Difference (I-J)	Std. Error	*p*
Baseline	After 4 wks	7.33 (*)	2.030	0.007
	After 8 wks	7.00 (*)	2.257	0.025
	After 12 wks	8.33 (*)	1.982	0.001
At 4 wks	After 8 wks	-0.33	1.396	1.000
	After 12 wks	1.00	1.615	0.991
At 8 wks	After 12 wks	1.33	1.333	0.906

Table-4: Trend of mean systolic and diastolic BP over study period

Duration	SBP (mmHg)	DBP (mmHg)
Baseline	159.7	92.0
4 weeks	146.7	84.7
8 weeks	141.3	85.0
12 weeks	138.3	83.7

DISCUSSION

Concomitant hypertension and dyslipidemia is a challenge as it can lead to serious cardiovascular events. Although a wide range of effective drugs are available yet its management is not optimised. Studies have documented that simultaneous control of both hypertension and dyslipidemia was not achieved in 90% of the cases despite effective treatment.[15] Similar effect of same combination regime was seen in this study, as blood pressure gradually decreased with time however lipid levels did not change in short period.

In the recent years new trends of fix dose combination of lipid lowering and anti-hypertensive drugs has been tried in various combination of which

amlodipine and atorvastatin is the first of its kind designed. It targets the two most common modifiable risk factors, hypertension and dyslipidemia, thus preventing the patients from its complicated consequences. It is also reported that different form of combination therapy as a single pill improves the efficacy as well as patients compliance.[13]

The comparative efficacy of amlodipine and atorvastatin alone and as a single pill in combination has been extensively studied and it is documented that more patients receiving combination therapy achieved blood pressure and lipid control.[16] The mean Framingham estimated 10 year CHD risk score was reduced from 15.8%–18.0% to endpoint values of 7.3%–10.7% in patients receiving combination therapy.[16] In the present trial blood pressure was reduced by 21.3/13.3 mmHg, serum cholesterol was reduced from 247 mg/dl to 193 mg/dl. Serum triglyceride and LDL cholesterol were reduced from 205.93 mg/dl to 169.23 mg/dl and 169.29 mg/dl to 124.17 mg/dl respectively, this is quite remarkable.

Two other similar studies carried out across the UK and Canada, and JEWELL-2 across the European countries revealed that 62.9% patients in JEWELL-1 and 50.6% in JEWELL-2 achieved both country specific BP and LDC goals. Blood pressure was reduced by 20.4/10.7 and 21.8/12.6 in JEWELL-1 and 2 respectively and reduction in LDC was 34.8 mg/dl and 42.2 mg/dl. Our results are also comparable with JEWELL studies.[17]

In Gemenii trial baseline blood pressure was 146.6/87.9 mmHg and mean LDC cholesterol was 152.9 mg/dl. It was seen that 57.7% of patients achieved BP and LDC control while 51.9% were successful in achieving the goal.[18] Our study is comparable to these results.

Adverse events reported most frequently in the combination therapy group compared with the placebo group were peripheral oedema (5.3% vs 2.1%), myalgia (4.8% vs 2.1%), and sinusitis (2.9% vs 0.8%) In present trial combination-treated patients did not experience any increase in treatment-related side effects compared with amlodipine or atorvastatin monotherapy. The most common treatment-related side effects were peripheral oedema (9.4% vs 2.7%), headache and dizziness compared to placebo. These events were mild to moderate in severity.[16] The incidence of treatment-related myalgia in combination-treated patients was low (1.0%) and similar to that in patients treated with amlodipine alone (1.4%), atorvastatin alone (1.1%), or placebo (1.8%).[16] In present study oedema was reported in 1 (3.3%) and myalgia in 2 (6.7%) patients.

CONCLUSION

Combination therapy was useful in improving the patients' compliance, and more effective in controlling hypertension and dyslipidemia than single pill. It is suggested that polypill should be prescribed instead of multiple drugs.

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