

Management of Familial Combined Hyperlipidemia Using both Guggul and Atrovastatin Drugs: Cardiovascular Benefits to Human Society

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Abstract: Aims and Objectives: To show the efficacy of guggul and combined effects of guggul and atrovastatin drugs on lipid profile in those people who are suffering from cardiovascular problems due to mixed hyperlipidemia. Methods: Data regarding lipid profile from 45 familial combined hyperlipidemic people (age ≥ 30 yrs) of Kalyani township area of the District Nadia, West Bengal, India, who use guggul or both guggul and atrovastatin drugs (prescribed by their physician) regularly for their cardiovascular problems. Data were analyzed using z-statistics at both 5% and 1% level of significance. Results: Long term use of guggul effectively lowers only serum triglycerides with elevated total-cholesterol, low density lipoprotein cholesterol and very low density lipoprotein cholesterol, but after combined therapy of guggul and atrovastatin shows very good beneficial effects on serum lipid profile level. Conclusion: The regular use of both guggul and atrovastatin drugs may be an effective hyperlipidemic measure in FCH people to protect from their future cardiovascular disorders.

Keywords: Atrovastatin, Cardiovascular disease, Familial combined hyperlipidemia, Guggul, Hyperlipidemia, Hypolipidemia, and Lipid profile.

I. INTRODUCTION

Familial combined hyperlipidemia (FCH) was first described as a new autosomal inherited lipid disorder in 1973 (1). FCH is suggested by the presence of a mixed hyperlipidemia with fasting triglyceride levels of 200-800 mg/dl, cholesterol levels of 200-400mg/dl, and decreased HDL-C levels in the absence of secondary cause of hyperlipidemia. Patients with FCH should be treated aggressively with lifestyle management and drug therapy. Statin, fibrate, niacin and cholesterol absorption inhibitors are all used, often in different combinations, to achieve adequate control of the lipids (2).

Oleo-gum-resin (known as guggul) from the guggul tree, *Commiphora mukul* or *Commiphora wightii*, found in India, Bangladesh and Pakistan, has been used to treat various diseases including hypercholesterolemia, atherosclerosis, rheumatism and obesity is described in Ayurveda, the ancient Indian medical system (3). Guggul was first introduced to the scientific world in 1966 by an Indian medical researcher GV Satyavati (4). In 1986, with proven efficacy and safety, guggul was approved for marketing in India as a hypolipidemic drug (5, 6). Guggul was introduced into the Western medical literature in the middle 1990s (7) and soon thereafter, the interest in using guggul to prevent hypercholesterolemia and cardiovascular diseases were widely spread in United states and other western countries. Guggulsterone, the bioactive constituent of guggul, has been identified as an antagonist at the nuclear receptor (farnesoid x receptor or FXR) (8, 9), a key transcriptional regulator for the maintenance of cholesterol and bile acid homeostasis (10, 11). A current study demonstrated that guggulsterone upregulates the expression of the bile salt export pump (BSEP), a rate-limiting efflux

transporter for eliminating cholesterol metabolites bile acids from the liver. Such upregulation is possibly mediated through the activating protein 1 (AP-1) signaling pathway (12).

As it is already strongly proved that dyslipidemia exerts harmful effects on cardiovascular system, here we have tried to found out the beneficiary effects of guggul or both guggul and atrovastatin drugs on regulating serum lipid profile levels as well as cardiovascular problems in FCH people. In this study it is found that the combined therapy of guggul and atrovastatin drugs will save FCH people from their future cardiovascular problems.

II. MATERIALS AND METHODS

Study subjects and data collection:

The clinical trials about the efficacy of guggul and combined role of guggul and atrovastatin (prescribed by their physician) on lipid profile of 45 familial combined hyperlipidemic (FCH) patients with cardiovascular diseases were studied by the author (Dr. M. Biswas) himself, in different clinical and hospital areas of the town Kalyani, District - Nadia, West Bengal, India. After long term (at least three months) use of guggul or both guggul and atrovastatin drugs for cardiovascular problems the patients were subjected to take data regarding lipid profile. Guggul extract was taken from the Himalaya Drug Company, Rajajinagar, Bangalore, India. Their product name is Shuddha guggulu produced from Indian bdellium tree (*Commiphora wightii*) that contains 250mg guggul extract per capsule. Blood samples were taken after subjects had fasted for 10-12 hours. Fasting blood samples collected from each individual during the survey were processed, refrigerated immediately and transported in cold storage to the laboratory and analyzed within 24 hours for fasting glucose, lipid profile and other biochemical parameters of interest using Prietest Easy Lab Semi-automated Biochemistry Analyzer, Robonik India Pvt. Ltd., Mumbai, India. The Friedewald (13) formula: $LDL-C = \frac{TC - HDL - Tg}{5}$ mg/dl, was used to calculate LDL-C for subjects with serum triglyceride (Tg) level ≤ 400 mg/dl and calculated using modified Friedewald (14) formula: $LDL-C = Non-HDL \times 90\% - Tg \times 10\%$, for subjects with serum Tg ≥ 400 mg/dl. VLDL-C is measured using equation: $VLDL-C = Tg/5$.

Statistical analysis:

All values were presented in the form of Mean \pm SEM. Data were analyzed statistically using SPSS 12.0 software for windows. Data were analyzed using z-statistics at both 5% and 1% levels of significance.

III. RESULTS

After long term (at least 3 months) use, the efficacy the drugs, guggul or both guggul and atrovastatin on lipid profile of FCH people were presented in the Table No.-1, Fig. No.-1 and Table No.-2.

Role of guggul and statin on serum total-cholesterol (T-C) level:

After long time use of 500mg and 1000mg guggul extract per day, it is found that serum total cholesterol is increased by 17.96% and 14.51% in FCH patients and this increment is statistically significant ($p < 0.01$). But combined therapy of guggul and atrovastatin shows significant ($p < 0.01$) reduction in serum cholesterol level in FCH people and it is decreased by 23.35% and 54.45% in guggul plus 5mg statin group and guggul plus 10 mg statin group respectively.

Role of guggul and statin on serum triglyceride (Tg) level:

Reduction of serum triglyceride level is found in all groups and it is reduced by 4.09%, 36.57%, 49.20% and 53.86% in 500mg guggul, 1000mg guggul, 1000mg guggul plus 5mg statin and 1000mg guggul plus 10mg statin groups respectively. It is significantly ($p < 0.01$) decreased in all three groups except 500mg guggul groups of FCH people.

Role of guggul and statin on serum high density lipoprotein (HDL-C) level:

Reduction of serum HDL-C level is found in all three groups except 1000mg guggul group and it is reduced by 2.31%, 2.83% and 3.87% in 500mg guggul, 1000mg guggul plus 5mg statin and 1000mg guggul plus 10mg statin groups respectively. It is significantly ($p < 0.01$) decreased in all three groups except 1000mg guggul groups of FCH people. No significant change is found in 1000mg guggul group.

Role of guggul and statin on serum low density lipoprotein (LDL-C) level:

After regular use of 500mg and 1000mg guggul per day, it is observed that serum LDL-C is increased by 3.67% and 2.11% in FCH patients and this increment is statistically significant ($p < 0.01$). But combined therapy of guggul and atorvastatin shows significant ($p < 0.01$) reduction in serum LDL-C level in FCH people and it is decreased by 2.96% and 8.48% in guggul plus 5mg statin group and guggul plus 10 mg statin group respectively.

Role of guggul and statin on serum very low density lipoprotein (VLDL-C) level:

After daily intake of 500mg and 1000mg guggul extract for 90days, it is found that serum VLDL-C is increased by 2.00% and 1.23% in FCH patients and this increment is statistically significant ($p < 0.01$ in case of 500mg guggul group and $p < 0.05$ in case of 1000mg guggul group). But combined therapy of guggul and atorvastatin shows significant ($p < 0.01$) reduction in serum VLDL-C level in FCH people and it is decreased by 0.95% and 1.83% in guggul plus 5mg statin group and guggul plus 10 mg statin group respectively.

Table-1: Effects of regular use (atleast 3 months) of guggul and statin drugs on serum lipid profile of familial combined hyperlipidemic people

Lipid profile Drugs / day	T-C Avg±SEM	Tg Avg±SEM	HDL-C Avg±SEM	LDL-C Avg±SEM	VLDL-C Avg±SEM
Before drugs	209.03±4.04	542.45±15.85	49.02±2.17	99.89±3.85	61.45±3.01
500mg guggul	246.58±6.45**	520.26±14.04	37.67±1.68**	136.60±4.00**	73.77±4.55**
1.0g guggul	239.37±7.28**	344.08±10.25**	49.44±2.03#	121.00±3.54**	69.04±3.25*
1.0g guggul + 5mg statin	160.22±2.58**	275.56±8.59**	35.13±1.11**	70.32±1.35**	55.56±2.92**
1.0g guggul + 10mg statin	95.17±2.02**	250.28±8.05**	30.04±0.95**	15.15±0.75**	50.19±1.48**

*= Significant at 5% ($p < 0.01$) level and **= Significant at 1% ($p < 0.01$) level.

Table-2: Changes of lipid profile in percent due to regular use (atleast 3 months) of guggul and statin in familial combined hyperlipidemic people

Lipid profile Drugs / day	T-C Avg	%	Tg Avg	%	HDL-C Avg	%	LDL-C Avg	%	VLDL-C Avg	%
Before drugs	209.03	-	542.45	-	49.02	-	99.89	-	61.45	-
500mg guggul	246.58	↑17.96	520.26	↓4.09	37.67	↓2.31	136.60	↑3.67	73.77	↑2.00
1.0g guggul	239.37	↑14.51	344.08	↓36.57	49.44	↑0.08	121.00	↑2.11	69.04	↑1.23
1.0g guggul + 5mg statin	160.22	↓23.35	275.56	↓49.20	35.13	↓2.83	70.32	↓2.96	55.56	↓0.95
1.0g guggul + 10mg statin	95.17	↓54.47	250.28	↓53.86	30.04	↓3.87	15.15	↓8.48	50.19	↓1.83

↑=Increase in % of lipid profile after drugs therapy; ↓= Decrease in % of lipid profile after drugs therapy

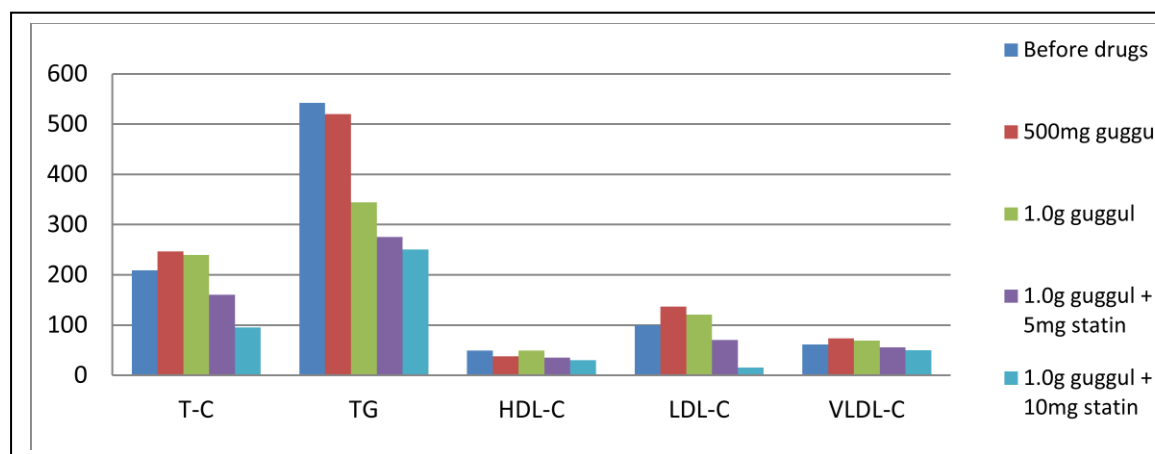


Fig. 1: Changes of lipid profile in average due to regular use (atleast 3 months) of guggul and statin in familial combined hyperlipidemic people

IV. DISCUSSION

From this study it is observed long time use of 500mg and 1000mg of guggul significantly increases the level of cholesterol (17.96% and 14.51% in case of 500mg guggul and 1000mg guggul groups respectively) but significantly decreases the level of serum triglyceride (4.09% and 36.57% in case of 1000mg guggul plus 5mg statin and 1000mg guggul plus 10mg statin groups respectively) level. But all five parameters of lipid profile like cholesterol (23.35% and 54.47%) and triglyceride (49.20% and 53.86%), LDL, HDL and VLDL can be regulated by using guggul plus statin in CFH people. Here guggul and statin act as a triglyceride and cholesterol regulator respectively in FCH people. Both guggul and statin therapy in FCH people is very much effective for the regulation of all parameters of lipid profile and thus it can be used to prevent cardiovascular disease.

A number of clinical trials have been conducted to evaluate the hypolipidemic effect of guggulipid. Maximum number of studies was carried out mainly in India and one in the United States. Although the US study was failed to detect the hypolipidemic effect of guggulipid. Besides previous studies, most of these clinical studies were reviewed very recent by some other researchers (8-12, 15, 16).

Multicentric clinical trials of the efficacy of guggulipid conducted at Bombay, Bangalore, Delhi, Jaipur, Lucknow, Nagpur and Varanasi have been reported by Nityananda and others. Two hundred and five (205) patients completed 12 weeks open trial with guggulipid in a dose of 500mg tds after 8 weeks diet and placebo therapy. One patients showed gastrointestinal symptoms which did not necessitate withdrawal of the drug. A significant lowering of serum cholesterol (average 23.6%) and serum triglyceride (average 22.6%) was observed in 70-80% patients (17).

A randomized controlled double-blind trial revealed that gum guggul at 2g twice daily or fraction "A" extract at 500mg three times daily for 21 days significantly reduced the serum lipid levels in hyperlipidemic non-obese patients. These beneficial effects of guggul were not found in hyperlipidemic obese subjects. This study exhibited that guggul therapy was obesity dependent (16, 18, 19).

Gugulipid is a mixture of serones obtained from 'gum guggul' which has been used in Ayurveda. Modest lowering of plasma cholesterol and triglycerides occurs after continued use of gugulipid. It is well tolerated: loose stool are the only significant side effect. Atrovastatin (a latest statin) is more potent and appears to have the highest LDL-C lowering efficacy at maximal daily dose of 80mg. At this dose a greater reduction in TGs is noted if the same was raised at baseline. All statins are remarkably well tolerated; overall incidence of side effects not differing from placebo (20).

In contrast to the results of previous clinical trials in India, the first clinical trial conducted in the population of United States draws a different conclusion about the efficacy of gugulipid on serum lipid level. In this randomized controlled trial, 103 patients with hypercholesterolemia were enrolled and assigned to three groups: the placebo and two treatment groups (low and high doses). Treatment of gugulipid at doses of 1000mg or 2000mg three times daily for 8 weeks resulted in an increase in LDL levels by 4% and 5%, respectively, whereas patients who received placebo exhibited a 5% decrease in LDL level. There were also no significant changes in levels of total serum cholesterol, HDL, VLDL and triglyceride following the treatment. Further analysis within the groups revealed that 18% of patients in treatment groups responded favorably to gugulipid treatment, with a more than 5% decrease in LDL. However, such response rate (18%) is much smaller than the 70-80% response rate observed in most of the previous studies. For the subjects (45 participants) with high baseline levels of LDL (160mg/dl or greater), gugulipid treatment significantly reduced serum triglyceride (14% and 10% decreases for high and low dose groups respectively), whereas triglyceride levels increased by 10% in subjects receiving placebo. The results from this study indeed raised a question regarding hypolipidemic effects of gugulipid (15, 16).

Our study had certain limitations. Subjects were chosen from a single locality, so we got small number of samples for this study and thus it may not be representative of affluent subjects throughout India. However, we took care to take data from studied subjects during field study, so that we can minimize sampling error.

V. CONCLUSION

As familial combined hyperlipidemia (FCH) is a mixed type of hyperlipidemia, it may or may not be regulated by using guggul or statin only. From this study it can be concluded that FCH is well regulated using both guggul and statin drugs. Here guggul acts as a triglyceride regulator and statin as a cholesterol regulator in FCH people. So, combined therapy of guggul and statin in FCH people will keep the patients safe from future cardiovascular diseases.

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