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Comparison of the efficacy and safety of atorvastatin monotherapy and atorvastatin plus fenofibrate combination therapy in combined dyslipidemia

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ABSTRACT

Dyslipidemia is a major risk factor for Coronary Artery Disease (CAD). Dyslipidemic patients display abnormal lipid profiles associated with elevated levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and very low-density lipoprotein cholesterol (VLDL-C), as well as reduced levels of high-density lipoprotein cholesterol (HDL-C).The present study aims at evaluating the efficacy and safety of atorvastatin monotherapy versus atorvastatin plus fenofibrate combination therapy in dyslipidemic patients from Tiruchirappalli (Tamil Nadu, India).This is a randomized, open-label, parallel study comparing the efficacy and safety of the atorvastatin monotherapy (10 mg) (Group A) with the atorvastatin plus fenofibrate combination therapy (10/135 mg) (Group B) for 24 weeks in dyslipidemic patients(n=80) with regard to lipid profiles. Both atorvastatin monotherapy and atorvastatin plus fenofibrate combination therapy were significantly effective in reducing the levels of TC by 16.24% and 15.95% (p<0.001, both),TG by 16.57% and 34.02% (p<0.001, both), LDL-C by 24.40% and 26.11% (p<0.001, both), and VLDL-C by 17.96% and 33.50% (p<0.001, both), respectively. Interestingly, atorvastatin monotherapy did not cause a significant increase in HDL-C level (0.63%, p=0.37), which was significantly increased by 25.48% (p<0.001) after atorvastatin plus fenofibrate combination therapy. The lipid profile changes appear to be gender-dependent, in which females responded better to both treatments. Both treatments were safe and caused no serious side effects. Overall, atorvastatin plus fenofibrate combination therapy is more effective than atorvastatin monotherapy. In sum, both treatments display high efficacy and safety in the treatment of hyperlipidemia.

Keywords: Atorvastatin; Fenofibrate; Dyslipidemia; Coronary Artery Disease; Efficacy; Safety.

INTRODUCTION

Coronary artery diseases (CAD) are becoming more prevalent in the developing countries particularly in the urban areas[1]. Dyslipidemia has emerged as one of the most common risk factors for CAD, and it represents a considerable health problem as the proportion of elderly people increases worldwide[2, 3].In the developing countries, as the pace of urbanization increases, the population is becoming more dependent on unhealthy diets, a problem that is exacerbated by low physical activity and sedentary lifestyle[4].Dyslipidemia is a metabolic disorder represented by abnormal levels of plasma lipids and lipoproteins. Disorders related to disrupted metabolism of lipoproteins including lipoprotein over-production and deficiency are classified as dyslipidemia. Dyslipidemia may

be reflected by elevated level of total cholesterol (TC),elevated level of triglyceride (TG), elevated level of low-density lipoprotein cholesterol (LDL-C),and/or decreased level of high-density lipoprotein cholesterol (HDL-C)[5].

Lipid and lipoprotein levels vary among different populations, with people consuming a Western type of diet generally having higher TC and LDL-C levels than those whose regular consumption of saturated fat is low[6].A comparison of the US to other countries shows a proportional relationship between CAD mortality rates and TC and LDL-C levels, whereas this relationship is an inverse one when HDL-C level is considered[7-9].A study involving 1,800 adult participants revealed a high incidence of dyslipidemia in India, with a significantly higher prevalence in males[10]. Almost 40% of males and 23% of females had TC levels above 200mg/dL. Moreover, high TC and TG levels were more prominent in adults who are more than 30 years of age compared to those under 30 years of age[11, 12].In a meta-analysis of data from 90,056 participants involved in 14 trials of statins, it was concluded that 1 mmol LDL-C reduction correlated with 23% reduction in the risk and incidence of a major coronary event[13].

Lipids comprise a large and diverse group of naturally-occurring organic compounds that are related by their solubility in non-polar organic solvents and general insolubility in water[6]. Lipids are a heterogeneous group of compounds related to fatty acids[6].Cholesterol is a lipid that is present in cell membranes and is the precursor for steroid hormones and bile acids[14].In plasma, cholesterol is found as distinct particles (lipoproteins) containing a lipid component and a protein component. Lipoproteins in humans are divided into classes according to their flotation constants and densities[9].Lipoproteins are spherical particles that transport neutral lipids, primarily triglycerides and cholesterol esters, through the bloodstream. Triglycerides and cholesterol esters are non-polar, hydrophobic lipids that comprise the core of the lipoproteins. Since the core of a lipoprotein molecule is hydrophobic in character, it is surrounded by a hydrophilic surface of phospholipids, un-esterified cholesterol, and specific proteins called apoproteins[15]. The hydrophilic surface coat makes the lipoprotein molecule soluble in plasma. Apoproteins also play a crucial role in the regulation of lipid transport/exchange and lipoprotein metabolism[15].

Statins are structurally similar to3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), a precursor of cholesterol. Statins inhibit HMG-CoA reductase, interrupting the conversion of HMG-CoA to mevalonate, the rate-limiting step in de-novo cholesterol biosynthesis[16]. Reduced LDL synthesis and enhanced LDL catabolism mediated through LDL receptors appear to be principle mechanisms utilized by statins to manifest their cholesterol lowering effects. Fibrates decrease hepatic triglyceride synthesis as well as reduce peripheral circulatory free fatty acids[17].The effects of fibrates are exerted through Peroxisome Proliferator-Activated Receptor α (PPARα), a nuclear receptor that serves as a transcription factor in several tissues including the liver, muscle, and adipose tissue[18, 19]. Activation of PPARα enhances lipoprotein lipase (LPL) synthesis and fatty acid oxidation[20].Activation of PPARα also leads to enhanced LDL receptor expression in the liver, and this effect has been particularly observed with second-generation fibrate agents (e.g. fenofibrate)[21].

Like other medications, statins inevitably have adverse side effects. The muscular system, hepatic function, and renal function have been documented to be affected by statin treatment[22].Yet, post-marketing data reveal that the overall adverse event frequency is <0.5% and the myotoxicity event rate is <0.1%[23].According to studies conducted in several Western countries, statins and fenofibrate have been shown to display high efficacy and safety[24]. However, similar studies focusing on the efficacy and safety of statins and fenofibrate are very scarce in India. Herein, we focus on examining that efficacy and safety of statins and fenofibrate in the people of South India, with specific emphasis on Tiruchirappalli (Tamil Nadu, India)in which the socio-economic status and life style of people is very different from people living in Western countries[25].The aim of the present study is to compare the efficacy and safety of the atorvastatin monotherapy and the atorvastatin plus fenofibrate combination therapy in dyslipidemic patients from Tiruchirappalli (Tamil Nadu, India).

EXPERIMENTAL SECTION

Patients and clinical evaluation

This was a randomized, open label, parallel study conducted to compare the efficacy and safety of the atorvastatin monotherapy and the atorvastatin plus fenofibrate combination therapy in 80 dyslipidemic patients (18-80 years old). The patients were selected from the OPD/in-patient wards of the Department of Cardiology in Multispecialty Hospital of Kavery Medical Centre at Tiruchirappalli (Tamil Nadu, India).The patients were selected as per the selection criteria and all study participants gave their signed informed consent for participation in the study. Patients having acute emergency hypertension, liver disease, chronic renal failure, renal transplants, malignancy condition, hereditary or acquired myopathy, allergy to atorvastatin and/or fenofibrate, as well as pregnant/lactating patients were excluded from the study. Eligible patients were divided into two groups. Group A patients were treated with atorvastatin (40 patients), while group B patients were treated with atorvastatin plus fenofibrate (40 patients). Both

drugs were given in a single oral daily dose (Group A: 10 mg of atorvastatin, Group B: 10 mg of atorvastatin plus 135 mg of fenofibrate) at bedtime for 24 weeks. At this time, a second blood analysis was performed. The study protocol was approved by the Institutional Ethics Committee and patient follow up prescription was collected in the selected departments. All the information and data required for the study were collected from the patients' case sheets, diagnosis charts, prescription charts, and lab investigation reports. The collected data were recorded in a data entry form.

Statistical analysis

The data were expressed as mean ± SD and mean percentage change. Statistical significance was determined by paired student's t-test using "GraphPad Prism 5.01" software. *p<0.01, and **p<0.001 were considered statistically significant.

RESULTS AND DISCUSSION

The clinical characteristics and baseline levels of lipid profile parameters of Group A and Group B patients were compared at the start of therapy. The characteristics of the study population displayed no statistically significant differences in the age, body mass index, body weight, proportion of smokers, diet, associated diseases, or gender distribution between two study groups**(Table 1)**.As shown in **Table 2**, there were no significant differences with regard to the baseline lipid profile levels of TC, TG, LDL-C, VLDL-C, and HDL-C between the two study groups before treatment.

Table 1.Characteristics of the study population

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	Atorvastatin Monotherapy	**Atorvastatin plus Fenofibrate Combination Therapy**
Number of Participants	40	40
Gender (Male/Female)	24/16	21/19
Age (years)	62.34 ± 10.58	65.27 ± 9.84
Body Mass Index (Kg/m^2)	25.4 ± 4.30	24.6 ± 3.87
Weight (kg)	75.2 ± 19.43	76.4 ± 17.61
Smokers/Non-Smokers (%)	35/65	32.5/67.5
Vegetarian/Mixed Diet (%)	25/75	32.5/67.5
Post-Menopausal Status (%)	37.5	30
Associated Diseases		
Diabetes Mellitus (%)	10	15
Hypertension (%)	15	10
Diabetes Mellitus& Hypertension (%)	5	10
Coronary Artery Disease (%)	2.5	5

Table 2.Effects of the atorvastatin monotherapy and the atorvastatin plus fenofibrate combination therapy on lipid profiles of dyslipidemic patients

	Atorvastatin Monotherapy			**Atorvastatin plus Fenofibrate Combination Therapy**		
	Pre-Treatment (mg/dL)	**Post-Treatment (mg/dL)**	**Change (%)**	**Pre-Treatment (mg/dL)**	**Post-Treatment (mg/dL)**	**Change (%)**
TC	180.4±29.81	151.1±19.77**	-16.24	176.2±44.86	148.1±23.07**	-15.95
TG	168.4±33.16	140.5±33.37**	-16.57	233.1±59.66	153.8±55.96**	-34.02
HDL-C	39.63±6.28	39.88±5.94	+0.63	33.67±7.83	42.25±13.83**	+25.48
LDL-C	110.3±26.64	83.49±11.58**	-24.40	105.2±41.19	77.73±17.75**	-26.11
VLDL-C	34.96±8.47	28.68±6.91**	-17.96	46.27±11.79	30.77±11.21**	-33.50

*Data presented are mean ±SD, n=40, p value *<0.01; **<0.001 compared with baseline.*

Lipid profile changes after the atorvastatin monotherapy and the atorvastatin plus fenofibrate combination therapy

The findings of our study revealed that atorvastatin monotherapy (Group A) and atorvastatin plus fenofibrate combination therapy(Group B) for 24 weeks were significantly effective in reducing the levels of TC by 16.24% and 15.95% (p<0.001, both),TG by 16.57% and 34.02% (p<0.001, both),LDL-C by 24.40% and 26.11% (p<0.001, both), and VLDL-C by 17.96% and 33.50% (p<0.001, both), respectively, all in comparison to the baseline levels **(Table 2)**.Interestingly, atorvastatin monotherapy (Group A) did not cause a significant increase in HDL-C level (0.63%, p=0.37), which was significantly increased by 25.48% (p<0.001) after the atorvastatin plus fenofibrate combination therapy (Group B) compared to the baseline levels **(Table 2)**.

The National Cholesterol Education Program (NCEP) underscored the importance of reducing LDL-C serum levels and elevating the HDL-C serum levels for the primary and secondary prevention of CHD[25]. This approach is clinically sound given that LDL is the major atherogenic lipoprotein and is directly implicated in the development of atherosclerosis and HDL is critically involved in the clearance of excess cholesterol from the bloodstream via the

liver[26]. As shown in **Table 2**, both atorvastatin monotherapy (Group A) and atorvastatin plus fenofibrate combination therapy (Group B) for 24 weeks caused a significant reduction in LDL-C levels by 24.40% and 26.11% ($p<0.001$, both), respectively. The atorvastatin monotherapy**(**Group A) for 24 weeks resulted in statistically significant fall in TC (16.24%), TG (16.57%), and LDL-C (24.40%) serum levels, while HDL-C level was not significantly affected (0.63% increase)**(Table 2)**. Our findings are consistent with those reported by Insull and colleagues in which TC, TG, and LDL-C serum levels were reduced by 27.6%, 22.1%, and 37.2%, respectively after 6 weeks of atorvastatin monotherapy[27]. However, unlike our findings, Insull and colleagues demonstrated that HDL-C serum level was significantly elevated by 7.40%after 6 weeks of atorvastatin monotherapy[27].

The atorvastatin plus fenofibrate combination therapy(Group B) resulted in statistically significant reduction in the serum levels of TC (15.95%), TG (34.02%), and LDL-C (26.11%)24 weeks post treatment **(Table 2)**. These findings are consistent with other studies in which the atorvastatin plus fenofibrate combination therapy caused a significant reduction in TC, TG, and LDL-C serum levels by 37%, 46%,and 50%,respectively[26, 28].Moreover, several studies revealed that the atorvastatin plus fenofibrate combination therapyis effective in elevating HDL-C serum level by 8-35%[29].Our study shows that the atorvastatin plus fenofibrate combination therapy caused a significant increase in HDL-C serum level by 25.48% **(Table 2)**. Based on our findings, the atorvastatin plus fenofibrate combination therapy, but not the atorvastatin monotherapy, is effective in elevating the HDL-C serum level, and hence, alleviates dyslipidemia and reduces the risk of CHD. Our study strengthens previously reported findings indicating that the atorvastatin plus fenofibrate combination therapy is of high efficacy to control the lipid profile of dyslipidemic patients. Generally, anti-hyperlipidemic drugs have been shown to increase the risk of myositis, whereas combination treatments of statins plus fenofibrate do not cause such side effects[30].

Gender-dependentlipid profile changes after the atorvastatin monotherapy and the atorvastatin plus fenofibrate combination therapy

The possible gender-dependent effects of the atorvastatin monotherapy and the atorvastatin plus fenofibrate combination therapy were assessed. As shown in **Table 3**, the atorvastatin monotherapy led to a reduction in TC serum levels by 15.84% in males and 17.02% in females ($p<0.001$, both). Similarly, the atorvastatin monotherapy led to a reduction in TG, LDL-C, and VLDL-C serum levels by 15.16% and 19.52% ($p<0.001$ and $p<0.01$), 22.56% and 26.99% ($p<0.001$, both), and 16.78% and 20.47% ($p<0.001$, both) in males and females, respectively **(Table 3)**. Although not statistically significant, HDL-C serum levelswere reduced by 0.58% ($p=0.32$) in maleswhile they were elevated by 3.10% ($p=0.37$) in females, after the atorvastatin monotherapy **(Table 3)**.

Table 3. Gender-dependent effects of the atorvastatin monotherapy in dyslipidemic patients

	Males (n=27)			Females (n=13)		
	Pre-Treatment (mg/dL)	**Post-Treatment (mg/dL)**	**Change (%)**	**Pre-Treatment (mg/dL)**	**Post-Treatment (mg/dL)**	**Change (%)**
TC	178.7±32.66	50.4±21.98**	-15.84	183.9±23.56	152.6±14.81**	-17.02
TG	170.8±35.21	144.9±37.53**	-15.16	163.4±29.12	131.5±20.93*	-19.52
HDL-C	39.43±5.01	39.2±5.99	-0.58	40.05±8.57	41.29±5.8	+3.10
LDL-C	107.7±27.39	83.4±11.5**	-22.56	114.6±25.41	83.67±12.22**	-26.99
VLDL-C	35.33±9.86	29.4±7.88**	-16.78	34.2±4.69	27.2±4.11**	-20.46

*Data presented are Mean ±SD, n=40, p value *<0.01; **<0.001 compared with baseline*

As shown in **Table 4**, the atorvastatin plus fenofibrate combination therapy led to a reduction in TC serum levels by 14.72% in males and 18.26% in females ($p<0.001$ and $p<0.01$). Similarly, the atorvastatin plus fenofibrate combination therapy led to a reduction in TG, LDL-C, and VLDL-C serum levels by 29.75% and 41.92% ($p<0.001$, both), 24.02% and 29.99% ($p<0.001$ and $p<0.01$), and 29.14% and 41.78% ($p<0.001$, both)in males and females, respectively **(Table 4)**. HDL-C serum levels were elevated by 28.64% in males and 20.70% in females ($p<0.001$ and $p<0.01$) after the atorvastatin plus fenofibrate combination therapy**(Table 4)**. Overall, it is concluded that the atorvastatin plus fenofibrate combination therapy is more effective than the atorvastatin monotherapy in reducing TC, TG, LDL-C, and VLDL-C serum levels. Moreover, the atorvastatin plus fenofibrate combination therapy, but not the atorvastatin monotherapy, is effective in elevating HDL-C serum levels. In addition, the lipid profile changes accompanying the atorvastatin monotherapy and the atorvastatin plus fenofibrate combination therapy seems to be gender-dependent, especially for TG, VLDL-C, and HDL-C serum levels **(Table 3** and **Table 4)**. Overall, females seem to benefit more than males with regard to the positive effects of both treatments on lipid profile changes **(Table 3** and **Table 4)**.

Table 4. Gender-dependent effects of the atorvastatin plus fenofibrate combination therapy in dyslipidemic patients

	Males (n=26)			Females (n=14)		
	Pre-Treatment (mg/dL)	**Post-Treatment (mg/dL)**	**Change (%)**	**Pre-Treatment (mg/dL)**	**Post-Treatment (mg/dL)**	**Change (%)**
TC	175.3±36.56	149.5±25.08**	-14.72	178±58.84	145.5±19.38*	-18.26
TG	232.3±65.27	163.2±64.09**	-29.75	234.7±49.82	136.3±31.48**	-41.92
HDL-C	31.25±5.8	40.2±9.67**	+28.64	38.15±9.27	46.05±19.24*	+20.70
LDL-C	106±34.33	80.54±18.55**	-24.02	103.6±53.11	72.53±15.45*	-29.99
VLDL-C	46.63±12.9	33.04±12.68**	-29.14	45.6±9.81	26.55±6.21**	-41.78

*Data presented are Mean ±SD, n=40, p value *<0.01; **<0.001 compared with base line.*

Safety evaluation after the atorvastatin monotherapy and the atorvastatin plus fenofibrate combination therapy

Drug safety was evaluated after both types of treatment. After the atorvastatin monotherapy, the mean urea and creatinine serum levels were 25.14and 1.18 mg/dL, respectively. The mean urea and creatinine serum levels were28.34 and 1.20 mg/dL, respectively, after the atorvastatin plus fenofibrate combination therapy. During the atorvastatin monotherapy, 2.5% of patients experienced arthralgia, diarrhea, and/or fatigue, 5% of patients experienced nausea, and 3.75% of patients experienced headache. During the atorvastatin plus fenofibrate combination therapy, 5% of patients experienced rhabdomyolysis, arthralgia, and/or diarrhea. These findings clearly indicate that both types of treatments to modulate lipid profiles in dyslipidemic patients are safe and raise no serious health concerns.

CONCLUSION

The present clinical investigation clearly suggests that the atorvastatin monotherapy and the atorvastatin plus fenofibrate combination therapy are effective in improving the lipid profiles in dyslipidemic patients. Overall, the atorvastatin plus fenofibrate combination therapy is more effective than the atorvastatin monotherapy in balancing the lipid profiles. Generally, the therapies significantly reduce the serum levels of TC, TG, LDL-C, and VLDL-C, while elevating HDL-C serum levels. Such lipid profile changes appear to be gender-dependent, in which females seem to respond better to both types of treatment. Furthermore, both treatments have no major side effects and are safe to use, at least for the duration tested (24 weeks).Finally, more studies are needed to further validate the reported findings of this study and to fine-tune the dosage and duration of treatment to achieve the best clinical results in patients with dyslipidemia.

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