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A PROSPECTIVE, RANDOMIZED, OPEN LABEL, COMPARATIVE STUDY OF ATORVASTATIN ALONE AND ATORVASTATIN WITH LYCOPENE IN PATIENTS WITH HYPERLIPIDAEMIA

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ABSTRACT

AIM:

To compare the efficacy and tolerability of Atorvastatin alone and Atorvastatin with Lycopene in the management of Hyperlipidaemia.

METHODOLOGY

This was an open label, comparative, randomized, prospective study. This study included 100 patients with Hyperlipidaemia, who wererandomized into two groups of 50 each. One group received T.Atorvastatin 10mg/day and other group received T.Atorvastatin 10mg/day with T.Lycopene 15mg/day for 8 weeks. They received routine follow-up fortnightly for 8weeks. Lipid profile was assessed at baseline and at the end of the study.

RESULTS

The baseline characteristics were similar in both the study groups. On comparing the groups at the end of 8weeks, there was a statistically significant reduction in Total cholesterol and LDL cholesterol levels (TC - $p < 0.001$; LDL- $p < 0.004$). The hematological, hepatic and renal function test did not show any significant change when compared to baseline. Minimal adverse effects were observed in both the study groups.

CONCLUSION

From this study we can conclude that,

1. Atorvastatin with Lycopene was effective in reducing the lipid levels.
2. Lycopene was well tolerated.

INTRODUCTION

Coronary Artery Disease (CAD) is one of the primary causes of death. The emphasis has been mainly on the relationship between serum cholesterol levels and the risk of Coronary artery disease. Oxidative stress induced by reactive oxygen species also plays an important role in the etiology of CAD. Antioxidants are believed to delay the progression of atherosclerosis by their ability to inhibit the harmful effect of oxidative damage.[1,2,3] The dietary antioxidants like Vit C, E, carotenoids and polyphenols have received much attention probably due to wide range of antiatherogenic properties.[4,5,6] Current dietary guidelines recommends increased intake of fruits and vegetables which are rich in antioxidants for prevention of chronic diseases like CAD, cancer etc.[7]

Among natural antioxidant, lycopene is an extract obtained from tomatoes which is one of the most potent and most effective antioxidant. It prevents the oxidation of lipids with its single-oxygen quenching ability whose potency is two times higher than β-carotene and 10 times than α-tocopherol.[8] It has a role in altering the metabolism and oxidation of lipids which predispose to the formation of atherosclerosis.

Lycopene has been shown to decrease by 37% in synthesis of cholesterol in J-774A.1 macrophage cell line, and it also augments the activity of macrophage LDL receptors. Macrophage enrichment with lycopene results in the suppression of cellular cholesterol synthesis by inhibiting the enzyme, HMG-CoA reductase. This effect leads to increased clearance of LDL from the plasma and due to this effect lycopene is being recognized as a hypolipidemic agent.[9]

Hence, the present study was planned to assess the efficacy of Lycopene in addition to atorvastatin in reducing total cholesterol and LDL-C and also to compare with that of atorvastatin when used alone.

2. MATERIALS AND METHODS

2.1. Study procedure

This was a randomised, open label, comparative and prospective study done at the Department of Medicine, Rajiv Gandhi Government General hospital (RGGGH), Madras Medical College, Chennai. The study was carried out from August 2013 to July 2014 with 8 weeks as treatment period for every patient and follow-up every fortnightly till the end of the study.

The study was carried out as per ICH, GCP guidelines, Declaration of Helsinki and after obtaining approval from the Institutional Ethics Committee, Madras Medical College,

Chennai, Tamilnadu, India. The patients attending out patient Department of Medicine, Rajiv Gandhi Govt. General Hospital, Chennai,were explained about the study procedure. A written informed consent was obtained before commencement of any study related procedure from those patients who were willing to participate.Patients were screened by medical history, physical examination and baseline laboratory investigations. Those who fulfilled the selection criteria were enrolled and randomised to either control or test group by simple randomisation with 50 patients in each group.

2.2.Selection Criteria

Inclusion Criteria:

1. Both genders.
2. Age- 25 – 60 yrs.
3. Subjects with total cholesterol level between 200-250 mg/dl.
4. Patients with Stage I Hypertension and Type II Diabetes with glycaemic control.
5. Patients willing to give written informed consent.

Exclusion Criteria:

1. Pregnant and lactating women.
2. Subjects with evidence of clinically significant gastrointestinal, renal, respiratory, endocrine, hematological, neurological, psychiatric or cardiovascular dysfunctions.
3. Triglycerides > 250 mg/dl.
4. Total cholesterol: HDL ratio > 4.5.
5. H/o allergy or intolerance to lycopene.
6. Patients unwilling or unable to comply with the study procedures.
7. Those with history of alcohol or drug abuse.

2.3.Treatment Plan

Control Group (n= 50) - Patients in this group received Tablet Atorvastatin 10mg/day for 8 weeks.

Test Group (n=50) - Patients in this group received Tablet Atorvastatin 10mg/day along with Lycopene 15mg/day for 8 weeks.

The medication was issued for 2 weeks. After assessing the compliance at the end of 2 weeks, study medications wereissued for the subsequent 2 weeks. The same procedure was followed till the completion of study.

2.4. Laboratory Investigation:

- Complete blood count (Hemoglobin, Total count, Differential count, ESR and Platelets)

- Fasting Blood sugar, Blood urea, Serum Creatinine.
- SGOT, SGPT
- Routine Urine Analysis

Fasting Lipid Profile: Serum (Total Cholesterol, LDL, VLDL, HDL & TGL)

The patients were followed up and provided routine medical care fortnightly till the end of 8 weeks. All the laboratory investigations were repeated at the end of the study.

2.5 Adverse Events:

Adverse event if any, reported by the patient or observed by the physician during the study was recorded. The onset of adverse event, causal relationship to the study drug and action taken was recorded.

2.6. Statistical analysis

The obtained data was analyzed statistically. Distribution of age was analysed using ANOVA and Sex distribution was analyzed by Chi square test.

The biochemical investigations were analyzed by students paired t test and independent t-test.

3. RESULTS

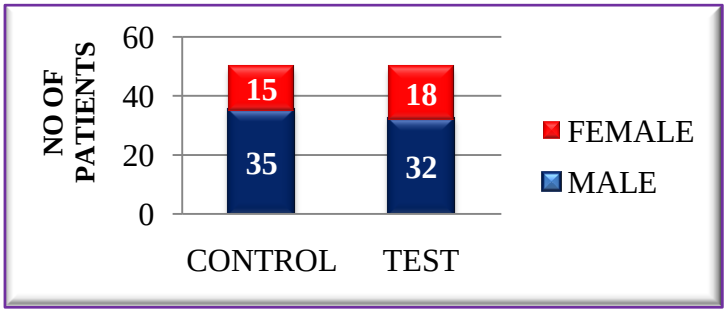
176 patients were screened. 60 patients were excluded from the study based on exclusion criteria. 16 patients who were eligible for the study were not willing to participate. 100 patients were enrolled and completed the study. There were no drop outs.

TABLE 1: AGE DISTRIBUTION

AGE IN YEARS	CONTROL		TEST	
	NO	PERCENTAGE	NO	PERCENTAGE
30-40	12	24%	10	20%
41-50	15	30%	13	26%
51-60	17	34%	20	40%
>60	6	12%	7	14%
TOTAL	50	100%	50	100%

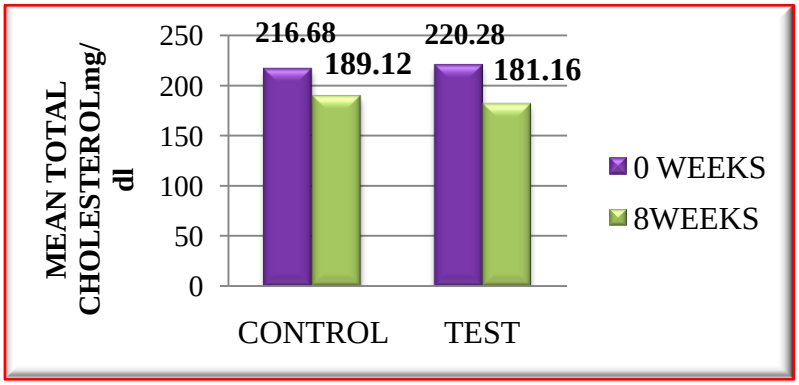
Table 1 shows the age distribution of both the study groups. Age group 51-60years had more number of patients followed by age group 41-50.

FIGURE 1: SEX DISTRIBUTION



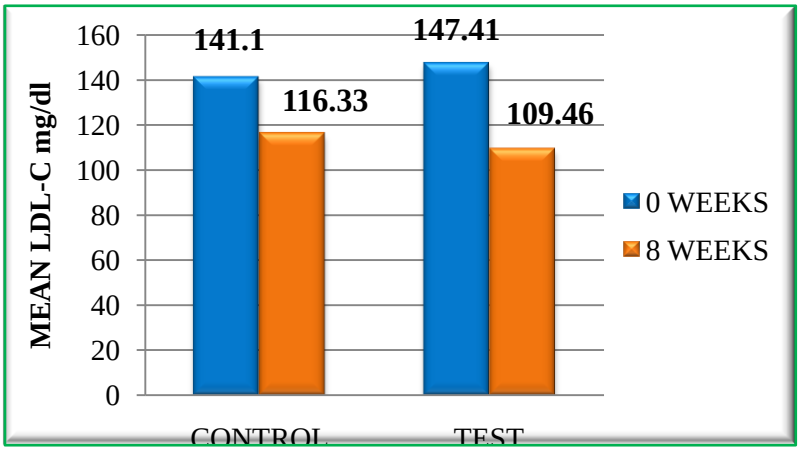
Males were more in number compared to females in both groups.

FIGURE 2: TOTAL CHOLESTEROL



On comparing with baseline, both groups showed a decrease in mean Total cholesterol.Statistical analysis within the groups showed a significant decrease in the Total cholesterol at the end of 8weeks (p <0.001).Statistical analysis between the groups showed a significant difference at the end of 8 weeks (p =0.01).

FIGURE 3: LDL CHOLESTEROL



There was a significant reduction in the mean LDL cholesterol levels in the test group (109.46mg.dl) compared to the control group (116.33mg/dl) at the end of 8 weeks.Statistical analysis within the group showed a significant decrease in both the study groups (p <0.001).Statistical analysis between the groups at the end of 8 weeks showed a significant difference (p<0.001).

TABLE 2: ADVERSE DRUG REACTION

ADVERSE DRUG REACTION	CONTROL GROUP	TEST GROUP
Nausea	3 (6%)	5 (10%)
Flatulence	3 (6%)	1 (2%)
Diarrhoea	3 (6%)	2 (4%)
Myalgia	4 (8%)	2 (4%)

DISCUSSION

Hyperlipidemia is a major modifiable risk factor in primary and secondary prevention of Coronary Artery Disease. Oxidative stress induced by reactive oxygen species (ROS) is also considered to play an important role in the pathogenesis of hyperlipidemia. While statins are highlyeffective in controlling cholesterol levels, side effects includingmuscle pain, muscle weakness, and neuropathy are experiencedby some patients.Lycopene is an antioxidant that suppresses cholesterol synthesis and prevents development of atherosclerosis.

The age and sex distribution did not show any statistically significant difference between the study groups. This shows that all the patients belonged to the same population.

Atorvastatin reduces the LDL levels which was observed in both the groups at the end of the study. But patients receiving Lycopene as add on therapy had a statistically significant reduction in LDL levels ($p < 0.01$). The reduction is about 18% in control group compared to 26% in test group. At the end of 8 weeks, the total cholesterol levels showed a significant reduction in patients receiving Atorvastatin alone (12.7%) and also in patients with Lycopene and Atorvastatin (17.7%) ($p < 0.001$). On comparing both groups, there was a statistically significant reduction in Total cholesterol levels in patients with Lycopene as add on therapy ($p < 0.001$) in comparison with those receiving Atorvastatin alone

This shows that addition of Lycopene contributes to a better reduction of both LDL and Total cholesterol levels. This was similar to the study conducted by Fuhrman et al[10], where reduction in plasma LDL-C level (14%) was observed. In a study conducted by Visioli et al[11], three weeks supplementation of tomato products showed a significant lycopene concentration in their blood and also reduced oxidizability of LDL. The HDL, VLDL, TGLs level did not show any significant difference between the groups. This shows that the addition of Lycopene did not affect these parameters. The hematological parameters like hemoglobin, total count, differential count, ESR and platelets did not show any significant difference in both study groups at the end of 8 weeks. There was no significant difference in biochemical parameters like blood sugar, urea, serum creatinine, SGOT, SGPT in both the groups at the end of the study period. This shows that addition of Lycopene did not affect the hematological and biochemical parameters. The number of adverse events observed was more in patients receiving Atorvastatin alone compared to patients receiving Lycopene as add on therapy. All the Adverse Drug Reactions were categorized as possible under WHO causality assessment scale. According to the Modified Hartwig and Siegel severity

assessment scale, all the reactions reported was mild. This shows that Lycopene did not increase the occurrence of adverse events.

As evidenced by earlier studies, our study has also modestly observed that addition of lycopene to Atorvastatin significantly reduced the total cholesterol and LDL cholesterol levels and thus resulted in significant improvement in the quality of life. Some limitations of our study includes shorter duration of study, increase in antioxidant levels after administration of lycopene which can be taken as marker of the effect of lycopene were not studied, and whether lycopene independently reduce lipid levels. Thus apart from limitations, lycopene may be considered as an alternative to low dose statins or it can be used in combination with low dose statins without side effects in patients with elevated cholesterol levels.

CONCLUSION

It can be concluded that, Lycopene as add on therapy to Atorvastatin is effective in reducing lipid levels and is well tolerated. Hence, lycopene may form part of the pharmacotherapy for hyperlipidemia since it reduces the oxidative stress.

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