EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 4
Issue: 10
789-793
Year: 2017

GUGULIPIDS, A NOVEL THERAPY FOR DYSLIPIDEMIA: COMPARATIVE ANALYSIS TO STANDARD REGIMEN

Kriti Malhotra[1], P. K. Agarwal*[2] and Sonam Bhatia[3]

[1]Assistant Professor, Pharmacology, GSVM Medical College, Kanpur.
[2]Professor, Pharmacology, Varun Arjun Medical College & Rohelkhand Hospital, Shahjahanpur.
[3]Assistant Professor, Biochemistry, ESI College, Faridabad.

***Corresponding Author: P. K. Agarwal**
Professor, Pharmacology, Varun Arjun Medical College & Rohelkhand Hospital, Shahjahanpur.

Article Received on 15/08/2017 **Article Revised on 04/09/2017** **Article Accepted on 25/09/2017**

ABSTRACT
Raised levels of lipids especially LDL-C are documented risk factors for cardiovascular disorders. Use of hypolipidemic drugs mainly Statins are mainstay in the treatment of dyslipidemias. Herbal drug Gugulipid carries hypolipidemic properties which in combination to Rosuvastatin may prove beneficial to such patients. Sixty patients with dyslipidemia were randomly allocated into Group I and II. Group I patients were administered Rosuvastatin 10 mg OD and Gugulipid 250 mg TDS with meals whereas Group II was administered Rosuvastatin 10 mg alone for six weeks. Baseline lipid levels were recorded and were compared to lipid levels at the end of six weeks. Primary end point was percent change in the lipid parameters of both the treatment groups. Our study concluded that the percent change at six weeks in the various parameters in Group I was superior to that in Group II patients. Also the combination demonstrated a substantial percent increase in the HDL-C levels as compared to the other study group. Both regimes were safe and well tolerated by all patients.

KEYWORDS: CVD, Rosuvastatin, Gugulipid, Lipid profile.

INTRODUCTION
Hyperlipidemias or dyslipidemias are defined as raised lipid levels which are well documented risk factor for Cardiovascular Disease (CVD). CVD has a multi-factorial etiology and is the most common contributor of morbidity and mortality in both developed and under-developed countries worldwide. It has been estimated that 78% of all deaths and 86.3% of all loss of disability adjusted life years are attributable to this cause.[1] Hyperlipidemia is one of the modifiable risk factor among other factors which plays a pivotal role in primary or secondary prevention of CVD. It is an established fact that high LDL-C concentrations attribute directly to the cardiovascular disease risk and are main target of therapy now. But the coronary disease risk assessment only on the levels of LDL is not judicious. There is a recent shift in the emphasis from only LDL-C assessment to atherogenic indices or lipoprotein ratios.

Nowadays, HMG-CoA reductase inhibitors or Statins are the most efficacious and standard therapy for dyslipidemias. They are not only hypolipidemic agents but also exert a number of *pleiotropic effects.*[2] Rosuvastatin, which is clinicians' favourite presently, has shown to lower TC, LDL-C and TG and increase HDL-C levels at various doses (10-40 mg).[3]

India is well known globally to have introduced Ayurvedic Medicine (use of plants) as a well accepted branch of science which is used to treat various ailments since time immemorial. One of the ayurvedic or herbal medicine which was recognised long ago for its beneficial effects is the resin of the tree, Commiphora mukul commonly known as Gugulipid. It is use in the treatment of many medical conditions including obesity, arthritis and disorders of lipid metabolism have been described in Sushrita Samhita in 600 BC.[4] It is also traditionally used for the treatment of liver problems, tumors, ulcers and sores, urinary complaints, intestinal worms, swelling, and seizures, and even as a heart tonic.[5,6] Studies in both animal models and humans have shown that Gugulipid also termed gum guggul, can decrease elevated lipid levels. The active agents in the oleo-resin of the plant extract have been identified as stereoisomers namely E- and Z-guggulsterones. Recent studies have shown that these compounds are antagonist ligands for the bile acid receptor, farnesoid X receptor (FXR), which is an important regulator of cholesterol homeostasis. Presumably the hypolipidemic effect exerted by the phytosteroids of the resin is due to this regulatory mechanism.[7] Guggul sterones appear to be fat-soluble, and the fat soluble portion is patented as Guggulipid. The standard dose of gugulipid (plant extract) is 400-500mg thrice daily[8] (or 50 mg/kg dose

/day) with meals for its hypolipidemic effects. There are evidences from some previous studies, that at this dose, many subjects under trials for its lipid lowering effect had experienced moderate to severe skin related allergic reactions, flu like syndrome or even hypersensitivity as an adverse reaction.[9] Taking into view the same, we chose Guglipid to be given at a dose of 250 mg thrice daily with meals (available as Health Vit Guggul 250 mg tablets).

Considering the above mentioned facts, Rosuvastatin and Gugulipid may prove a novel combination as hypolipidemic agents which may better the lipidogram of the patients translating into improved clinical outcomes. So, to establish the safety and effectiveness of the combination as potent hypolipidemic agents, we designed a research study where we compared the efficacy and safety of Rosuvastatin and Gugulipid in combination with Rosuvastatin alone in dyslipidemic patients. The primary end point of our study was the percent change in the lipid levels of the patients after six weeks of pharmacotherapy in both the drug regimes.

AIM OF THE STUDY

The aim of the present study was to evaluate and compare the percent change in lipidogram with Rosuvastatin and Gugulipid used in combination to Rosuvastatin used alone in dyslipidemic patients.

MATERIAL AND METHODS

The present study was a randomized six - week, prospective, parallel group, open study conducted on sixty patients with dyslipidemia .Patients of both sexes between the ages of 18-80 years who presented in the Medicine OPD of Rama Medical College Kanpur were considered .The study design was approved by the Institutional Ethics Committee and written informed consent was obtained by each patient prior to the commencement of the trial. Patients with deranged lipid levels (any one or more) with Total cholesterol > 200mg/dL, HDL-C < 40mg/dL for men & < 50mg/dL for women, LDL > 100mg/dL and TGs > 150mg/dL and who have undergone a wash out period of four weeks after statin therapy were included in our study. Patients with history of allergy to statins or any other drug, alcohol intake, pregnant and lactating females, history of asthma or chronic obstructive pulmonary disease, unexplained increase in creatine kinase to >3 times, Serum creatinine > 2.5mg/dL and Alanine amino transferase (ALT) or aspartate amino-transferase (AST) values >3 times the upper limit of normal were excluded from our study.

Baseline (at 0 weeks) lipid levels were recorded and documented for every patient .Sixty patients fulfilling the inclusion criteria were randomly and equally divided into study groups. Group I patients were administered Rosuvastatin 10 mg OD in the morning and Gugulipid 250 mg TDS (available under brand-name Health Vit Guggul 250mg) after meals with luke warm water for six weeks. In Group II, the patients were administered Rosuvastatin 10 mg OD in the morning, alone, for six weeks. At the same time, enrolled patients were educated and instructed to take a low fat diet along with a 30 minutes moderate walk every day. They were followed up at three weeks for compliance of the therapy, diet and exercise. Any adverse effect experienced was asked to be reported promptly during the pharmacotherapy. Drop outs were not included because it was an intention to treat trial. At 6 weeks, lipid profile was repeated, recorded and the results were compared from the baseline (at week 0). Safety and tolerability were evaluated throughout the study on the basis of adverse events reporting.

RESULTS

The present study was conducted on sixty patients with dyslipidemia who were ramdomly divided into Group I (Rosuvastatin and Gugulipid therapy) and Group II (Rosuvastatin therapy alone). The lipid parameters for all patients were recorded and compared from baseline to the end of six weeks for both treatment groups. Continuous variables were expressed as Mean ± SD and categorical variables were expressed as percentage. For comparison between pre- and post treatments, the Student's paired't' test was used. Difference between groups or independent variables was compared by an unpaired t test for normally distributed variables. The level of significance was determined by probability value (p value). The baseline demographic pattern showed no statistical difference between the treatment groups. The mean of the lipid parameters were comparable at baseline for both Group I and Group II. The levels of TC, HDL-C, TG and LDL-C showed significant improvement at the end of six weeks.

Table 1: Comparison of Lipid Parameters of Group I and Group II at Baseline and at six weeks.

LipidParameter (in mg %)		Group I			Group II			T – Test
		Mean	SD	p-values	Mean	SD	p-values	
TC	At Baseline	273.12	56.58	<0.0001	241.71	61.86	<0.0001	0.045
	At 6th Week	178.85	52.87		184.89	39.92		0.619
HDL	At Baseline	37.65	7.94	<0.0001	43.73	14.07	0.58	0.044
	At 6th Week	48.49	8.67		45.66	14.51		0.363
TG	At Baseline	232.77	45.09	<0.0001	224.12	53.26	<0.0001	0.499
	At 6th Week	156.21	37.40		163.43	48.78		0.523
LDL	At Baseline	183.88	49.15	<0.0001	187.16	44.66	<0.0001	0.788
	At 6th Week	116.19	29.27		122.05	32.32		0.465

The TC concentrations were significantly reduced in both study groups (34.52% in Group I and 23.51% in Group II) ($p < 0.0001$). While the HDL-C values were significantly increased in Group I by 28.79% ($p < 0.0001$). There was no significant increase recorded for HDL-C levels in Group II at six weeks. (04.41% increase, p=0.58) (Tables 1 & 2). The average LDL–C levels of the patients of Group I showed a significant decrease of 36.81% from baseline levels of 183.88 ± 49.15 to 116.19 ± 29.27 by six weeks ($p < 0.0001$). While in Group II it was reduced from 187.16 ± 44.66 to 122.05 ± 32.32 with significant percent change of 34.79%. ($p < 0.0001$). Similarly, the TG concentrations were also significantly reduced by 32.89 % and 27.08% by sixth week in Group I and Group II patients respectively ($p < 0.0001$) (Table 1 & 2; Figure 1).

Table 2: Comparison of percent change of Lipid parameters from Baseline to six weeks for Group I and Group II.

Lipid Parameters (in mg%)		Group I	Group II	% Difference
TC	At Baseline	273.12	241.71	-11.50
	At 6th Week	178.85	184.89	3.38
	% change	-34.52	-23.51	
HDL	At Baseline	37.65	43.73	16.15
	At 6th Week	48.49	45.66	-5.84
	% change	28.79	4.41	
TG	At Baseline	232.77	224.12	-3.72
	At 6th Week	156.21	163.43	4.62
	% change	-32.89	-27.08	
LDL	At Baseline	183.88	187.16	1.78
	At 6th Week	116.19	122.05	5.04
	% change	-36.81	-34.79	

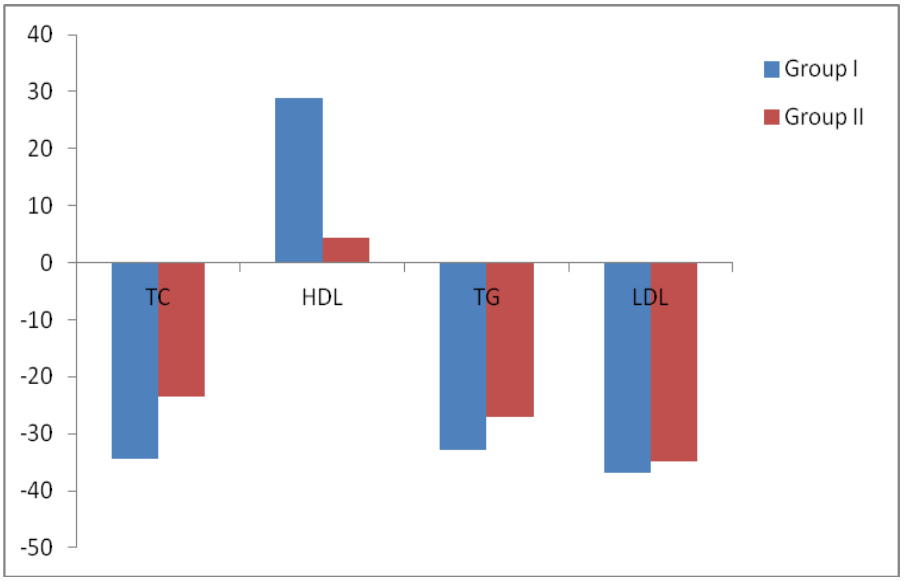

Figure 1:- Percent change of Lipid Parameters from baseline to six weeks for Group I and Group II.

DISCUSSION

LDL-C is a well documented risk factor for cardiovascular disease. Studies have shown to decrease the incidence of morbidity and mortality by lowering the LDL-C levels in at risk or high risk patients. There is a recent change in the perspective of the clinicians regarding to the exclusive evaluation of LDL-C as atherogenic in nature. The latest and current trend of risk assessment pivots around atherogenic indices or lipid ratios as primary or secondary preventions of CVD. In the present prospective, randomized, comparative, open label six weeks clinical trial we compared Rosuvastatin in combination with herbal drug Gugulipid to Rosuvastatin alone. We found that both the regimens were effective in improving the various parameters of atherogenic lipid profile.

On comparison of both the regimens amongst themselves to determine the superiority of one therapy regime over the other; we found that both the therapies affect the lipid characteristics of the patients but Rosuvastatin with Gugulipid (Group I) showed improved lipid profile

results than Rosuvastatin (Group II) used alone. The percent change in the various lipid concentrations from baseline of the latter was lower as compared to that of the combination (Table 1 & 2). Moreover the safety profiles of both the therapies appeared to be similar and none of the side effects in both groups necessitated discontinuation of the therapy.

Consequently our study demonstrates that the mean change in various lipid parameters and percent difference from baseline in Group I patients were statistically significant when compared to the percent change in Group II. It is worth noting that our results also illustrated the combined effect of the drugs in Group I patients were seen to improve the HDL-C levels to a considerable greater extent (percent increase by 28.79%) whereas the other group showed no appreciable change in the HDL-C levels (Table 1 &2; Fig 1).

A study carried out by Nityanand et al.[10] on 125 patients showed a significant lowering of serum cholesterol (av. 23.6%) and serum triglycerides (av. 22.6%) in 70-80% patients with gugulipid therapy. Further he documented that with gugulipid, the average fall in serum cholesterol and triglycerides was 11 and 16.8% respectively. Our observation in Group I in fact, showed a superior efficacy to the above study results in the lipid profile in TC and TG levels (34 and 32%). This may be because of the use of additional lipid lowering drug, Rosuvastatin 10 mg. On the contrary, the results of the study completed by Szapary et al.[11] demonstrated that with standard dose of Gugulipid (1000 mg TDS) LDL-C raised by 4% compared to placebo (p=0.01) but there were no significant changes in levels of total cholesterol, HDL-C, triglycerides response to treatment with guggulipid. These results are also consistent with the case reports submitted by Das et al.[12] In the same pipeline data submitted by Kelly M (13) in a double blind eight week study on hypercholesterolemic patients showed that placebo group had a 5% decrease in LDL cholesterol as compared with a 4% increase with 1000mg TDS of Gugulipid. CSIR-CDRI Symposium on Recent Advances in Pharmaceutical Sciences for Drug Discovery & Development issued a data in 2015 where they compared Gugulipid (500 mg TDS) with clofibrate (500 mg TDS) therapy. They reported that serum cholesterol levels declined by 12.6% with guggul and 14.7% with clofibrate, and mean triglyceride levels fell 16.4% and 23.2%, respectively. Statistical significance was not reported.[13]

The study outcomes of the aforementioned are asynchronous to our study observations where there was a stastistically significant percent change in the lipid profile of Group I patients who took Gugulipid. The significance in the percent change can be explained by the add-on effect of Rosuvastatin 10 mg along with Gugulipid intake. The integration proved to be clinically potent for improving the lipidogram of patients.

The beneficial effects of Gugulipid in hyperlipidemic patients are not clear due to fewer studies available. While some studies suggest a potential role of Gugulipid in lipid lowering, some research shows no benefit at all. In this light, our study demonstrated that a combined effect of Gugulipid and Rosuvastatin was beneficial than Gugulipid used alone. It was also confirmatory by our observations that Rosuvastatin alone could not yield results parallel to the combination drug therapy.

Li et al.[14] demonstrated that a daily dosing of Rosuvastatin decreased LDL-C by 37.5% with once-daily dosing for a period of six weeks ($p > 0.05$). In a similar study conducted by Marias et al.[15] also demonstrated a 19 % reduction of LDL-C with the use of Rouvastatin10 mg daily for six weeks. In another Indian study performed by Jayaram et al.[16] administration of Rosuvastatin 10mg daily for six weeks resulted in 41% mean reduction of LDL-C level as compared to the baseline. Trials by Teramoto et al.[17], Deedwania et al.[18] and Farnier et al.[19] reported a reduction of 42-52%, 45% and 16% reductions in LDL-C level by daily administration of Rosuvastatin.

A study done by Schuster[3] presented that in mild/moderate hypercholesterolemia, Rosuvastatin 10 mg reduced LDL cholesterol significantly. Similar study by Stalenhoef et al[20] showed the superiority of 10 mg Rosuvastatin compared to other statins in lowering the atherogenic LDL-C along with other lipid characteristics. Percent change at 12 weeks from baseline in Rosuvastatin 10 mg was significantly more beneficial than atorvastatin 10 mg and placebo in achieving LDL-C goals. The study results are supportive and parallel to our results in Group II.

The effects of pharmacotherapy in both the study groups were considered safe and were well tolerated. Out of the total enrolled patients only one experienced mild skin allergy which was self limiting in Group I. None from Group II reported any ADR with Rosuvastatin use alone. This reflects the safety of our study trial. When we compared the results of intergroup percent change in lipids from baseline, reductions achieved by Group I were found to be greater than Group II. Both the therapies were safe, effective and well-tolerated by all patients not necessitating discontinuation from the trial.

Despite our best efforts we had limitations in our study. First, the study was not blinded and was performed on a limited number of patients from a single centre. We focused on the short term outcome of the lipid profile of the patients and no follow up was conducted after the completion of the study. It would be prudent if a larger group of dyslipidemic patients who are at risk or high risk, undergo the study and are followed up routinely. This may translate into improved understanding and better clinical correlations and proves to be a beneficial tool for curtailing the CVD associated morbidities and mortalities as well as Daily adjusted life years.

REFERENCES

1. Ismail J, Jafar TH, Jafary FH, White F, Faruqui AM, Chaturvedi N. Risk factors for non-fatal myocardial infarction in young South Asian adults. Heart, 2004; 90: 259–63.
2. Papageorgiou N, Tousoulis D, Antoniades C, Giolis A, Briasoulis AR, Stefanadis C.The Impact of Statin Administration in Acute Coronary Syndromes. Hellenic J Cardiol, 2010; 51: 250-61.
3. Schuster H. Rosuvastatin--a highly effective new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor: review of clinical trial data at 10-40 mg doses in dyslipidemic patients. Cardiology, 2003; 99(3): 126-39.
4. Thomas P Bersof, Drug therapy of hypercholesteremia and hyperlipidemia in Goodman and Gilman's the pharmacological basis of therapeutics. 12th ed. Macgraw Hill USA, 877-908.
5. Guggul. Review of Natural Products. Facts & Comparisons.St. Louis, MO: Wolters Kluwer Health Inc; December 2011. Available from drugs.com.
6. Shah R , Gulati V, Palombo EA. Pharmacological properties of guggulsterones, the major active components of gum guggul Phytother Res, 2012 Nov; 26(11): 1594605.
7. Urizar NL[1], Moore DD GUGULIPID: a natural cholesterol-lowering agent. Annu Rev Nutr, 2003; 23: 303-13.
8. Available from : https://examine.com/supplements/guggul/
9. Nohr LA, Rasmussen LB, Straand J. "Resin From the Mukul Myrrh Tree, Guggul, Can It Be Used for Treating Hypercholesterolemia? a Randomized, Controlled Study. "Complementary Therapies in Medicine, 2009 Jan; 17(1): 16-22.
10. Nityanand S, Srivastava JS, Asthana OP. Clinical trials with gugulipid. A new hypolipidaemic agent. J Assoc Physicians India, 1989 May; 37(5): 323-8.
11. Szapary PO Guggulipid for the treatment of hypercholesterolemia: a randomized controlled trial. JAMA, 2003 Aug 13; 290(6): 76572.
12. Das Gupta R. Gugulipid: pro-lipaemic effect. J Assoc Physicians India, 1990; 38(12): 346.
13. Kelly M. Shields, Michael P. Guggul for Hypercholesterolemia American Journal of Health-System Pharmacy, 2005; 62(10): 1012-1014.
14. Li JJ, Yang P, Liu J, Jia YJ, Li ZC, Guo YL et al. Impact of 10 mg rosuvastatin daily or alternate-day on lipid profile and inflammatory markers.Clinica Chimica Acta, 2012 Jan 18; 413(1): 139–42.
15. Marais AD, Raal FJ, Stein EA, Rader DJ, Blasetto J,Palmer M, et al. A dose titration and comparative study of rosuvastatin and atorvastatin in patients with homozygous familial hypercholesterolaemia. Atherosclerosis, 2008; 197: 400-06.
16. Jayaram S, Lahoti S, Chandrasekharan S, Mishra AB, Jain MM, Anwaruddin K et al. Rosuvastain in Hypercholesterolemia: The First Indian Study. Ind J Clin Prac.2003 Dec; 14(7): 35-40.
17. Teramoto T, Watkins C. Review of efficacy of rosuvastatin 5 mg. Int J Clin Pract, 2005 Jan; 59(1): 92-01.
18. Deedwania PC, Gupta M, Stein M , Ycas J, Gold A. Comparison of Rosuvastatin versus Atorvastatin in South –Asian patients at risk of Coronary Heart Disease. Am J Cardiol, 2007 Jun 1; 9(11): 1538-43.
19. Farnier M, Averna M, Missault A , Vaverkova H, Viigimaa M, Massaad R, et al. Lipid-altering efficacy of ezetimibe⁄simvastatin 10⁄20 mg compared with rosuvastatin 10 mg in high-risk hypercholesterolaemic patients inadequately controlled with prior statin monotherapy – The IN-CROSS study. Int J Clin Pract, 2009 Apr; 63(4): 534–35.
20. Anton F.H. Stalenhoef et al. A COmparative study with rosuvastatin in subjects with METabolic Syndrome: results of the COMETS study. European Heart Journal, 2005; 26: 2664–2672.