Comparative clinical study on the efficacy of biocor plus compared with simvastatin for the management of hypercholesterolemia

Zeeshan Ahmed Sheikh[1,2], Khan Usmanghani[1,2], Halima Nazar[1], Allah Nawaz[1,2], Lala Rukh Jahanzeb[1] and Irshad Ahmad[3]

[1]Faculty of Eastern Medicine, Hamdard University, Karachi, Pakistan
[2]Department of Research and Development, Herbion Pakistan (Pvt) Limited, Korangi Industrial Area, Karachi, Pakistan
[3]Department of Pharmacy, The Islamia University of Bahawalpur, Bahawalpur, Pakistan

Abstract: Hypercholestriolemia is major risk factor that enhances the incidence of cardiovascular disease and coronary artery disease. The present study was conducted to normalize the lipid profile in the blood by using Biocor Plus for hypercholesterolemia compared with Simvastatin. It was prospective randomized case control study conducted on 70 diagnosed patients of hypercholesterolemia at Sohail Memorial Hospital, Karachi and Amir Habib Medical Center and Maternity Home, Karachi. Patients of both genders (30-70 years) with clinical diagnosis of Hypercholesterolemia. Sample sizes for this study included total of 70 subjects. There was statistically significant difference when comparing the effectiveness of test drug, Biocor Plus to control drug, Simvastatin for the treatment of primary hypercholesterolemia. This is clearly evident that the herbal coded test drug, Biocor Plus possesses a therapeutic value for the treatment of primary hypercholesterolemia. There were no untoward or significant side effects associated with the use of Biocor Plus that proved its good acceptability by the patients. Moreover there was subjective feeling of wellbeing regarding breathlessness and chest tightness or pressure in the patients taking Biocor Plus. This makes an interesting point to focus on this effective alternative drug for primary hypercholesterolemia.

Keywords: Hypercholesterolemia, Low-density Lipoproteins (LDL), lipid profile.

INTRODUCTION

Hypercholesterolemia is the condition that is characterized by increased concentration of lipids or fats (triglycerides, cholesterol) and lipoproteins in the blood. This increase of lipids in the blood can lead to serious heart diseases and pancreatitis. Most of the time hyperlipidemia has no symptoms and usually it has been diagnosed on routine lab investigation or during secondary investigations held primarily for other symptom or disease. Once baseline lipid levels are determined, they should be checked and controlled for every 3 to 4 months, or at least once a year. Regular aerobic exercise is shown reduce cholesterol. Discontinuing smoking and avoid or limit consumption of alcohol can also lower cholesterol. Hyperlipidemia refer to "elevated levels of the total cholesterol, low density lipoprotein cholesterol (LDL-C), triglycerides and lower levels of high density lipoproteins (HDL-C) <35mg/dL". The plasma lipid levels recommended by National Cholesterol Education Program (NCEP), USA that desirable amount of "total Cholesterol is <200mg/dL, borderline range is 200-239mg/dL high range is above or equal to 240mg/dL and for triglycerides normal value is <150mg/dL, borderline 159-199mg/dL, high 200-499mg/dL and very high≥500mg/dL. In case pf LDL-Cholesterol the optimal value is <100mg/dL, near optimal/ above optimal is 100-129mg/dL, borderline high 139-159mg/dL, high 160-189mg/dL and very high≥190mg/dL. The HDL-Cholesterol level low is below <40mg/dL and high values is equal or above 60mg/dL" (Robert WM and Thomas PB, 2001). The depiction of healthy cholesterol levels and hypercholesterolemia are given in fig. 1 and fig. 2 where as in healthy cholesterol levels low density lipoproteins, triglycyrrhides and high density lipoproteins have been figured out in fig. 1 and fig. 2. In case of hypercholesterolemia low-density lipoproteins, high lipoproteins are found in abundance that elicits the causes of hyperlipidemia. Its diagnosis is done usually by testing lipid profile of the patients after an overnight fasting (10 to 12 hours). Adults with normal lipid profile should have their cholesterol checked after every five years and those who treated should cholesterol levels measured every two to six months and also liver functions tests.

The major risk factors that modify low-density lipoprotein include age, smoking status, hypertension, high-density lipoprotein levels, and family history. The concept of "CHD equivalent" is introduced conditions requiring the same vigilance used in patients with coronary heart disease. Patients with diabetes and those with a 10-year cardiac event risk of 20 percent or greater are considered CHD equivalents. Once low-density lipoprotein cholesterol is at an acceptable level, physicians are advised to address the metabolic syndrome and hypertriglyceridemia. The classification of cholesterol is shown in table 1.

**Corresponding author:* e-mail: zeeshan.ahmed@herbion.com

Herbal formulation either could be one of the options which can exert better response to treat hypercholesterolemia with least or elicit even no side effects. The test drug (Biocor Plus) is formulated from this point of view from the combination of various medicinal plants (*Bombyx mori Cocoon., Commiphora mukul Engl., Trigonella foenum-graecum* Linn., *Origanum vulgare* Linn., *Rauwolfia serpentina* (L.) Benth. ex Kurz) having the anti-hyperlipidemic activity that is also proven by literature search. This test drug is also applied to selected individual with specific time duration and dosage and to observe effects on biochemical test at every follow up visits at given hospital. While Statins considered as the drug of choice and have been shown the better results in reducing the plasma lipid levels thereby preventing coronary events was used as control.

Epidemiological evidence

High risk of hypercholesterolemia is present worldwide however it is more so in India and Pakistan. According to a survey carried out in about 3143 adults >40 years of 12 randomly selected communities in Karachi, Pakistan, women were more likely to develop high cholesterol than men. The evidence shows that people living in South Asia have higher readings compared to the data equivalent of living in Europe, China and North America. This index can be used as a marker of the presence of small plates that may progress to rupture and contribute to coronary occlusion and ischemia potential (Jafar and Qadri, 2008).

According to another study "conducted in the department of epidemiology and public health at University College London, UK", the risk of developing cardiovascular disease in adult men belonging to the upper class, fed butter and saturated fats by sedentary with lipid profiles in the upper limits were higher compared to individuals belonging to low socioeconomic class with normal lipid profiles without hypertension in South Asia (Liberopoulos EN *et al*., 2005).

Objectives

The objective of the study was to treat the patients suffering from hypercholesterolemia with herbal medicine. So a new alternative treatment will be available to the patients in terms of good efficacy of drugs, lesser side effects, cost effectiveness and easy availability.

Methodology

It was prospective randomized clinical case control study conducted on patients at the OPD of "Sohail Memorial Hospital", Karachi and "Amir Habib Medical Center and Maternity Home", Karachi for the comparison of efficacy of herbal coded test drug "BIOCOR PLUS" with the control drug "Simvastatin". All patients gave verbal or written, informed consent for their participation, and the protocol was approved by the appropriate Independent Ethics Committee of Faculty of Eastern Medicine.

The test group

Test group n=35 was developed following inclusion criteria and were treated with Biocor Plus tablet 600mg twice daily for 12 weeks following two week follow up visits for lipid profile.

The control group

Similarly control group n=35 was developed following inclusion criteria and were treated with Simvastatin 20mg once daily for 16 weeks following monthly follow ups for lipid profile and liver function tests.

Follow up visits

After administration of test and control drug the lipid profiles of the cases were tested after 2, 4, 8 and 12 weeks and analyzed through T-test using SPSS version 18.0.

Method of preparation of dosage form

The herbal dosage form was designed as follows:

Selection of herbal drugs for hypercholesterolemia

The herbal drugs were selected for hypercholesterolemia after thorough Qarabadini and published literature from electronic journals. These herbs show ethno botanical and scientific evidences for the treatment of hypercholesterolemia. Five herbs i.e. *Bombyx mori, Commiphora mukul, Trigonella foenum-graecum, Origanum vulgare and Rauwolfia serpentina* were selected and used to formulate the dosage which was in film coated tablet form.

Collection and identification of herbs

The selected herbs for hypercholesterolemia were purchased from the local market at Joria Bazaar except *Commiphora mukul,* which was imported from India. Organoleptic evaluations and certain Physical and chemical test for the validations of herbal medicines were carried out in the Pharmacognosy lab of Faculty of Eastern Medicine under the supervision of Prof. Dr. Usmanghani Khan and also Research & Development laboratory / Quality Control Laboratory of Herbion Pakistan (Pvt.) Limited.

Preparation of the formulation

Batch Size: 06 Kg
No. Units: 10,000.0 tablets /111Bottles (90 tablets/ Bottle)
Weight of Each Tablet: 600 mg

Quantity of drugs

Bombyx mori (Abresham)	=	10.0Kg Raw Herb	= 1 Kg Spray Dried Powdered Extract
Commiphora mukul (Guggle)	=	10.0Kg Gum	= 1 Kg Spray Dried Powdered Extract
Trigonella foenum-graecum (Methi)	=	10.0Kg Raw Herb	= 1 Kg Spray Dried Powdered Extract
Origanum vulgare (Aamla)	=	10.0Kg Raw Herb	= 1 Kg Spray Dried Powdered Extract
Rauwolfia serpentina (Chandan)	=	10.0Kg Raw Herb	= 1 Kg Spray Dried Powdered Extract
Excipients:	=	10.0Kg	

RESULTS

All selected cases were thoroughly examined and clinical history was recorded in the clinical trial proforma. The therapeutic evaluation of the drug was made on the basis of improvement in the lipid profiles, i.e. reduction in total cholesterol, triglycerides, LDL-cholesterol and increase in HDL-cholesterol levels at periodic intervals of 4 weeks during 12 week of the course of study. The data of 70 cases was collected in the years from 1st July 2012 to 31st January 2013, which completed the clinical trial protocol. Out of 35 cases 20 were males and 15 were females in the test group and 18 were males and 17 were females in the control group. The mean age of 20 males in test group was 47.06±9.09 years and of 15 males in control group were 46.62±9.73 years while the age of 20 females in test group was 50.95±9.81 years and of 23 females in control group was 48.17±10.69 years. The mean age of 35 patients (both males and females) in test group was 48.62±9.48 and the mean age of 35 patients (both males and females) in control group was 47.34±10.11 and the distribution of patients was classified in different class interval ranging as shown in table 2.

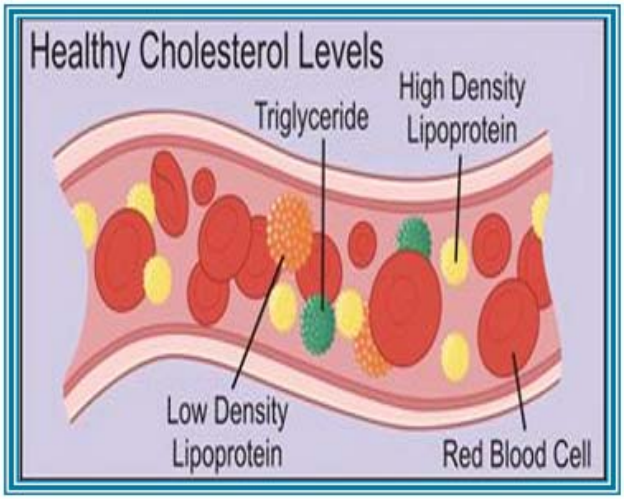

Fig. 1: Healthy cholesterol levels

After exclusion of drop-outs (changes in according to exclusion/inclusion criteria), the sample population comprised 70 people who had fulfilled the criteria at baseline or at follow up. The patient's gender, age, and baseline clinical features at the time of enrolment were recorded in both treatment arms. So overall, 35 patients were assigned to 50% for herbal coded formulation test drug (Biocor Plus) and 50% for control drug (Simvastatin). A monthly record of lipid profile and liver function tests was maintained for analyzing the improvement in hypercholesterolemia and any changes in the liver function tests.

The test drug was administered to 35 cases whose mean cholesterol level was 246.571±53.036 mg% at the base line and control drug was administered to 35 cases whose mean cholesterol level was 286.0571±74.915mg%. After 12 weeks drug administration total cholesterol levels were reduced to 176.71±23.544mg % from the base line in test group and 194.3143±55.176mg% in control group as shown in table 3-5.

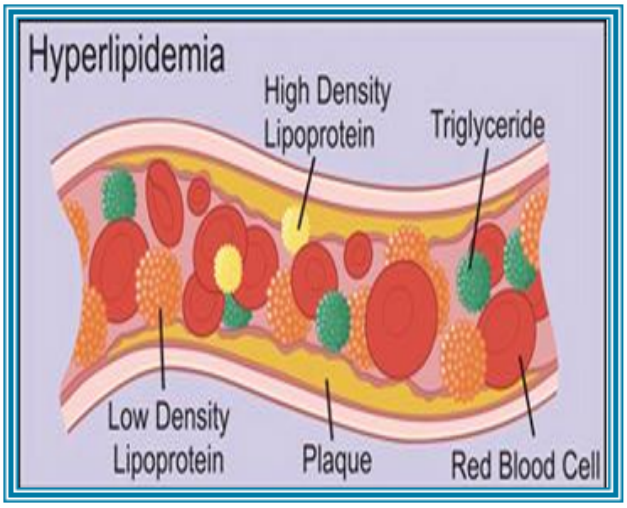

Fig. 2: Hypercholesterolemia

Effect on triglycerides levels

The test drug was administered to 35 cases whose mean triglycerides level was 177.8857±69.852mg% at the base line and control drug was administered to 35 cases whose mean triglycerides level was 183.828±72.362mg%. After 12 week drug administration total triglycerides levels were reduced to 130.4±48.067mg % from the base line in test group and 148.0857±54.667mg% in control group.

Table 1: ATP III Classification of LDL, Total and HDL Cholesterol (mg/dL)

LDL cholesterol-primary target of therapy	
<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
≥190	Very high
Total cholesterol	
<200	Desirable
200-239	Borderline high
≥240	High
HDL cholesterol	
<40	Low
≥60	High
Serum triglycerides (mg/dl)	
<150	Normal
150-199	Borderline high
200-499	High
≥500	Very high

Effect on HDL-cholesterol levels

The test drug was administered to 35 cases whose mean HDL-Cholesterol level was 31.5429±9.24612mg% at the

Table 2: Distribution of Age Group in Total Patients

Age Group	Treatment Group		Total (n)
	Test (n)	Control (n)	
30-35 Years	1	2	3
36-40 Years	3	2	5
41-45 Years	6	5	11
46-50 Years	6	8	14
51-55 years	8	9	17
56-60 years	4	3	7
61-65 years	5	5	10
66-70	2	1	3
Total	35	35	70

Table 3: Mean Total Cholesterol before and after Treatment

Statistics					
		Total Cholesterol Before Treatment in Test Group.	Total Cholesterol After Treatment in Test Group	Total Cholesterol Before Treatment in Control Group	Total Cholesterol After Treatment in Control Group
N	Valid	35	35	35	35
	Missing	0	0	0	0
Mean		246.5714	176.71	286.0571	194.3143
Std. Deviation		53.03677	23.544	74.91522	55.17607
Minimum		200.00	140	190.00	110.00
Maximum		420.00	210	520.00	350.00

Table 4: Paired Samples Correlations

Paired Samples Correlations				
		N	Correlation	Sig.
Pair 1	Total Cholesterol Before Treatment in Test Group. & Total Cholesterol After Treatment in Test Group	35	.441	.008
Pair 2	Total Cholesterol Before Treatment in Control Group & Total Cholesterol After Treatment in Control Group	35	.643	.000

Table 5: Paired Samples Test

Paired samples test									
		Paired differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence interval of the difference				
					Lower	Upper			
Pair 1	Total cholesterol before Treatment in Test Group Total cholesterol after Treatment in test group	69.85714	47.61188	8.04788	53.50189	86.21239	8.680	34	.000
Pair 2	Total cholesterol before Treatment in control group- Total cholesterol after Treatment in control group	91.74286	57.78935	9.76818	7189152	111.59419	9.392	34	.000

base line and control drug was administered to 35 cases whose mean HDL-cholesterol level was 29.8000 ±8.92056mg%. After 12week drug administration HDL-Cholesterol levels were increased to 35.2286±7.13766mg % from the base line in test group and 27.8571 ±8.02255mg% in control group.

LDL-Cholesterol levels

The test drug was administered to 35 cases whose mean LDL-Cholesterol level was 193.2±20.0818mg% at the base line and control drug was administered to 35 cases whose mean cholesterol level was 207.6±18.49197mg%. After 12 week drug administration LDL-Cholesterol

levels were reduced to 134.257±21.108 mg % from the base line in test group and 156.3143±32.05mg% in control group and the data was significant i.e $p<0.005$.

Adverse effects profile

All patients enrolled in the study were evaluable for safety. Side effects were defined as sign and symptoms that fist occurred or become more severe during the course of treatment. The majority of adverse events were assessed as mild in severity and self limiting in nature.

Three patients treated with the test drug experienced the dryness of mouth, bloating of abdomen and mild sweating which disappeared within two to three days and continued the treatment while one patient had discrepancy in eating habits due to traveling out of the city and taken fatty food in official dinners. His plasma lipid levels shoot out for few days but later on he corrected his diet. While two patients in the control group reported lethargy and mild pain in legs but not consistent. They all continued the control drug. Therefore, none of the patients withdrew from the study due to these adverse events in test and control group. No significant adverse effects were recorded in any group.

DISCUSSION

Researchers from all over the world have been focusing their interest toward the natural sources to explore medicinal plants that have hypolipidaemic activity with minimum or no side effects (Mashour *et al*., 1998). It is due reason that all commercial available lipid lowering medicines have therapeutics value but have associated with the side effects (Ghatak and Asthana, 1995). Out of these the *Rauwolfia serpentina* has significant role in this respect and have shown adequately proved that it does have a significant effect in this direction. The coded herbal formulation plants in literature search have shown their efficacy for the management of hyper-cholesterolemia. In this study, a significant decrease in TG levels was observed in patients treated with the coded formulation (Biocor Plus) upon use for three months as already cited in literature. Biocor Plus. This activity may be due to activation of lipase enzyme that can hydrolyzes the TG under normal condition (Sharma *et al*., 1997) or another interpretation can be put forth that this may be due to the excretion of TG through feces (Sukla *et al*., 2004). In addition to this cholesterol level decrease may be due to lessen endogenous cholesterol re-absorption or elevated secretion into the gastro-intestinal tract or both (Bahramika and Yazdanparast, 2008). As already reported in literature that the root of *Rauwolfia serpentina* may become an excellent option for treating the atherosclerosis, which results in decrease in the serum level of LDL-C. in addition overall performance of coded formulation Biocor Plus containing *Bombyx mori cocoons, Commiphora mukul, Trigonella foenum-grecum and Origanum vulgare* have shown good promise to directly acting on lowering the lipid profile of hypercholesterolemia and indirectly assisting as subsidiary material to circumvent the sign and symptoms, ultimately in unison like fashion where in the chemical compounds altogether bring about synergistic effect to reduces the malaise.

CONCLUSION

The finding from this study demonstrated the following clinical assessment showing statistically significant difference when comparing the effectiveness of test drug, Biocor Plus with control drug, Simvastatin for the treatment of primary hypercholesterolemia. This is clearly evident that the herbal coded test drug, Biocor Plus possesses a therapeutic value for the treatment of primary hypercholesterolemia.

There were no untoward or significant side effects associated with the use of Biocor Plus that proved its good acceptability by the patients. Moreover there was subjective feeling of wellbeing regarding breathlessness and chest tightness or pressure among the patients taking Biocor Plus. Further basic clinical studies on mega scale are needed to further confirm its efficacy and safety.

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