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RESEARCH ARTICLE

ANTIHYPERTENSIVE EFFECT OF ROSUVASTATIN IN NORMOCHOLESTEROLEMIC HYPERTENSIVE PATIENTS AND ITS ASSOCIATION WITH FLOW MEDIATED DILATION AND OXIDATIVE STRESS

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ABSTRACT

Hypertension is an important public health problem worldwide. Subjects with hypertension are known to have a two-fold higher risk of developing coronary artery disease (CAD), four times higher risk of congestive heart failure and seven times higher risk of cerebrovascular disease and stroke compared to normotensive subjects. Hypertension has been identified as one of the leading risk factors for mortality, and is ranked third as a cause of disability adjusted life-years. Statins are unequivocally useful for lowering cholesterol levels in patients with dyslipidemias characterized by elevations in total and/or low-density lipoprotein cholesterol. The beneficial effects of statins to lower serum cholesterol translate into significant reductions in cardiovascular morbidity and mortality. In addition to lowering cholesterol levels, statins have other biological effects relevant to cardiovascular homeostasis including anti-inflammatory actions and down regulation of angiotensin type 1 receptor expression that contribute to improvements in endothelial function and arterial compliance. Since endothelial dysfunction and reduced arterial compliance are important pathophysiological determinants of essential hypertension, these actions of statins raise the possibility that statin therapy may be useful for simultaneously treating dyslipidemias and hypertension¹⁻⁴. The present study was done to evaluate antihypertensive effect of rosuvastatin in normocholesterolemic hypertensive patients and its association with endothelial dysfunction and oxidative stress marker.

INTRODUCTION

Objective

To study the effect of rosuvastatin therapy in normocholesterolemic patients when added to antihypertensive agent on (a) Blood pressure in stage 1 hypertensive individuals.(b) Endothelial function and oxidative stress levels in stage 1 hypertensive individuals.

MATERIALS AND METHODS

It was randomised double blind study. Sample size for each group was 50. Both the groups were advised for salt restriction, low fat diet and similar life style modifications. The study design was approved by the Bioethics Committee. An informed consent was obtained in all the subjects. Hundred patients with hypertension who were not taking any lipid lowering but were on antihypertensive therapy (amlodipine or telmisartan) were included in the study. Detailed history and clinical examination was done including the anthropometry, measurement of blood pressure (2 to 3 readings, 5 mins. apart), heart rate and fundus examination.

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- Routine investigations and serum cholesterol levels were checked at the time of recruitment. Patients with serum cholesterol <160mg/dL were included for randomization.
- After confirming the inclusion of the subject baseline parameters were taken for
 - 1) Blood pressure readings (at least 3 readings with average)
 - 2) Flow Mediated Dilation
 - 3) Oxidative stress levels [S. Malondialdehyde (MDA), Ferric Reducing Ability of Plasma (FRAP)]

After this the subjects were randomised to either placebo or statin group (rosuvastatin 10mg) according to a computer generated randomization table. Subjects were followed up every two weeks and their BP recordings will be obtained for a period of 8 weeks. Special investigations (FRAP, MDA, FMD) were done in beginning and at the end of the study.

RESULTS

- The reduction in mean SBP was significant ($p < 0.001$) for rosuvastatin group but not for placebo ($p = 0.0722$).
- There was no significant change in mean diastolic blood pressure in both rosuvastatin as well as placebo group ($p < 0.099$).

- There was significant fall in mean pulse pressure in rosuvastatin group ($p < 0.001$), but no significant change was seen in placebo group ($p = 0.088$).
- The significant ($p < 0.001$) increase in mean antioxidant (FRAP) was observed in rosuvastatin group however no such changes were seen in placebo group ($p = 0.731$).
- After 8 weeks of study, non-significant change was found in MDA levels in both rosuvastatin as well as placebo group ($p = 0.417$).
- There was significant improvement in mean FMD ($p < 0.001$) for rosuvastatin group but not for placebo group ($p = 0.500$).
- There was significant decrease in mean total cholesterol ($p < 0.001$) and triglyceride ($p < 0.001$) for statin group but no similar changes were seen in placebo group for both total cholesterol ($p = 0.072$) and triglyceride levels ($p = 0.101$).

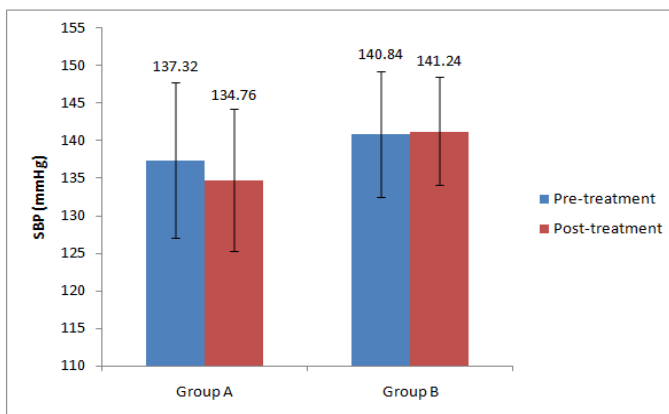


Fig. 1. Effect of rosuvastatin on systolic blood pressure in hypertensive patients

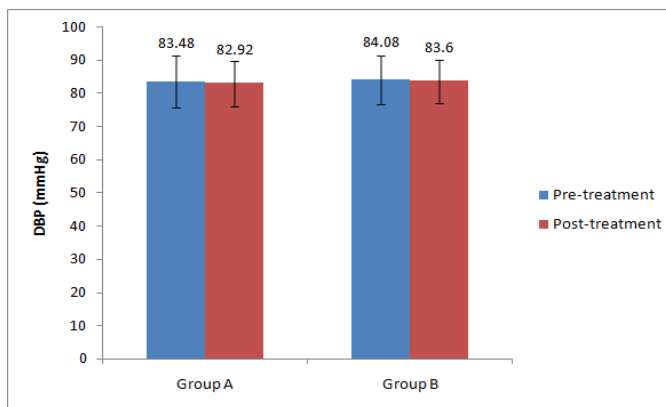


Fig. 2. Effect of rosuvastatin on diastolic blood pressure in hypertensive patients

DISCUSSION

- In the present study the effects of rosuvastatin (10 mg) versus placebo on blood pressure, oxidative stress markers (FRAP, MDA), FMD and serum lipid levels were studied in normocholesterolemic patients having total cholesterol < 160 mg/dl and aged between 40 years to 60 years with comparable baseline age, sex, BMI, WHR, blood pressure (SBP, DBP, PP), FMD, oxidant (MDA) and antioxidant (FRAP) distribution. It was a randomized double blind placebo controlled study. One hundred patients were randomly assigned to either

placebo or rosuvastatin group and were followed up for 8 weeks. Pre and post treatment investigations in addition to FMD and oxidative stress markers were done along with BP monitoring every 2 weeks. Results of this study suggests significant decrease in systolic blood pressure and pulse pressure, rise in antioxidant (FRAP), improvement in FMD in subjects receiving rosuvastatin (10mg) as compared to placebo in well matched subjects with stage 1 hypertension controlled on calcium channel blocker (amlodipine) or angiotensin receptor blocker (telmisartan). After 8 weeks of therapy, a significant decline in both total cholesterol and triglyceride value was also observed.

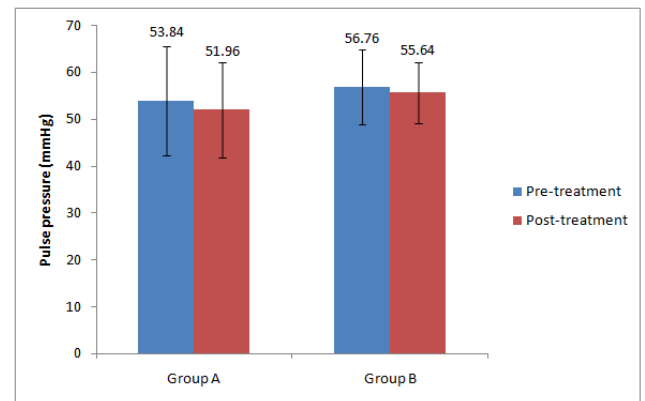


Fig. 3. Effect of rosuvastatin on pulse pressure in hypertensive patients

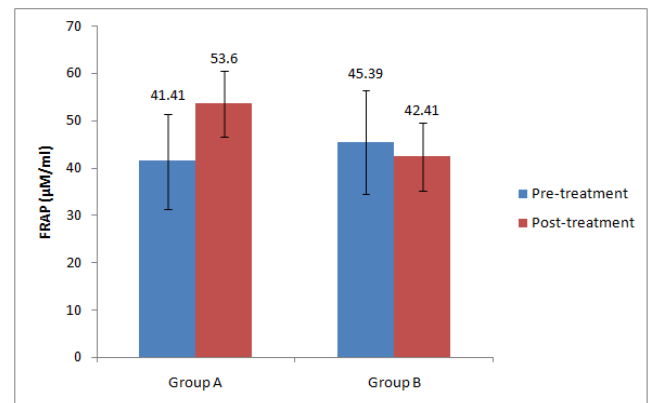


Fig. 4. Effect of rosuvastatin on FRAP in hypertensive patients

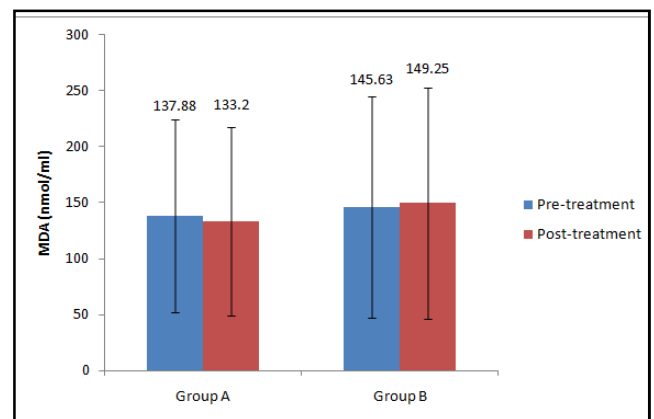


Fig. 5. Effect of rosuvastatin on MDA in hypertensive patients

- Most of the literature available has used pravastatin⁵⁻⁷, simvastatin^{8,9}, atorvastatin¹⁰⁻¹², rosuvastatin¹³⁻¹⁵,

fluvastatin¹⁶ and lovastatin¹⁷ in varying dosages (5 mg to 80 mg). The present study is unique in the sense that rosuvastatin, the latest and the most potent addition to the family of statins, has been shown to produce a significant fall in systolic blood pressure and pulse pressure in normocholesterolemic subjects. Three previous small studies including one in hypertensive animal model have documented hypotensive effect but in the presence of dyslipidemia. Susicet *et al*¹⁵ documented that rosuvastatin reduced arterial pressure, improved systemic and regional hemodynamics in animal hypertensive models by reducing the vascular resistance independently of cholesterol level. The authors postulated that the beneficial effect was possibly mediated by amelioration of endothelial dysfunction present in experimental models. The clinical evidence of reduction of systolic blood pressure to the tune of 4.7/5 mm Hg (SBP/DBP) and 6.3/0.2 mm Hg (SBP/DBP) has been documented in two studies by Pena *et al*⁸⁷ and Seki *et al*¹³.

- The lowering of SBP has been consistently demonstrated ranging from 2.8-8 mm Hg in different studies involving various statins namely, pravastatin, simvastatin, atorvastatin, lovastatin and fluvastatin. The decrement in DBP has been shown only in one study where the above mentioned drugs have been used. On the other hand, few studies have not been able to document these BP lowering changes^{18,19}. The various factors which could have affected their effect included small size, short duration, inadequate follow up, different method of BP measurement, effect of concomitant antihypertensive treatment etc. The present study was adequately powered to look at the BP, oxidative stress marker and flow mediated dilation and with a short follow up of 8 weeks because these patients were normocholesterolemic and main stress was on pleiotropic mechanism of statins.
- Significantly all these studies had a small sample size when compared to our study and more importantly the reduction in pulse pressure has not been documented in most of the previous studies. It is well known that both systolic blood pressure and pulse pressure are better indicators of clinical end point such as stroke rather than DBP. Also the reduction of 2.5 mm Hg in systolic blood pressure is significant in terms of reduction of clinical complications of hypertension as proven by large studies of antihypertensive therapy and is in no way small decrement provided by a drug which is likely to be a common co-medication in a number of conditions due to its significant pleiotropic effects in addition to those seen in primary and secondary prevention. The hypotensive effect has been further documented in two studies by using ambulatory blood pressure measurement (ABPM) with increase in nocturnal BP decline^{4,14}.
- The recent emphasis on high intensity and moderate intensity statin therapy in the setting of acute coronary syndrome has been endorsed by ACC and AHA guidelines. In hypertensive patients the statin therapy is still prescribed on the basis of total risk assessment. Two studies done by Ferrier¹⁰ and Tycinska⁴ have used atorvastatin 80 mg for anti-hypertensive effect and demonstrated equivocal reduction when compared to smaller doses. Therefore the antihypertensive effect can be classified as a class effect of statins and the effects are almost similar in medium to high dose therapy as per current standards.
- Experimental¹⁵ and clinical investigations have demonstrated that endothelial dependent vascular relaxation is impaired in hypertensive patients. There are several reports that HMG-CoA reductase inhibitors can improve endothelial function and the endothelium dependant vasodilation that are altered in patients with increased plasma cholesterol. The result of our study suggests that hypotensive effect of rosuvastatin is related to FMD improvement in hypertensive patients. A similar effect has been documented in earlier studies. Even in normocholesterolemic subjects the total cholesterol was reduced by approximately 13% rather than almost more than double reduction expected with rosuvastatin 10mg. Therefore lipid lowering effect could not have contributed much in the observed hypotensive effect.
- Effect on oxidative stress is one of major and most widely investigated and accepted pleiotropic effect of statins. Statins inhibit oxidised-LDL uptake, attenuation of vascular and endothelial superoxide anion formation via inhibition of NADH-oxidase via Rho dependent mechanism and preserve the relative levels of vitamin E, vitamin C and endogenous antioxidants such as ubiquinone and glutathione in LDL particles²⁷. Thus, statins not only decrease oxidant but also restore antioxidant, thereby possibly reducing the level of oxidative stress in vascular milieu. Statin also act by inhibiting synthesis of isoprenoids, which are important lipid attachment for intracellular signaling molecule Rho and Rac²⁰.
- Wassmann *et al*²¹ demonstrated that administration of atorvastatin in normocholesterolemic spontaneously hypertensive rats (SHR) decreased vascular AT-1 receptor expression thereby leading to reduced production of reactive oxygen species (ROS), improved endothelial function, decreased AT-2 driven vasoconstriction and finally lowering of blood pressure. In addition, the statin cause upregulation of vascular enhancement of endothelial cell NO synthase (eNOS) expression and eNOS activity. Other potentially important effects of statins affecting endothelial functions include reduction of ET-1, MCP-1 synthesis, modification of inflammatory response of macrophages and endothelial cells, suppression of ICAM-1 expression and enhancement of fibrinolytic activity in endothelial cells and inhibition of migration of monocytes etc.
- Danaoglu *et al*⁹ demonstrated that addition of simvastatin to ACE inhibitor treatment in newly diagnosed hypertensive patients with normal cholesterol level significantly reduced pulse pressure and facilitated BP control but did not affect endothelial dependent dilatation. The study had small sample size of 39 patients only and was not adequately powered for these end points and had higher female population and possibly was affected by a selection bias.
- Kohet *et al*²² and Strazzullo *et al*²³ also demonstrated significantly lower systolic BP in patient on statin than in those on placebo. There was also a trend for lower diastolic BP in patients on statin therapy compared with control. In general, higher the baseline BP, the greater the effect of statin on BP was also documented. However, the BP response to statin was unrelated to age, change in serum cholesterol or length of the trial. In addition Koh *et al* showed that statin significantly lowered BP in patients with uncontrolled hypertension than patients with controlled hypertension or normotensive.

- Tycinska *et al*⁴ using 80mg atorvastatin showed decreased BP and the greater reduction concurrent with FMP improvement. The decrease in BP was correlated with increase in nitric oxide (NO) and decrease in autoantibody against oxidized LDL. They also demonstrated in a cross-over design that following cessation of statin therapy SBP significantly increased along with FMD impairment. But the study failed to demonstrate significant relation between oxidative/antioxidative stress markers and endothelial dysfunction.
- The increase in total antioxidant status as seen in this study was similar to that demonstrated in our study indicating a lasting antioxidant statin effect. This synergistic effect of combining statin with an antihypertensive e.g. amlodipine has been recognized by Geet *al*². They have shown markedly decreased SBP and DBP as compared to amlodipine alone along with inhibition of inflammatory production and reduction of LV hypertrophy when amlodipine alone was compared with amlodipine and atorvastatin together.
- Thus the major effect of statin in improving endothelial dysfunction was attributable to its capability to decrease oxidative stress and anti-inflammatory effect has been shown in a small study in healthy normocholesterolemic young men and women with improved endothelial function within 24 hours of treatment with atorvastatin 80 mg and rapid impairment on statin withdrawal after 30 days^{24,25}. One more study comparing atorvastatin 10 mg/d plus dietary therapy with dietary therapy alone in postmenopausal women with hypercholesterolemia, showed a significant improvement in brachial artery vasoreactivity as early as 2 weeks after beginning atorvastatin compared with dietary therapy alone²⁶. Thus it is quite clear that effect of statin on oxidative stress and endothelial function can be seen as early as within 24hours as compared to the effect on lipid change. We included only normocholesterolemic patients in our study and there was less than half of expected decline in serum cholesterol with standard dose of 10mg during the study period it is therefore logical to deduce that blood pressure lowering effect in the current study is independent of the lipid lowering effect of rosuvastatin and is attributed to effect on endothelium and oxidative stress marker.

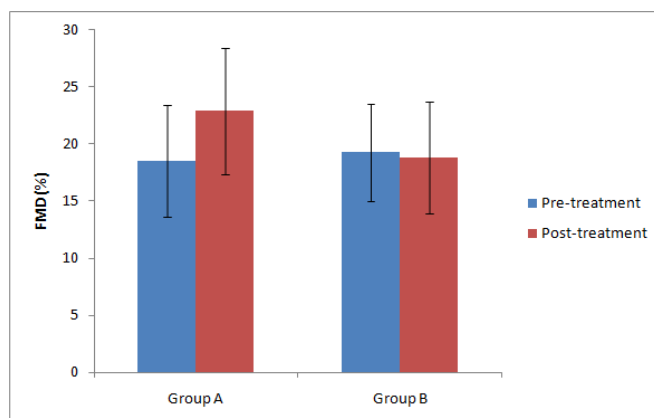


Fig. 6. Effect of rosuvastatin on Flow Mediated Dilatation

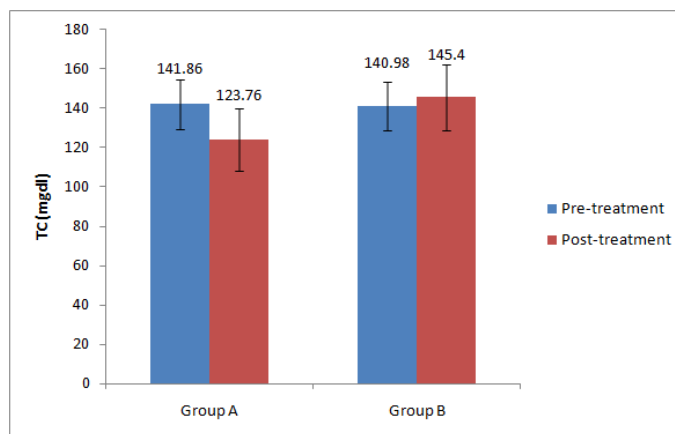


Fig. 7. Effect of rosuvastatin on total cholesterol

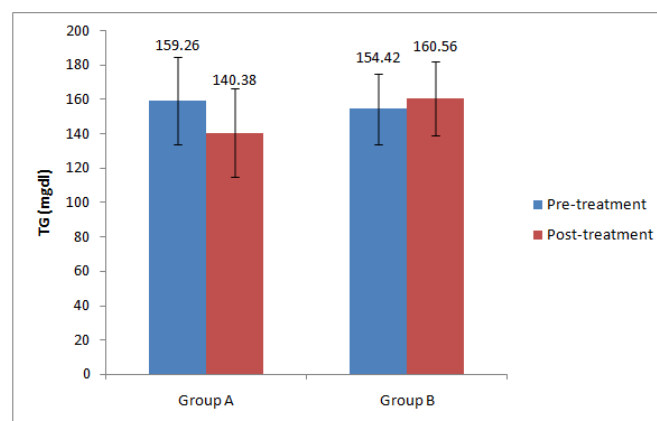


Fig. 8. Effect of rosuvastatin on triglycerides

Conclusion

The current study concludes that addition of rosuvastatin in normocholesterolemic subjects who are already on antihypertensive treatment lead to significant fall in mean systolic blood pressure and mean pulse pressure. In addition, it causes improvement of antioxidant level and endothelial function. Both hypercholesterolemia and hypertension are major risk factors for cardiovascular disease and often coexist. The risk of major cardiovascular disease is higher in the patients with both conditions than in hypertension or hypercholesterolemia alone. Statin induced improvement in endothelial function causes improvement of vascular tone and blood pressure. Rosuvastatin can suppress progression of atherosclerosis, decrease serum CRP production and reduce cardiovascular events. This study reinforces relatively poorly understood and under-reported hypotensive potential of statin, one of many pleiotropic effect associated with the class of statin. There is no doubt about efficacy of statin therapy in high risk hypertensive patients to reduce the morbidity and mortality associated with hypertension, but the result of this study makes a strong case for prescribing statin in all the patients of hypertension irrespective of risk for the sheer hypotensive effect itself. The reduction of systolic blood pressure and pulse pressure have been strongly linked to reduced incidence of stroke in hypertension and any intervention leading to reduction in these parameters however small will go a long way in arresting the crippling consequences.

Conflict of interest: There was no conflict of interest among authors.

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