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Combination Of Biotin With Atorvastatin Achieves Favourable Total Cholesterol : Hdl Ratio In Secondary Dyslipidemia : A Single Centre, Prospective, Open Label, Parallel Group, Comparative Study.

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Abstract: The aim of our study is to determine the efficacy and side effect profile of the combination therapy of Biotin with Atorvastatin with the monotherapy group which received only Atorvastatin.
Methodology: A total of 60 patients were randomly allocated to two groups, group A received tablet Atorvastatin 20 mg daily at bedtime and group B received tablet Biotin 5 mg along with atorvastatin 20 mg daily at bed time for 6 weeks. Fasting lipid profile was done at the end of 1, 2, 4 and 6 weeks. The primary efficacy measure was the reduction in the Total Cholesterol :HDLratio after the 6 weeks of treatment.
Results: The combination therapy group had a 16.90% reduction at 1st week followed by a 39.89% reduction in LDL levels at the end of 2nd week, 42.62% reduction at the end of the 4th week and 43.28% reduction at the end of the 6th week which was greater than the 34.35%, 35.89% and 36.95% reduction seen in the control group at 2nd, 4th and 6th week respectively. The group which received combination therapy was able to achieve desirable levels of total cholesterol : HDL ratio of ≤ 3.5 at 4th and 6th weeks.
Conclusion: It can be concluded that combination therapy of Biotin 5 mg with Atorvastatin 20 mg is more efficacious than Atorvastatin 20 mg alone in terms of reduction in Total cholesterol :HDLratio with less side effects.

I. INTRODUCTION

Dyslipidemias and their complications are now emerging as a major public health challenge globally and it is estimated that by 2020 cardiovascular diseases secondary to dyslipidemias will be the largest causes of disability and death in the developing countries, especially in India with 2.6 million Indians predicted to die due to cardiovascular diseases[1]. There is still an unmet need for newer therapies to effectively control these dyslipidemias.

Studies investigating the effect of Biotin administration on the concentration of plasma lipids have shown that Biotin treatment has significant effects on cholesterol and have concluded that pharmacological doses of biotin decrease hypertriglyceridimia[2] . Epidemiological data has shown that most patients with premature CAD also have low HDL cholesterol levels. Hence the total cholesterol and HDL cholesterol ratio has been recognised as a more important determinant of CAD risk [3]. We designed a comparitive study to find out the effect of addition of 5 mg of biotin on the total cholesterol and HDL cholesterol ratio of patients with secondary dyslipidemias already receiving atorvastatin 20 mg per day.

II. METHODOLOGY

We conducted the single centre, Prospective, Open label, Parallel group, Comparative study in the Hypertension clinic of the Department of Government Stanley hospital, a tertiary care hospital in south India from March 2013 to February 2014 after obtaining approval from the Institutional Ethics Committee.

Newly diagnosed cases of dyslipidemia with Plasma total Cholesterol > 200 mg/dl, Plasma LDL levels = 100-189 mg/dl ,Plasma triglyceride >150 mg/dl, Plasma VLDL >30 mg/dl, Plasma HDL <40 mg/dl and who were willing to give informed consent were selected for the study. Patients with Diabetes mellitus (Type 2) and/or hypertension (systolic Bp<160 mm hg and diastolic Bp<100 mm hg) were allowed to participate in this study.

We excluded patients with age less than 45 years or more than 60 years. Other exclusion criteria were high plasma levels of LDL cholesterol (i.e., more than 190 mg/dl) alone or high plasma levels of triglyceride (i.e., more than 151 mg/dl) alone. Patients with very high levels of plasma total cholesterol (i.e., more than 500 mg/dl) and very high levels of plasma triglyceride (i.e., more than 500 mg/dl), uncontrolled Diabetes Mellitus (i.e., Fasting Blood Sugar>140 mg/dl), uncontrolled hypertension (i.e., systolic BP >160 mm hg and diastolic BP >100 mm hg), history or clinical evidence of ischaemic heart disease or unstable angina or stable angina or

cerebrovascular disease or peripheral arterial disease or neuromuscular disorders, history or laboratory evidence of liver dysfunction, history or clinical evidence of renal dysfunction, metabolic or hormonal disorders, history of smoking or alcoholism, thyroid dysfunction, on antiplatelet drugs were excluded.

A total of 80 patients who were willing to participate in this study and willing to give written informed consent were selected for screening. Written informed consent in their own language was obtained from the selected patients. Screening procedure consisted of a detailed medical and drug history, thorough clinical examination followed by laboratory investigations , which included Complete hemogram ,Fasting Plasma lipid profile - Total Cholesterol, LDL, Triglycerides, VLDL,HDL, Liver function tests-SGOT,SGPT, Renal function tests-Blood urea, Serum creatinine, Creatinine phosphokinase. After screening 20 patients were excluded based on selection criteria.

A total of 60 patients of both sexes and age between 45 to 60 years who fulfilled the selection criteria were recruited for the study. Each patient was registered as a new Dyslipidemia case and a case record form was maintained for each patient. The study subjects were randomly assigned using a computer generated randomization either of the two groups Group A and Group B, each group consisting of 30 patients.

Study Design

The 30 patients of group A were started on tablet atrvastatin 20 mg daily after dinner and patients of group B were assigned to receive T.Biotin 5 mg and T.Atorvastatin 20 mg daily after dinner. Tablet Atorvastatin 10 mg was obtained from govt. supply at Government Stanley Hospital. Tablet Biotin 5 mg (trade name ESSYVIT, Ranbaxy Pharma) purchased from retail outlets. The batch number, date of manufacturing, bill number from retailer, date of purchase were entered in the drug treatment form used for each patient. At the initial visit tablets were given for one week according to the above treatement allotment. Patients were advised to continue their anti hypertensive or antidiabetic medication as before. No special diet instruction was given.

Participants were instructed to come in between if any myalgia or any other adverse event occurred. All patients were reviewed at the end of 1^{st}, 2^{nd}, 4^{th} and 6^{th} week. At each visit fasting lipid profile was done and plasma lipid levels were noted and adverse event monitoring was also done throughout the study period. Study drugs were given till the next visit. After treatment period of 6 weeks the study medications were stopped and participants were referred back to their respective departments and received Atorvastatin 20 mg daily at bedtime for 6 more weeks. The study participants were followed up till the 12^{th} week. Plasma lipid profile and laboratory parameters of both the groups were repeated at the end of 12 weeks to find out any delayed effects of Biotin. Adverse event monitoring was done for the 12 weeks of study period and the adverse events and the additional observed effects were noted and tabulated.

III. STATISTICAL ANALYSIS

Baseline characteristics of both the groups including the mean age, sex distribution, associated diseases like diabetes mellitus, hypertension and baseline lipid profile were assessed and tabulated. Plasma lipid profile was repeated at 1^{st}, 2nd, 4th and 6^{th} week of treatment and the percentage change in each of the plasma lipoproteins from baseline was calculated and statistically analyzed by students independent 't' test.

Data was expressed as mean ± standard deviation. Students independant ' t' test was used for comparing quantitative data between the two groups. At the end of the study the effects of Atorvastatin alone and combination of Atorvastatin with biotin on lipid profile was compared in terms of therapeutic efficacy and adverse effects. The primary effiacacy measure was the percentage reduction in the plasma total cholesterol and HDL after the 6 weeks of treatment. Safety evaluation was based on the spontaneously reported adverse events and the changes in the liver function tests and laboratory values after the study.

Results:

During the study period from March 2013 to February 2014 a total of 80 dyslipidemic patients were selected and screened for the study. Based on the selection criteria, 20 patients were excluded and the remaining 60 patients were randomly allocated into two groups of 30 patients each. There were no dropouts in each of the groups. After 6 weeks of treatment, Biotin was stopped and both the study and control groups received mono therapy with Atorvastatin in their respective departments for the next 6 weeks .

TABLE no. 1: BASELINE CHARACTERISTICS OF THE TWO GROUPS

BASELINE CHARACTERISTICS	CONTROL GROUP(30) mean	STUDY GROUP(30) MEAN
1. Mean age in yrs	50.70	50.13
2. Number of males (%)	13(43.3)	13(43.3)
3. Number of females (%)	17(57.7)	17(57.7)
4. Diabetes Mellitus (%)	7(23.3)	8(26.6)
5. Hypertension (%)	28(93.3)	27(90)
6. Total Cholesterol (mg/dl)	263.76	286.73
7. LDL Cholesterol (mg/dl)	158.06	173.76
8. Triglyceride (mg/dl)	170.03	210.6
9. VLDL Cholesterol (mg/dl)	36.33	41
10. HDL Cholesterol (mg/dl)	46.44	47.33
11. Total CH:HDL ratio	5.63	6.06

The baseline demographic characteristics and lipid profile of both the groups are shown in table no 1. The mean age and gender distribution of both the groups were similar. The incidence of hypertension and diabetes of thmellitus was also similar in both the groups. The mean total cholesterol of the control group was **263.76mg/dl *vs.*** mean total cholesterol of **286.73 mg/dl** in the study group. The mean HDL of the control group was **46.44 mg/dl *vs.* mea**n HDLof **47.33 mg/dl** in the study group.The total cholesterol : HDL ratio of the study group was 6.06 and 5.63 in the study and control groups at the beginning of the study

The mean total cholesterol levels and percentage reduction in cholesterol levels of both the groups during the study are shown in table no 2and table n 3 respectively. The mean total cholesterol levels in both the groups and the percentage reduction from the baseline at 1st, 2nd, 4th, 6th &12th week are given in table no 2. The percentage reduction in total cholesterol levels from the baseline was 34.66% at the second week, 41.33% at the fourth week , 40.37% at the sixth week. From the seocnd week these reductions were statistically significant when compared to control group.till the sixth week. Similiarly the mean HDL levels of both the groups and the percentage change from baseline HDL levels are shown in table n 4 and 5 re spectively. The study group had a greater increase in mean HDL levels when compared to control at fourth and sixth week of th e study but the difference was not statistically significant.

Table no 2 : Comparison of mean total cholesterol levels in both the groups

	Control		Study	
	Mean TC level (mg/dl)	**% redn**	**Mean TC level (mg/dl)**	**% redn**
Baseline	263.76	-	286.73	-
1st week	221.00	16.7%	240.4	16.06%
2nd week	194.00	**26.32%**	186.2	**34.66%**
4th week	189.00	**28.33%**	167.46	**41.33%**
6th week	188.00	**28.68%**	169.8	**40.37%**
12th week	191.00	27.56%	208.3	29.96%

Table no 3: Comparison of % reduction from Baseline in Total Cholesterol between two groups

	Control(% redn)		Study(% redn)		
	Mean	**SD**	**Mean**	**SD**	**'p' value**
Baseline	-	-	-	-	
1stweek	16.7%	5.6	16.06%	4.37	0.623
2nd week	**26.32%**	4.4	**34.66%**	8.52	**0.000****
4th week	**28.33%**	5.05	**41.33%**	7.74	**0.000****
6thweek	**28.68%**	5.56	**40.37%**	9.91	**0.000****
12thweek	27.56%	5.7	26.96%	5.02	0.671

** $p \leq 0.010$ it implies (Highly Significant), * $p \leq 0.050$ it implies (Significant) , $p > 0.050$ it implies Not Significant

Figure no 1: Comparison of % change in Total Cholesterol between two groups

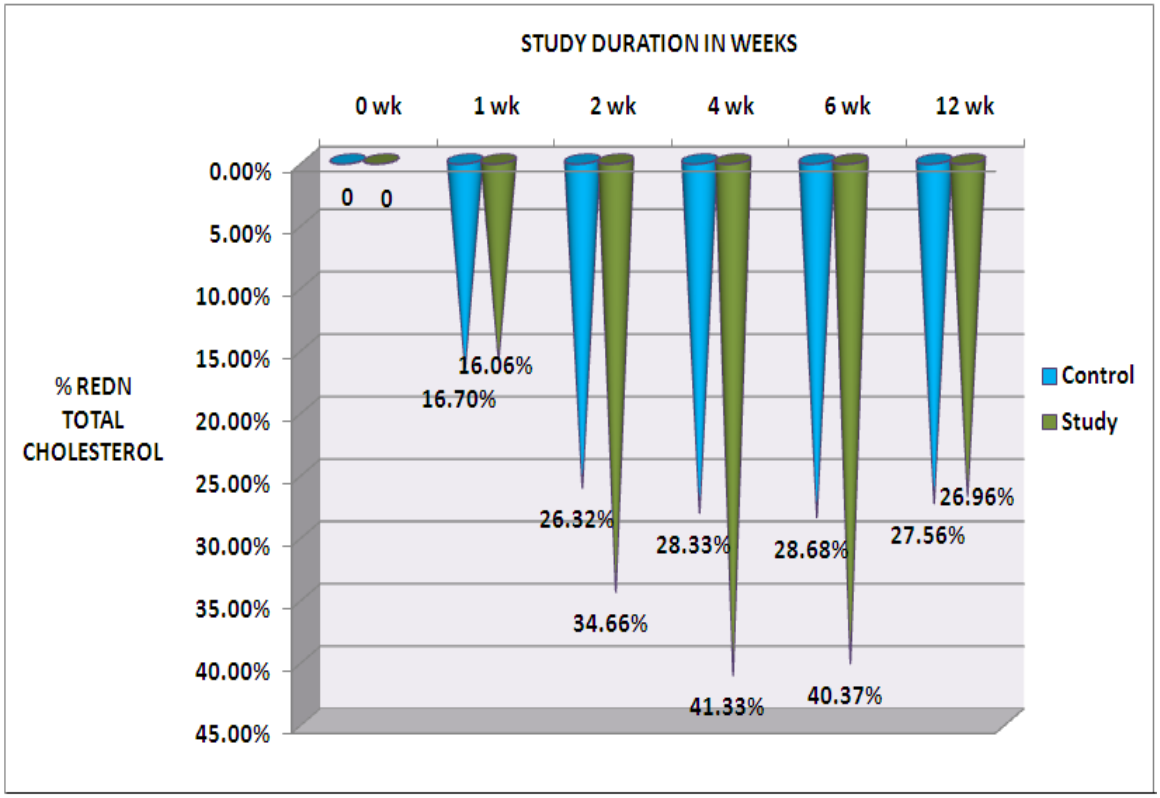


Table 4: Mean HDL levels in both the groups

	Control		Study	
	Mean HDL mg/dl	**% change**	**Mean HDL mg/dl**	**% change**
Baseline	46.44	-	47.3	-
1st week	45.6	-1.26	46.22	-2.29%
2nd week	46	-0.25	47.17	-0.35%
4th week	46.26	-0.11	48.39	2.32%
6th week	47.5	2.83	47.9	4.17%
12th week	48.76	6.11	47.66	3.47%

Table no 5: Comparison of % change from Baseline in HDL levels between two groups

	Control(% change)		Study(% change)		'p' value
	Mean	**SD**	**Mean**	**SD**	
Baseline	-	-	-	-	
1stweek	-1.26%	6.54	-2.29%	2.95	0.09
2nd week	-0.25%	8.01	-0.35%	7.36	0.620
4th week	-0.11%	5.60	2.32%	7.23	0.150
6thweek	2.83%	6.84	4.17%	9.01	0.518
12thweek	6.113%	8.80	3.47%	4.09	0.142

** $p \leq 0.010$ it implies (Highly Significant), * $p \leq 0.050$ it implies (Significant) , $p > 0.050$ it implies Not Significant

Figure no 2: Comparison of % reduction from Baseline in HDL levels between two groups

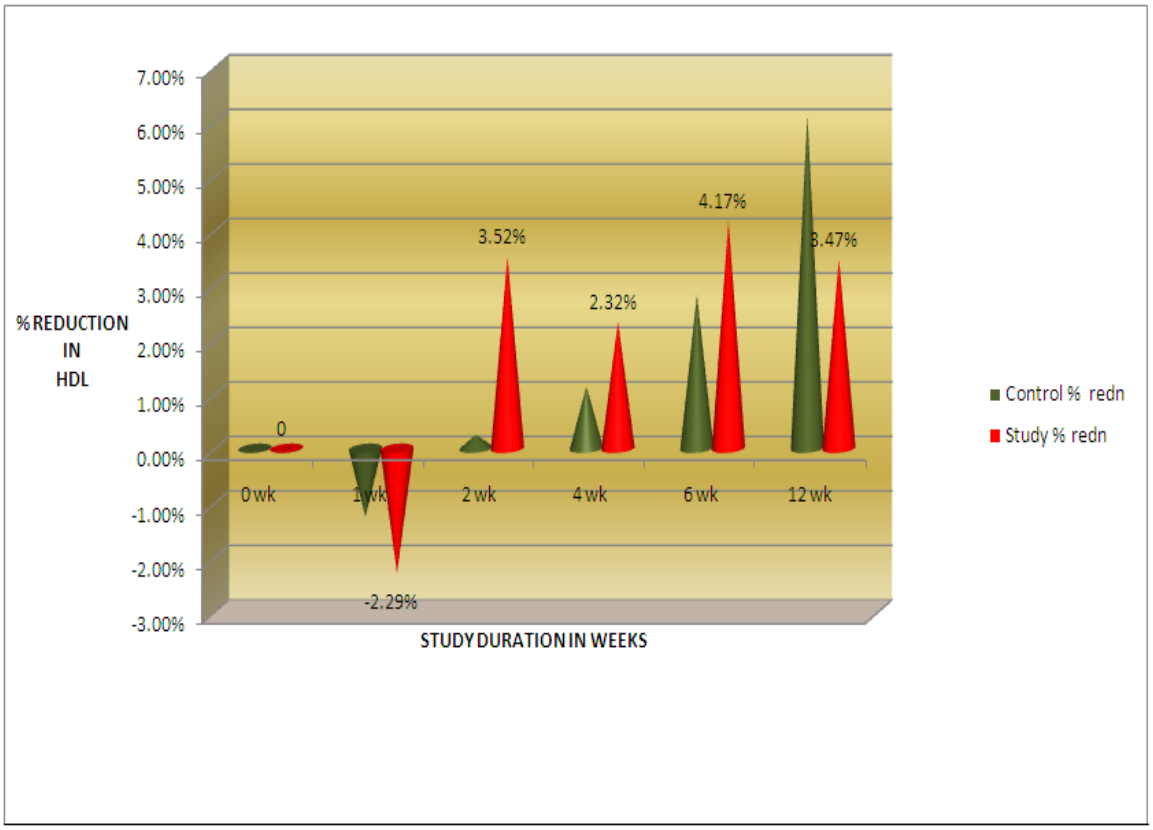
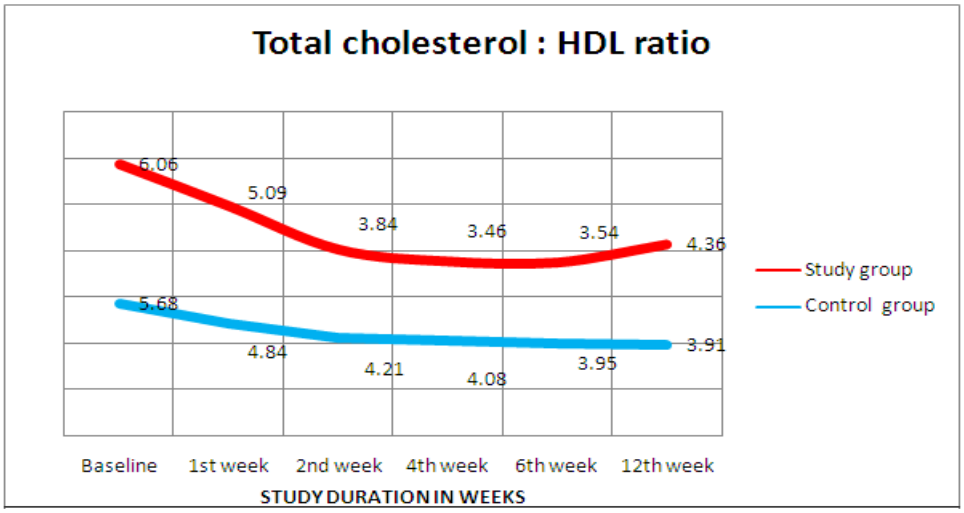


Table no 6: Comparison of Total cholesterol: HDL-cholesterol ratio between study and control groups

	Mean total CH:HDL CH ratio	
	Control group	**Study group**
Baseline	5.68	6.06
1st week	4.84	5.09
2nd week	4.21	3.84
4th week	4.08	**3.46**
6th week	3.95	**3.54**
12th week	3.91	4.36

Figure no3: Comparison of the total: HDL ratio of both the groups



The ratio of total cholesterol and HDL cholesterol in both the groups during the study is shown in **Table no 6 In th** control group the total cholesterol : HDL cholesterol ratio was 5.68 at baseline, thereafter it reduced to 4.84 at 1st week, 4.21 at 2nd week, 4.08 at 4th week, 3.95 at 6th week and 3.91 at 12th week.
In the study group the total cholesterol: HDL cholesterol ratio was 6.06 at baseline, later it reduced to 5.09 at 1st week and 3.84 at 2nd week. From the 4nd week onwards the ratio was in the desirable level of ≤3.5 till the sixth week

IV. DISCUSSION

Biotin is a water soluble vitamin that acts as a prosthetic group of carboxylases [4]. Studies in mice have proved that of biotin given in pharmacological concentrations reduces serum triglycerides and the expression of lipogenic genes[5]. These evidences and the lack of toxic effects of the vitamin at higher doses suggest that biotin could be used in the management of hyperlipidemias.

In our study the mean age of the patients in the **study group and control group were 50.13 yrs and 50.7 yrs** respectively (vide table no 1 & figure no 1).

Though we have included patients of both sexes in the study, there was a **female preponderance (57%)** in both the groups. The sex distribution of the patients of both the groups were found to be same (vide table no 3 & figure no 2).

The reduction in total cholesterol levels in the monotherapy group are similar to those observed in other studies by Wilinski et al[6].

In our study all the patients had associated hypertension but it was of moderate severity and was well treated. We have included patients with type 2 diabetes mellitus in the study and the incidence of diabetes mellitus was **26.6% in control group and 23.3% in study group** (vide table no 1).

In our study the combination of biotin 5 mg with atorvastatin 20 mg resulted in a greater reduction in total cholesterol when compared to from the 2nd week onwards which was well maintained till the 6th week, this difference was also **statistically significant.** the combination therapy group was able to achieve desirable levels of **total cholesterol : HDL ratio of ≤ 3.5 at 4th and 6th weeks**. In the monotherapy group the total cholesterol : HDL ratio was > 3.5 through out the study.

Both the groups tolerated the medications and had few minor side effects. The incidence of adverse effects in the control group was similar to those seen in previous studies with atorvastatin 20 mg [7]. In the control group 3 out of 30 patients (10%) complained of myalgia and 4 out of 30 patients (12%) complained of general body weakness. The study group had less myalgia (6.66%) and body weakness(10%).The occurrence of gastrointestinal distress was similar in both the groups. In addition one male patient reported reduced hair fall during the study. This observation correlated with studies showing the effects of Biotin in androgenic alopecia by Fameneni et al [8,9].

Biotin is a very safe vitamin and levels upto 300 times the normal have shown to be non toxic. Thus the addition of Biotin had resulted in fewer side effects and some additional observed effects also. None of the patients had any significant abnormality in the laboratory investigations performed.

From this study we can infer that combination therapy of biotin and atorvastatin produced significantly more reduction of total cholesteroland favourable total cholesterol:HDL ratio. This lipid lowering effect of biotin is attributed to the regulation of genes associated with intermediary metabolism and maintanence of glucose and lipid hemostasis [10].

V. CONCLUSION

It can be concluded that combination therapy of Biotin 5 mg with Atorvastatin 20 mg is more efficacious than Atorvastatin 20 mg alone in terms of reduction in Total cholesterol : HDL ratio. Thus, Biotin is a safe and well tolerated adjuvant hypolipidemic agent in secondary dyslipidemias

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