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Original Research Article

A Comparative Study of Effect of Angiotensin Receptor Blocker Alone and with Atorvastatin on Biochemical Parameters in Mild to Moderate Hypertensive Patients

Kavita Rathore*[1], Renu Sharma[2], Avika Mathur[3], Jitendra Zaveri[4]

[1]Assistant Professor, Department of Pharmacology, Ananta Institute of Medical Sciences and Research Center, Rajsamand, Rajasthan, India

[2]Associate Professor, Department of Biochemistry, Ananta Institute of Medical Sciences and Research Center, Rajsamand, Rajasthan, India

[3]Senior Demonstrator, Department of Pharmacology, JLN Medical College, Ajmer, Rajasthan, India

[4]Professor, Department of Pharmacology, Ananta Institute of Medical Sciences and Research Center, Rajsamand, Rajasthan, India

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Corresponding author: Dr. Kavita Rathore

Conflict of interest: Nil

Abstract

Background: Hypertension is one of leading cause for cardiovascular, renal and other serious illnesses world-wide. Angiotensin receptor blockers (ARBs) and Statins are the mainstay for the treatment. In this study, we compared effect of Telmisartan alone and with Atorvastatin in mild to moderate hypertensive patients.

Methods: Total 137 patients were included. Group I (n=69) received Telmisartan 40 mg OD and Group II (n=68) received Telmisartan 40 mg OD with Atorvastatin 10 mg OD for 16 weeks. Baseline and post-treatment estimation of biochemical parameters like fasting and postprandial plasma glucose levels, serum Na+, serum K+ levels, lipid profile, Monitoring of Systolic and diastolic BP, pulse rate and adverse drug effects evaluation were carried out.

Results: Telmisartan alone significantly decreased Plasma glucose levels (fasting and post prandial) as compare to the Telmisartan with atorvastatin. Even, with atorvastatin showed slight increase in fasting blood glucose levels. Both groups showed favourable results on lipid profile but decrease was more with Telmisartan with atorvastatin. There was an increase in HDL-cholesterol was noted in both the groups. Both the groups shows significant decline ($p < 0.05$) in systolic and diastolic blood pressure levels. Pulse rate changes were minimal in both the groups. Slight increase in Serum K+ level was noted in both the groups ($p > 0.05$). Adverse events profile showed that Telmisartan alone (group I) produce less adverse effects as compare to Telmisartan with Atorvastatin.

Conclusion: Telmisartan improves biochemical parameters along with significant reduction in blood pressure and it gives synergistic effects with Atorvastatin.

Keywords: Telmisartan, Atorvastatin, Angiotensin receptor blocker (ARB), Hypertension, Hyperlipidemia, Anti-hypertensives.

Introduction

One of the most important modifiable risk factors for the development and progression of micro- and macro vascular damage and its aftereffects, such as

coronary heart disease, heart failure, ischemic and hemorrhagic stroke, chronic kidney disease, and peripheral arterial disease (PAD), is hypertension [1, 2]. When combined with other cardiovascular (CV) comorbidities, such as dyslipidemia, hypertension is more frequently associated with atherosclerosis [3]. Antihypertensive and lipid-lowering medications are frequently required, especially in individuals at higher CV risk, to achieve the optimal therapeutic targets after non-pharmacologic therapies as the first therapeutic approach [4].

The renin-angiotensin system (RAS) inhibitors are currently the medications with the chosen mechanism of cardiovascular protection for antihypertensive therapy.[5] Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are two kinds of medications that have been found to have RAS inhibitory action, albeit through various methods. While ARBs prohibit angiotensin II from interacting with its receptor (AT1), which in turn limits the secretion of aldosterone, ACE inhibitors prevent the synthesis of angiotensin II by inhibiting ACE. However, ACE inhibitors may also cause the synthesis of several immune-modulatory peptides, such as substance P and bradykinin, which can cause angioedema and a dry cough. ARBs, in contrast, offer enough BP reduction without these side effects because of their selectivity for AT1 (angiotensin receptor - 1).[6]

Telmisartan is a potent once-daily medication for blood pressure control since it is an angiotensin II receptor blocker with a significant selectivity for the angiotensin II type I receptor and a long half-life [7]. Telmisartan, which has been found to successfully treat cardiovascular diseases (CVD) in Asian individuals, is an equivalent to Ramipril.[8] It has been discovered to be well tolerated and efficient in lowering mortality and CVD risks in high-risk patients.[9,10] By partially activating the peroxisome proliferator-activated receptor, Telmisartan, unlike other angiotensin II receptor blockers, also exerts pleomorphic effects on the cardiovascular system.[10] It works effectively for managing hyperglycemia and can lessen inflammatory responses in heart cells.

Along with hypertension, dyslipidemia is also a major risk factor for cardiovascular disease. People with hypertension are more likely than people with normal blood pressure to develop dyslipidemia, and vice versa.[11] A statin (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor) is the main medication used to treat dyslipidemia. Statins offer long-term therapeutic benefits in lowering cardiovascular events and mortality, mostly through lowering cholesterol levels. However, there is growing interest in statin's other effects, such as reducing blood pressure [12].

In this study, we observed and compared effects of ARB (Telmisartan) alone and with co-administration of statin on some biochemical, pathological and physical parameters like blood pressure, pulse rate and adverse drug events in mild to moderate hypertensive individuals.

Materials and Methods:

After institutional ethical approval, a prospective, open label, non-randomized, Observational, before-after study was conducted. Sample size calculation was done by G*Power 3.1.9.4 software. We enrolled 70 patients in each group. Newly diagnosed patients with mild to moderate or grade I and II hypertension as per JNC VIII (joint national committee report) (SBP ≥ 140 mmHg and /or DBP ≥ 90 mmHg) of 20 to 70 years with both sexes male and female were included in the study. According to JNC VIII patients with serum cholesterol more than 200 mg/dl and/or LDL cholesterol more than 130 mg/dl and who have family history of

cardiovascular diseases, hyperlipidaemia were given ARBs with Atorvastatin.

The Unwilling patients, or known to have history significant hepatic, renal, gastrointestinal, pulmonary, musculoskeletal, endocrine, neuropsychiatric, cardiovascular disease other than hypertension and Patients on any other medications (e.g. sedatives, antipsychotics, antidepressants, antihistaminic). Pregnant women and lactating women. Patients suffering with Diabetes Mellitus were excluded from study. Written informed consent was obtained from the patients. After withdrawal of patients who failed to come for follow up, group I (n=69) received Telmisartan 40 mg OD, group II (n=68) received Telmisartan 40 mg OD with Atorvastatin 10 mg OD for 16 weeks. Patient selection, treatment or drug, dose and route were solely decided by physicians from Dept. of Medicine, J.L.N. Medical College and associated hospital. All patients underwent a complete clinical examination. Baseline and post-treatment estimation (after 16 weeks) of biochemical parameters including, fasting and postprandial plasma glucose levels, blood urea, serum creatinine, serum Na+, serum K+ levels, lipid profile, SGOT and SGPT. Hematological parameters like ESR, Hb, TLC, monitoring of Pulse rate, systolic and diastolic BP and adverse drug effects were noted. All the laboratory findings were obtained from patient's case sheets and reports.

Statistical Evaluation

The data were analysed calculating mean, SD, t value, p value by statistical software Graph Pad Prism and SPSS version 22. Normally distributed data of like blood Pressure, biochemical & hematological tests were compared by paired student's- t-test. Results with $p < 0.05$ considered statistically significant. Inter drug comparison was done by unpaired t- test. The observed result were discussed against the back drop of known facts and published work.

Results

Out of total 137 patients who completed the study, 53 patients (39%) were male and 84 patients were female (61.3%). After administration of Telmisartan 40 mg alone in Group I (Table: 1), a significant ($p<0.05$) decrease in plasma glucose levels in both fasting (111.20±10.75 to 110.21±10.53; $p < 0.05$) and post prandial (153.62±12.15 to 151.89±12.04; $p < 0.05$) were observed. Serum cholesterol and LDL- Cholesterol were also decreased significantly. There is significant increase in HDL cholesterol and decrease in Triglycerides and VLDL levels was observed but results were not statistically significant. Serum Na+ remain almost unchanged after administration of Telmisartan but slight increase noted in serum K+ levels (4.4±0.38 to 4.5±0.43; $p > 0.05$) but not statistically significant. Changes in Systolic Blood pressure (157.86±13.67 to 137±9.66; $p< 0.05$) and diastolic blood pressure (97.44±8.61 to 83.56±5.44; $p< 0.05$) were statistically significant after administration of Telmisartan 40 mg. Although there is not much difference note in pulse rate after Telmisartan administration.

Table 2: Shows effect of Telmisartan (40 mg) with Atorvastatin (10 mg) OD in mild to moderate hypertensive patients. A slight increase in plasma glucose (fasting) level was noted (110.75±14.23 to 111±13.85; $p >0.05$) but results were not statistically significant. Post prandial glucose levels were remain unchanged. There was statistically significant decrease noted in serum total cholesterol, LDL, VLDL and triglycerides levels ($p<0.05$). HDL-cholesterol also increased significantly ($p<0.05$). Serum electrolytes (Na+ & K+) shows not significant changes, although serum K+ levels were slightly increased. There was significant decrease noted (151.94±10.90 to 132.88±8.39; $p <0.05$) in

systolic and diastolic blood pressure (94.74±6.76 to 83.25±5.49; p <0.05) diastolic blood pressure. A decrease in pulse rate was noted but not statistically significant.

Figure: 1 shows the pre-treatment base line values of both the groups

Table 3, Fig. 2 shows comparative effect of drugs in both the groups. Telmisartan shows more decrease in blood glucose levels (both fasting and post prandial) as compare to the group II (Telmisartan with atorvastatin). Even Telmisartan with atorvastatin shows slight increase in fasting blood glucose levels also. Inter drug comparison shows statistically significant ($p < 0.05$) decrease in serum total cholesterol, LDL, VLDL, triglycerides and decrease was more in Telmisartan with atorvastatin (group II). There was slight increase in HDL-cholesterol was noted in both the groups. Both the group shows significant decrease ($p < 0.05$) in systolic and diastolic blood pressure levels. Pulse rate changes were minimal in both the groups.

There was not much difference was observed in pre and post treatment levels of other biochemical and hematological parameters like Serum Creatinine, Urea, SGOT, SGPT, HB, TLC and ESR in both the groups.

Figure 3: shows adverse drug events in both the groups after administration of Telmisartan alone and with atorvastatin. We noted that no incidence of nausea and vomiting reported in both the groups. Dizziness was more reported in group I (23.07%) as compare to group II (19.6%) patients. Headache was reported by 15.38% and 21.57% patients in group I and group II respectively. Muscle spasm was only reported in group II (27.45%). Fatigue and nervousness was more in group II (19.6% and 13.73 %) as compare to group I.

Table 1: Effect of Telmisartan alone on Biochemical and Physical Parameters

Parameters	Pre-treatment	Post-treatment	p
Plasma-glucose (fasting)(mg/dl)	111.20±10.75	110.21±10.53	< 0.05 S
Plasma-glucose (post prandial) (mg/dl)	153.62±12.15	151.89±12.04	< 0.05 S
Serum-cholesterol (mg/dl)	190.76±10.17	188.43±10.78	< 0.05 S
LDL-cholesterol (mg/dl)	120.6±7.88	119.2±8.12	< 0.05 S
VLDL-cholesterol (mg/dl)	27.8±2.2	27.7±2.3	> 0.05 NS
HDL-cholesterol (mg/dl)	43.21±6.79	44.88±6.60	< 0.05 S
Triglycerides (mg/dl)	139.19±10.95	138.67±11.26	> 0.05 NS
Serum Na+ (mEq/L)	139.3±3.88	139.0±3.51	> 0.05 NS
Serum K+ (mEq/L)	4.4±0.38	4.5±0.43	> 0.05 NS
Systolic-blood pressure(mmHg)	157.86±13.67	137±9.66	< 0.05 S
Diastolic-blood pressure(mmHg)	97.44±8.61	83.56±5.44	< 0.05 S
Pulse rate (beats/min)	84.5±6.25	84.2±6.08	> 0.05 NS

Table 2: Effect Of Telmisartan With Atorvastatin On Biochemical And Physical Parameters

Parameters	Pre-treatment	Post-treatment	p
Plasma-glucose (fasting)(mg/dl)	110.75±14.23	111±13.85	> 0.05 NS
Plasma-glucose (post prandial)(mg/dl)	148.45±8.71	148.37±8.14	> 0.05 NS
Serum-cholesterol (mg/dl)	232.78±27.83	216.65±33.28	< 0.05 S
LDL-cholesterol (mg/dl)	131.6±16.51	119.0±18.93	< 0.05 S
VLDL-cholesterol (mg/dl)	28.3±4.45	22.2±4.61	<0.05 S
HDL-cholesterol (mg/dl)	45.40±4.24	48.67±4.10	< 0.05 S
Triglycerides (mg/dl)	139.43±20.63	124.33±21.61	< 0.05 S

Serum Na+(mEq/L)	141.6±3.33	141.3±2.89	> 0.05 NS
Serum K+ (mEq/L)	4.4±0.48	4.5±0.41	> 0.05 NS
Systolic-blood pressure(mmHg)	151.94±10.90	132.88±8.39	< 0.05 S
Diastolic-blood pressure(mmHg)	94.74±6.76	83.25±5.49	< 0.05 S
Pulse rate (beats/min)	86.1±8.61	85.6±8.36	> 0.05 NS

Table 3: Comparative Effect of Telmisartan Alone and Telmisartan with Atorvastatin on Biochemical and Physical Parameters (Values are Expressed as Mean of Difference ±SD)

Parameters	Telmisartan	Telmisartan with Atorvastatin	p
Plasma-glucose (fasting)(mg/dl)	0.99±1.45	0.25±1.82	< 0.05 S
Plasma-glucose-(post prandial)(mg/dl)	1.73±1.49	0.08±1.69	< 0.05 S
Serum-cholesterol (mg/dl)	2.33±5.11	16.13±12.22	< 0.05 S
LDL-cholesterol (mg/dl)	1.3±1.8	12.5±11.5	< 0.05 S
VLDL-cholesterol (mg/dl)	0.1±0.5	6.1±3.7	< 0.05 S
HDL-cholesterol (mg/dl)	1.66±2.44	3.27±2.49	< 0.05 S
Triglycerides (mg/dl)	0.51±2.42	15.18±11.26	< 0.05 S
Serum Na+ (mEq/L)	0.3±1.3	0.3±1.3	> 0.05 NS
Serum K+(mEq/L)	0.0±0.2	0.1±0.6	> 0.05 NS
Systolic-blood pressure(mmHg)	20.86±10.61	19.05±9.75	> 0.05 NS
Diastolic-blood pressure(mmHg)	13.88±7.79	11.49±7.00	> 0.05 NS
Pulse rate (beats/min)	0.46±2.46	0.5±2.10	> 0.05 NS

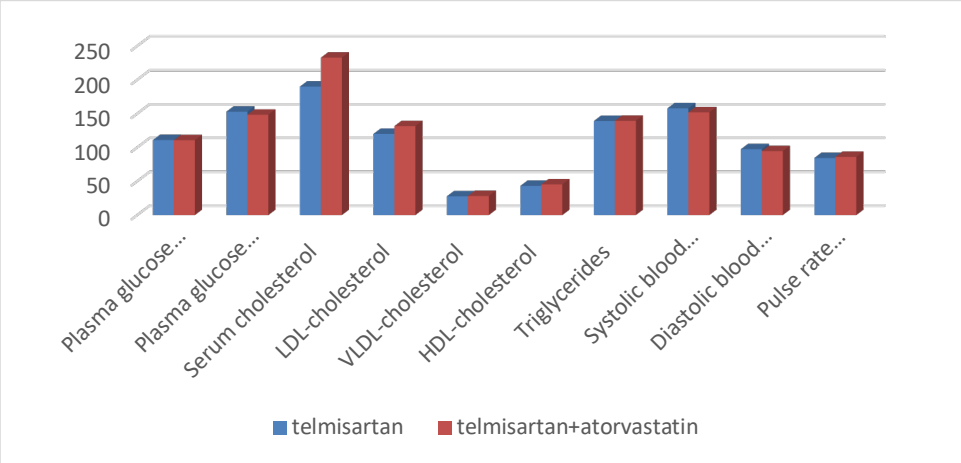

Figure 1: Base line values of Both the Groups

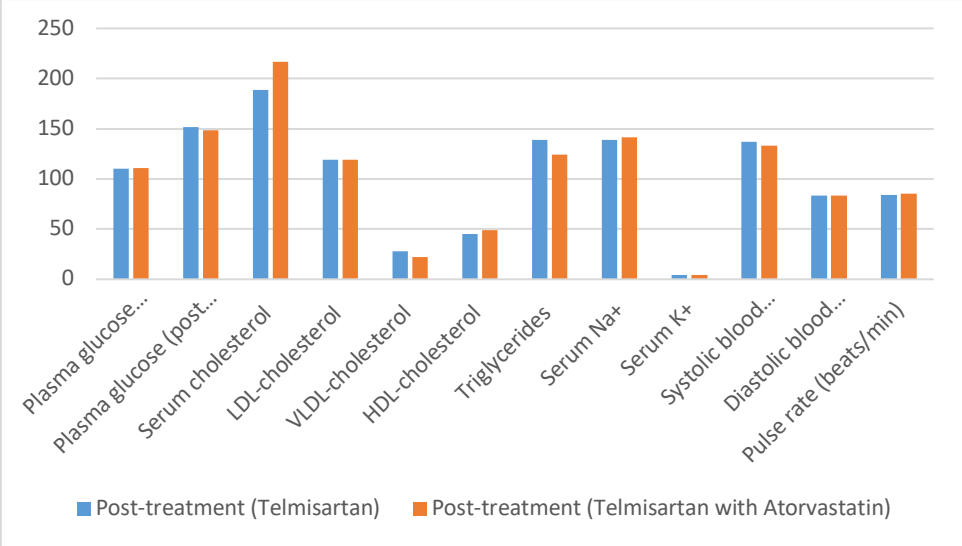

Figure 2: Post –Treatment values in both the groups

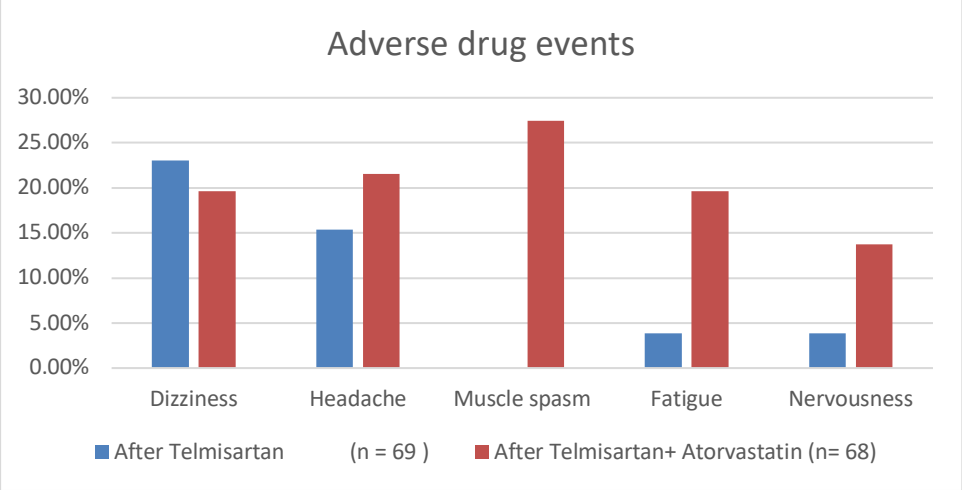

Figure 3:- Adverse drug events in both the groups

Discussion

In present study male & female percentages were 39% and 61.3% respectively. This shows prevalence of hypertension is more in female as compare to male patients. Similar results were observed by previous studies [13]. In one previous study, [14] they observed cardio-metabolic risk is more in old age indian females then in males.

According to previous studies, Telmisartan has a high affinity for the angiotensin II type 1 receptor, high tissue distribution, lipophilicity, and a long half-life (24 h), which results in long-lasting antihypertensive effects [15]. Telmisartan lowers blood pressure for a longer period of time and reduces day to day blood pressure variability. The reduction of central oxidative stress and inflammation by Telmisartan may also dramatically reduce central sympathetic activity [16]. Telmisartan considerably decreases the size of left ventricular and left atrial myocardium and lowers the left ventricular mass index as compared to Olmesartan. Telmisartan improves the cardio-metabolic profile of obese and hypertensive patients by increase of adiponectin concentrations and decrease of IL-6 levels [17].

Some studies [18] documented that statins also have some BP lowering activity. From the literature, statins have been shown to promote the actions that may contribute to

vasodilation such as increase in endothelial production of nitric oxide (NO) and inhibition of reactive oxygen species (ROS) production [19] as well as inhibit the synthesis of Angiotensin II and aldosterone [20].

In our study, there was a significant ($p < 0.05$) decrease in systolic and diastolic blood pressure observed in both the groups after drug treatment. Inter drug comparison also shows almost similar decrease ($p > 0.05$) in both the groups and atorvastatin has no deleterious effect on blood pressure (table 3). Similar results were found by some scientists [15, 21, 22].

One study [23] stated that Central BP more closely related to future cardiovascular risks than brachial BP. As compare to other anti-hypertensives, Angiotensin receptor blockers have revealed more promising effect of lowering central BP. Although, they found Telmisartan/statin group has more significantly reduced mean central BP & brachial BP than the Telmisartan monotherapy in patients with hypertension and mild dyslipidaemia as Statins have a beneficial role in arterial stiffness also. In our study, there was no significant changes observed in pulse rate after administration of Telmisartan alone and with atorvastatin. Our results are in consistence with previous studies [24, 25]. Another study [26] also reported that Telmisartan has no clinically significant effects on heart rate.

In present study, there was a significant decrease (< 0.05) observed in both plasma glucose fasting & postprandial levels after administration of Telmisartan (40 mg) alone. In group II after Telmisartan (40 mg) with atorvastatin (10 mg), a slight increase in plasma glucose (fasting) level was noted but result was not statistically significant ($P > 0.05$). Post prandial glucose levels were remaining unchanged. Similar results observed by some researchers [27,22, 28].

Telmisartan has pleiotropic effect. The partial PPARγ- agonistic activity and angiotensin receptor blockade activity of Telmisartan have been shown to have multiple clinical benefits, including anti-diabetic and cardiovascular effects. In addition, Telmisartan is reported to have PPARα and PPAR-δ agonist activity. Telmisartan would be an ideal alternative dual-purpose medication for patients with diabetes mellitus type 2, hypertension and other cardiovascular disorders.[29] Telmisartan increases PPAR-r gene expression more than amlodipine, and improves glycaemic control and insulin resistance.[30]

Statins are thought to act on beta cells, which decrease insulin secretion and block glucose uptake in adipocytes and skeletal muscles, resulting in insulin resistance, hyperglycemia, and diabetes [31,32]. Statins therapy causes insulin resistance and increase risk of new onset type 2 diabetes mellitus [33]. On the other hand, RAS (rennin Angiotensin system) inhibitors improves both endothelial dysfunction and insulin resistance [34]. One researcher found that Telmisartan showed superior ability to improve insulin resistance induced by rosuvastatin 10 mg compared to other ARBs [35]. In patients with atherosclerotic cardiovascular disease who had impaired fasting glucose (IFG) and needed high-intensity statins, Telmisartan retained insulin secretion, caused a regression from IFG to euglycemia, and prevented new-onset diabetes mellitus. [27]

In our study, both the group showed favourable effect on lipid profile. There was significant decrease in Serum cholesterol, LDL- cholesterol and increase in HDL- cholesterol ($p < 0.05$) observed after Group I (Telmisartan alone) and in Group II (Telmisartan + Atorvastatin). However, there was significant ($p < 0.05$) decrease observed in triglycerides and VLDL-cholesterol levels in group II only. Comparative analysis shows that

Telmisartan with Atorvastatin was more effective in reducing serum –cholesterol, VLDL, LDL, Triglycerides and increase HDL cholesterol as compare to Telmisartan alone. Combination of ARB with statin is more beneficial for patients of hypertension with hyperlipidemia. Similar findings observed by some previous studies. [23, 36, 37, 38]

Atherosclerosis can be caused by persistent or postprandial hypertriglyceridemia and hyperglycemia, which are known to contribute to endothelial damage and dysfunction through oxidative stress. [39] The co-administration of Statins with ARBs produce synergistic effect. Since, they act by independent mechanisms to regulate cholesterol levels. A combination of an ARB and statins has been shown to decrease oxidative stress, possibly due to an associated antioxidant activity, [40] thereby offering a promise of decreasing endothelial damage, an independent cardiovascular risk factor.

Atorvastatin is a popular lipid lowering drug. Telmisartan is a partial agonist of peroxisome proliferator-activated receptor γ (PPARγ) [41]. High lipophilicity allows it to enter into the nucleus of the PPARγ receptor. Telmisartan also has indirect impact on adipokines system [42] Telmisartan increases adiponectin production due to PPARγ agonistic activity [43]. The expression of genes involved in carbohydrate and lipid metabolism is also influenced by PPARγ. It has been reported that Telmisartan may improve lipid profiles, especially triglycerides levels, and reduce cholesterol absorption. [44]

In this present study, serum electrolytes (Na+) remain almost unchanged after administration of Telmisartan but slight increase in serum K+ level noted. Although, findings were statistically not significant. Similar results were observed after administration of Telmisartan with Atorvastatin. Hyperkalemia with ACEIs/ARB could be due to decreased aldosterone concentrations, decreased delivery of sodium to the distal nephron, abnormal collecting tubule function, and excessive potassium intake [45].

Although, these drugs were well tolerated and quite safe but some of adverse drug reactions were noted after administration of Telmisartan alone (group I) and combination of Telmisartan with atorvastatin (group II). We observed dizziness was more in group I as compare to group II patients. Headache, fatigue and nervousness was more observed in group II and Muscle spasm (27.45 %) was only observed after Telmisartan with Atorvastatin administration. Several scientists [46,47] found that statins are associated muscle pain, spasm and rhabdomyolysis. Rhabdomyolysis is believed to be a decrease in ubiquinone (coenzyme Q) produced by the HMG-CoA pathway. In present study, the overall incidence of side effects was considerably lower with the ARB alone as compare to with co-administration of Atorvastatin. However, in present study, none of the patients was withdrawn from the study due to any adverse drug reaction with either of the drugs.

Conclusion

In this study, we observed that Telmisartan alone and with Atorvastatin, effectively reduces systolic and diastolic blood pressure with maintaining the heart rate. Although, the co-administration of Telmisartan with atorvastatin showed slight rise in fasting glucose levels as compare to Telmisartan alone. Being PPAR- ϒ agonist, Telmisartan showed beneficial effect on plasma glucose levels (fasting and post prandial) and on lipid profile. Telmisartan alone and with atorvastatin showed significant improvement in lipid profile also, but improvement was more with Telmisartan with Atorvastatin. So, in patients with mild

to moderate hypertension both Telmisartan alone and with Atorvastatin shows improvement but with hypertension along with hyperlipidaemia the combination of angiotensin receptor blocker (ARB) with Statin is more beneficial than ARB alone.

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