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RESEARCH ARTICLE

Efficacy and Safety of Resveratrol as an Adjuvant Therapy in Patients with Dyslipidemia: Result of a Randomized Active Controlled Clinical Study

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ABSTRACT:

The aim of this study was to investigate the efficacy and safety of resveratrol as an adjuvant therapy in newly diagnosed dyslipidemic patients. In this randomized active-controlled study, dyslipidemic patients(male/female) aged 20-65 years were randomized to receive atorvastatin 10 mg or atorvastatin 10 mg plus resveratrol 1 gram daily for 12 months. Efficacy variables included change inlipid profile (total cholesterol [TC], serum triglycerides [TGA], low-density lipoprotein [LDL] and high-density lipoprotein [HDL]) from baseline and were followed-up for every 3 months. Treatment-emergent adverse events (TEAEs) were assessed. A total of 60 dyslipidemicpatients were analyzed (atorvastatin [n=30] andatorvastatin plus resveratrol [n=30]). Resveratrol as an adjuvant withatorvastatin significantly reduced plasma TC, TGA and LDL as compared to atorvastatin monotherapy ($p<0.001$ for eachparametre). Meanlevels of HDL were significantly higherin atorvastatin plus resveratrol group than atorvastatin ($p<0.001$). Both the study drugs have similar safety profile, and found well tolerable.

Keywords: Dyslipidemia; Resveratrol; Lipid profile; Atorvastatin

INTRODUCTION:

In India, overall prevalence of dyslipidemia ranged from 10-73%. The prevalence of hypercholesterolemia was 28% in urban subjects as compared to 22% in the rural subjects.[1]It has been clear that dyslipidemia plays a central role in causative relationship in etiology of CAD.[2]It has been reported that there were approximately 29.8 million patients with CAD in the year 2003. Out of these, 14.1 million resided in urban areas, while the remaining 15.7 million were rural residents.[3]It has been projected an annual new event or death occur in 2.9 million persons per year with nearly 1.5 million people dying due to CAD every year.[3]Prevalence and economic burden related todys lipidemia have been increasing and are projected to be continued to increase.[4]

The most common side effect of currently available gold standard therapy (statin) for primary and secondary prevention of coronary heart disease are liver damage and muscle pain. Adverse events of other lipid lowering therapy including statin are: muscle pain; liver damage; gastrointestinal disturbance; rash or flushing; increased blood sugar or type 2 diabetes and neurological side effects.[5-7]FDA recently generates safety issue of statin therapy, it was found that statin group of medication causes cognitive side effects (memory loss and confusion) and increased blood sugar and glycosylated hemoglobin (HbA1c) levels.[8] To manage dyslipidemia effectively, often combination therapy and adjusting dose of gold standard therapy from low to high is required to prevent mortality. This may results in long term safely issues and reduce financial burden to patients and their family. The agent that helps in controlling blood lipid profile is the better options for diabetes treatment. The combination treatment therapy may also slow down the natural disease progression and reduces the complications associated with the diabetes. To prevent side effects and financial burden due to combination therapy and high dose of gold standard therapy, there is need of an effective adjuvant therapy which is free from side effects, cost effective and enhances the efficacy of current gold standard therapy without

the need of switching to aggressive therapy. Also there is a need of adjuvant therapy which keeps us healthy and useful as prophylaxis for the patients with risk factor of cardiovascular disease.

Resveratrol is a plant based anti-dyslipidemic agent of stilbenoid type of natural phenol, and a phytoalexin produced naturally by several plants.[9]Resveratrol had significant anti-atherogenic and anti-inflammatory effects in an animal model with rabbits fed a hypercholesterolemic diet (1% cholesterol).[10]Another pre-clinical study suggested that Statin and resveratrol in combination induces cardioprotection against myocardial infarction in hypercholesterolemic rat.[11] Thisindicates that the possible use of resveratrol in combination with current anti-dyslipidemic therapy as an adjuvant therapy would be effective in preventing and treating dyslipidemia. Short term clinical use of Resveratrol 1 gram/daily (500 mg BD) was found to be effective in decreasing blood lipid level when compared to Placebo after 45 days.[12]Another 4-week clinical study (in 10 subjects) suggested that there was no change in lipid level after administration of resveratrol (1g/daily).[13]

We hypothesized that Resveratrol could be one of the adjuvant therapy along with gold standard anti-dyslipidemic therapy, which may led to significantly improve the effectiveness of gold standard therapy in management of dyslipidemia and also decrease the financial burden to the patients along with good safety profile. Moreover, no long term clinical efficacy and safety study of Resveratrol in dyslipidemia patient has been conducted. Based on the above facts, the proposed clinical study designed to evaluate efficacy and safety of Resveratrol, as adjuvants in patients with recently diagnosed with dyslipidemia who were stable on atorvastatin mono-therapy.

SUBJECTS AND METHODS:

A prospective, randomized, parallel, open label, comparative, active controlled clinical study was conducted at single study center in India. From Sep 2014 to Aug 2015, 60 patients of either sex of 20-65 years who had dyslipidemia and stable monotherapy of atorvastatin 10 mg were enrolled. Pregnant women, lactating mothers, history of diabetes, severe heart disease, hepatic disease and renal dysfunction, willing to use other antioxidant supplementation rather than resveratrol, grapes allergy, the patient was receiving drug which affect blood lipid level and regular alcoholics were excluded from this study. During the screening visit on the day before surgery, medical history was obtained; physical examination and laboratory investigations were performed. Medications considered necessary for the patient and which does not interact with the study medication were allowed. All patients were explained the procedure clearly and written informed consent from each participant was obtained before their participation in the study. The protocol was approved by Safety, Health and welfare Ethics committee, registered under DCGI (Reg no: ECR/632/Inst/MH/2014). The study was conducted in compliance with the Ethical principles of Declaration of Helsinki; Good Clinical Practices guidelines issued by the Central Drugs Standard Control Organization (CDSCO), Ministry of Health, Government of India; Ethical guidelines for biomedical research on human participants, Indian Council of Medical Research (ICMR), New Delhi; and International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use – guideline for Good Clinical Practices. The trial was registered with Clinical Trial Registry-India (CTRI) before initiation of study. Enrolled patients were randomized in 1:1 in 2 groups asper the computer generated sheet. The patients randomized in interventional group (test group) were received atorvastatin 10mg once daily along with oral Resveratrol 500 mg twice a day (a total of 1 g/daily). The patients randomized to control group were received only atorvastatin 10mg once daily. The treatment duration was 12 months for both the groups.

Compliance to study drugs was assed using pill count method at each assessment visit after dispending study drugs to patients.

Both systolic and diastolic blood pressure (BP) was assessed twice with 2 minutes apart after a 5-minute rest in the sitting position, using anauscultatory method of measurement with a properly calibrated and validated mercury sphygmomanometer. Heart rate was measured for one minute in the two minute interval between BP measurements. Body temperature was measured by thermometer. A complete lipid profile (total cholesterol, serum triglycerides, low-density lipoprotein and high-density lipoprotein) were measured at baseline (before the start of study treatment), end of 3 months, 6 months, 9 months and 12 months in both the treatment groups. All blood tests were performed at the same laboratory at any time point (baseline, 3 months, 6 months, 9 months and 12 month) for every enrolled patient in order to avoid the laboratory to laboratory variation in the results.

Statistical Analysis

Based on a power of 80% and a type I error rate of alpha= 0.05 (2-tailed), a sample size of at least 46 patients per group is required to detect a clinically significant difference of 7 mg/dl in the change in blood lipid level (with an SD of 8.40[12]) between both the groups. Considering dropout rate of 20 %, total sample size will be approx. 60 patients (60 patients in each group). Categorical data was presented as absolute number/percentage of patients while quantitative data was presented as mean ± SD. Depending on the distribution of data appropriate parametric or non-parametric test was used to find p value. Unpaired "t" /Man Whitney test was used to analyze the quantitative data for between group comparisons. Within group comparison was performed using paired t test or Wilcoxan test for quantitative data based on the distribution of data. Missing data was handled using Mean substitution or Last observation carried forward (LOCF) method. Chi-square test /fisher exact test was used to compare the categorical or

qualitative data of both thetreatment groups. Normality tests (KS and SW test) were used to detect distribution of data for numerical data. P value of less than 0.05 was considered as statistical significant difference.

RESULTS:

There was no patient dropout from each group during the study period. At the end of the study, total 30 patients in each group (control and intervention group) completed the study and subjected in statistical analysis. A consort diagram is presented showing the flow of participants through the study (Figure 1).

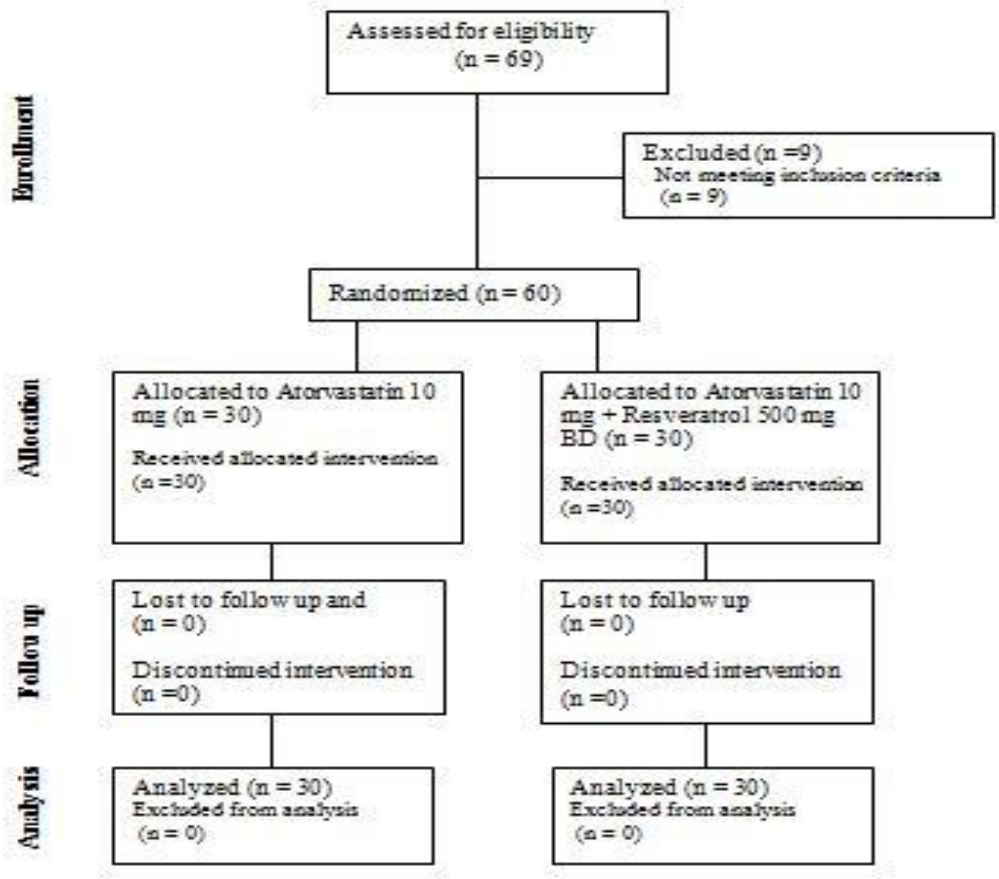

Fig.1 Flow of participants through the study

Demographic and clinical characteristic of patients of both the treatment groups were comparable (Table 1). At the baseline, there was no significant difference between the two groups regarding age, gender, bodyweight, duration of disease, smoking and lipid level (total cholesterol [TC], serum triglycerides [TGA], low-density lipoprotein [LDL] and high-density lipoprotein [HDL]). The prevalence of dyslipidemia in the family was also comparable in both the treatment groups (Table 1).

Table 1: Demographic and baseline clinical characteristics

Patient characteristic	Control N =30	Test (N = 30)	P value
Demography			
Gender (Male/Female)	20/10	22/8	>0.05
Age (year)	36.7± 3.44	38.8 ± 4.6	>0.05
Height (Cm)	168.2 ± 5.23	169.2 ± 4.51	>0.05
Weight (Kg)	76.7 ± 7.00	79.2 ± 4.36	>0.05
Smoking			
Yes	24	23	>0.05
No	6	7	
Duration of disease(months)	1.5± 0.7	1.4 0.9	>0.05
Family history of dyslipidemia			
Yes	27	28	>0.05
No	3	2	

Control= Atorvastatin 10; Test= Atorvastatin 10 mg+ Resveratrol 500 mg twice daily. Values are expressed as Mean±Standard deviation except for gender, family history of dyslipidemia and smoking. Absolute values are expressed for gender, family history of dyslipidemia and smoking. P value by Un-paired t test for continuous variables, Fisher exact test for gender, family history of dyslipidemia and smoking.

Before the start of study drug treatment (at baseline), blood lipid levels (TC, TGA, LDL and HDL) were comparable in both the treatment group. There was gradual reduction in blood TC, TGA, LDL levels over a period of 12 months hours in both the treatment groups as observed from the reduction trend in the blood TC, TGA, LDL levels from baseline. In both the

treatment groups, reduction in blood TC, TGA, LDL levels was statistically significant when compared to baseline (within group comparison). Between groups comparison showed that reduction in blood TC, TGA, LDL levels was significant greater in test group at 3 months, 6, 9 and 12 months when compared to control ($p<0.005$ at each time point) [Table 2].

Table 2:Lipid levels at baseline and over the period of 12 month after study drug treatments

Parameters	Control (N =30)	Test (N = 30)	P value
Baseline			
Total cholesterol	281.9 ± 4.86	283.8 ± 8.25	>0.05
TG	288.8 ± 7.81	288.8 ± 8.82	>0.05
LDL	174.6± 5.74	178.4 ± 5.16	>0.05
HDL	30.6 ± 2.72	28.7 ± 2.07	>0.05
End of 3 months			
Total cholesterol	274.9 ± 4.42*	267.3 ± 9.42*	<0.05
TG	280.8 ± 7.30*	270.0 ± 10.89*	<0.05
LDL	168.5± 5.61*	160.0 ± 5.49*	<0.05
HDL	35.5 ± 2.30*	40.9 ± 2.40*	<0.05
End of 6 months			
Total cholesterol	268.5 ± 6.36*	258.0 ± 6.63*	<0.05
TG	273.6 ± 8.19*	259.7 ± 8.78*	<0.05
LDL	163.0± 4.34*	150.1 ± 7.54*	<0.05
HDL	39.4 ± 2.01*	47.1 ± 4.72*	<0.05
End of 9 months			
Total cholesterol	264.3± 7.59*	252.4 ± 5.63*	<0.05
TG	270.0 ± 8.90*	253.5± 9.74*	<0.05
LDL	159.1 ± 8.11*	145.8 ± 6.12*	<0.05
HDL	41.4 ± 2.65*	51.6± 5.56*	<0.05
End of 12 months			
Total cholesterol	262.5± 5.39*	249.6 ± 5.18*	<0.05
TG	268.1 ± 6.90*	251.4± 8.71*	<0.05
LDL	156.9 ± 6.15*	143.1 ± 4.24*	<0.05
HDL	42.6 ± 2.87*	53.1 ± 3.97*	<0.05

Values are expressed as Mean± Standard deviation. *p<0.05 from baseline by paired t test (within group comparison). Between group comparison was done using Un-paired t test.

There was significant improvement in blood TC, TGA, LDL and HDL levels in both the treatment groups from baseline. However, improvement in blood TC, TGA, LDL and HDL level at 3 months, 6, 9 and 12 months from baseline was significantly greater in test group as

compared to control group. The difference between the treatments for the change in blood TC, TGA, LDL and HDL level from baseline was statistically significant (Table 3).

Table 3: Change in Lipid levels from baseline to 3 months, 6, 9 and 12 after study drug treatments

Parameters	Control (N =30)	Test (N = 30)	P value
End of 3 months			
Total cholesterol	-7.0± 5.52*	-16.5± 8.71*	<0.05
TG	-8.0 ± 5.77*	-18.8± 9.62*	<0.05
LDL	-6.1± 4.63*	-18.3± 8.38*	<0.05
HDL	+4.8 ± 2.72*	+12.2±3.21*	<0.05
End of 6 months			
Total cholesterol	-13.4± 6.80*	-25.8± 11.18*	<0.05
TG	-15.2± 8.28*	-29.1± 12.18*	<0.05
LDL	-11.6± 4.92*	-28.3 ± 9.80*	<0.05
HDL	+8.8 ± 3.80*	+18.4± 5.70*	<0.05
End of 9 months			
Total cholesterol	-17.6± 7.50*	-31.4± 7.95*	<0.05
TG	-18.8± 8.43*	-35.3±8.20*	<0.05
LDL	-15.5± 8.43*	-32.6±8.59*	<0.05
HDL	+10.8 ± 4.45*	+22.9±6.56*	<0.05
End of 12 months			
Total cholesterol	-17.6± 7.50*	-31.4± 7.95*	<0.05
TG	-18.8± 8.43*	-35.3±8.20*	<0.05
LDL	-15.5± 8.43*	-32.6±8.59*	<0.05
HDL	+10.8 ± 4.45*	+22.9±6.56*	<0.05

Values are expressed as Mean± Standard deviation. *p<0.05 from baseline by paired t test (within group comparison). Between group comparison was done using Un-paired t test.

DISCUSSION:

In this prospective, randomized, parallel, open label, comparative, active controlled, single center clinical study**,** resveratrol as adjuvant therapy significantly decrease TC, TGA and LDL in patients with dyslipidemia. Also resveratrol significantly increases HDL level in patients with dyslipidemia. Resveratrol as adjuvant therapy having acceptable safety profile, and the most common adverse event is gastrointestinal disturbance. Our study suggested that the addition of resveratrol to gold standard therapy of anti-dyslipidemic class of drug and significantly improve the efficacy of gold standard therapy, possibly due to synergistic action.

The potential effect of resveratrol in management of dyslipidemia has been established in pre-clinical setting. In rodent model, resveratrol was effective in preventing obesity and oxidative stress and reducing the risk of hypertension and dyslipidemia in adult rats.[14]Resveratrol is effective for protecting against diet-induced dyslipidemia in high fat diet-fed mice[15], and the total cholesterol (TC) content in mice was significantly decreased by resveratrol (22.5 mg/kg BW).[16] Our finding is consistent with the previous reports that resveratrol combined with statinact synergistically and induces cardioprotection against myocardial infarction in hypercholesterolemic rat[11];this may reduce the therapeutic doses of statin necessary in the treatment of dyslipidemia. In rodent model, resveratrol ameliorated dyslipidemia induced by the atherogenic diet, and its beneficial effects were associated with the altered expression of hepatic genes involved in lipid metabolism.[17]Also resveratrol improved dyslipidemia and hyperleptinemia in obese rats.[18] Moreover, our study results were also consistent with the previous clinical reports, short term clinical use of resveratrol 1 gram/daily (500 mg BD) was found to be effective in decreasing TC, TGA and LDL level and improve HDL when compared to Placebo after 45 days.[12] Another 4 week clinical study (in 10 subjects) suggested that there was no change in lipid level after administration of resveratrol (1g, 1.5g and 2g/daily).[13]

In our study, resveratrol significantly increases HDL levels in patients with dyslipidemia. We also observed that resveratrol as adjuvant therapy was found to be effective in improving HDL level in dyslipidemia. Results of our study showed the combination of resveratrol and gold standard therapy of anti-diabetic class of drug significantly improve level of other lipid levels by increasing level of good cholesterol as compared to the monotherapy, this was possibly due to synergistic action. Our study results with respect to hypolipidemic effect of resveratrol were consistent with previous report.[12, 13]Our study support the long term clinical efficacy and safety study of resveratrol along with gold standard therapy in dyslipidemia patients, and suggested

synergistic effect of resveratrol when given along with gold standard therapy as adjuvant therapy in clinical setting in management of dyslipidemia.

CONCLUSION:

Resveratrol as an adjuvant therapy was found to be well tolerated and effective in dyslipidemia. Both the study drugs have comparable safety profile and found well tolerable. Resveratrol plus atorvastatin was found to be superior over atorvastatin monotherapy in reducing TC, TGA and LDL and significantly increased the HDL levels in patients with dyslipidemia.

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