Section: Pharmacology

Original Research Article

EVALUATION OF EFFECTIVENESS AND SAFETY OF A GUGGUL-BASED FORMULATION IN THE TREATMENT OF HYPERLIPIDEMIA IN COMPARISON TO ATORVASTATIN

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Received : 09/03/2024
Received in revised form : 30/04/2024
Accepted : 14/05/2024

Keywords:
Guggul-Based, Hyperlipidemia, Atorvastatin.

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DOI: 10.47009/jamp.2024.6.5.165

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2024; 6 (5); 862-865

Abstract

Background: The present study was aimed to establish the lipid-lowering activity of gugulipid in triton-induced hyperlipidemic rats in comparison to atorvastatin. At the same time, we explored the combination of gugulipid and atorvastatin for any possible synergistic effect and to find out the optimum dose of the individual agents. **Materials and Methods:** Fifty patients are randomly devided into 2 groups. Each group consists of 25 patients, for these patients study medication was allocated which contained Atorvastatin 20mg or Guggulu-250mgafter a through clinical examination, fasting blood sample was obtained to get a baseline cholesterol levels. A base line routine such as Hb%, CBC, platelet count, and biochemical investigations for renal functions such as blood urea and serum creatinine level, liver function tests such as bilirubin, SGPT and SGOT were estimated for safety evaluation. Patients were examined for every 15 days. All baseline investigations were repeated after 45 days of study course. **Result:** Out of the 50 patients only 45 were available for efficacy analysis, 34 in guggulu group and 11 in Atorvastatin group and the rest were dropouts. There was a statistically significant reduction in LDL-C from the baseline value in Atorvastatin group (25.9%) in comparison with guggulu group (9%). HDL-C values are raised in Atorvastatin group 6% and no change in guggulu group. There was a statistically significant reduction in serum cholesterol from baseline value in Atorvastatin group (15%) in comparison with guggulu group (6%), the levels of VLDL-C (4%) in guggulu group and no change in Atorvastatin group. **Conclusion:** Atorvastatin is superior to Guggulu in lowering LDL-C and raising HDL-C, but it is better to use guggulu in patients having liver disease or hypersensitive to statins.

INTRODUCTION

Hyperlipidemia is highly predictive risk factor for atherosclerosis, coronary artery disease, and cerebral vascular diseases.[1] Atherosclerosis of arteries is a generalized disease of the arterial network known as progressive disease and silent killer characterized by the formation of lesions called atherosclerosis plaques in the walls of large and/or medium-sized coronary arteries which reduce blood flow to the myocardium called coronary artery disease.[2] Hyperlipidemia is not only secondary metabolic dysregulation associated with diabetes but also represent increased risk factor for the development of diabetes.[3-5] Plants are important sources of medicinal compounds and more than 70% of population of developing countries is dependent on traditional medicine therapies for their ailments. In the traditional system of Indian medicine, plant formulation and combined extracts of plants are used as drug of choice in hyperlipidemia.[6] In the present study, the selection of gugulipid is based on the back up evidence that this natural cholesterol lowering agent, a oleo resin obtained from the plant Commiphora mukul belonging to the family of Burseraceae, has been used in Ayurvedic medicine practice for more than 2000 years to treat a variety of ailments such as rheumatism, arthritis, hyperlipidemia, obesity, and atherosclerosis.[7] Gum resin resides in the ducts located in the soft bark of the tree and with a circular incision made on the bark stem, a pale yellow aromatic fluid exudates that quickly solidifies to a golden or reddish-brown agglomerate from which Z and E gugulsterones have been isolated as active agents possessing lipid lowering activity. Urizar et al. showed in both animal models and humans that this resin, termed gum guggul, decreased elevated lipid levels.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Recent studies have shown that these compounds are antagonist for the bile acid receptor also known as farnesoid X receptor, a nuclear receptor that regulates the expression of the genes regulating cholesterol and bile acid homeostasis. It is likely that this effect accounts for the hypolipidemic activity of these phytosteroids.[8]

Moreover, HMG Co-A reductase inhibitors (statins) are the mostly used drug class in the treatment of hyperlipidemia but there is a possibility of some serious adverse events such as rhabdomyolysis, proximal myopathy, and hepatotoxicity.[2] Incidence of these adverse effects increases with respect to the duration of treatment and the dose. Atorvastatin is used in varying doses in humans (from 10 to 80 mg), needless to say more is the dose, more the chances of having adverse effects. The striking feature of gugulipid is, it is remarkably free from serious adverse effects. Apart from headache, diarrhea, and skin rash, it is devoid of any adverse effects on hepatic, renal function, or in hematological parameters when administered at a dose of 400 mg/day for 4 weeks.[8,9]

The present study was aimed to establish the lipid-lowering activity of gugulipid in triton-induced hyperlipidemic rats in comparison to atorvastatin. At the same time, we explored the combination of gugulipid and atorvastatin for any possible synergistic effect and to find out the optimum dose of the individual agents.

MATERIALS AND METHODS

Materials used: Lipivas (Atorvastatin-20mg)
Tablets Suddha guggulu (Guggulu-250mg) capsules
Grouping of patients:
Fifty patients are randomly devided into 2 groups
Group-I (Atorvastatin group)
Group-II (Guggulu group)
Each group consists of 25 patients, for these patients study medication was allocated which contained Atorvastatin 20mg or Guggulu-250mgafter a through clinical examination, fasting blood sample was obtained to get a baseline cholesterol levels. A base line routine such as Hb%, CBC, platelet count, and biochemical investigations for renal functions such as blood urea and serum creatinine level, liver function tests such as bilirubin, SGPT and SGOT were estimated for safety evaluation. Patients were examined for every 15 days. All baseline investigations were repeated after 45 days of study course.

Statistical Analysis: All data were checked for completeness and statistically analyzed. Descriptive data were represented as mean and standard deviation. Different levels were expressed at 95% confidence interval and $P < 0.05$ was considered statistically significant. Mean values of same group before and after triton administration (paired situation) were compared using Wilcoxon's matched pair's signed-rank test. Mean values of different groups were compared using Kruskal–Wallis ANOVA followed by Mann–Whitney U-test after prior analysis of data for distribution (Kolmogorov–Smirnov test). All statistical analyses were performed using statistical software packages such as Statistical Package for the Social Sciences (Windows version 11.5.; SPSS Inc., Chicago [IL], USA) and Microsoft Excel.

RESULTS

Out of the 50 patients only 45 were available for efficacy analysis, 34 in guggulu group and 11 in Atorvastatin group and the rest were dropouts. There was a statistically significant reduction in LDL-C from the baseline value in Atorvastatin group (25.9%) in comparison with guggulu group (9%). HDL-C values are raised in Atorvastatin group 6% and no change in guggulu group. There was a statistically significant reduction in serum cholesterol from baseline value in Atorvastatin group (15%) in comparison with guggulu group (6%), the levels of VLDL-C (4%) in guggulu group and no change in Atorvastatin group.

Table 1: GROUP-I (Atorvastatin group).

Parameter	Before	After
SERUM CHOLESTEROL	234	166
LDL-C	148	109
HDL-C	51	53
SERUM TRIGLYCERIDES	178	134

Table 2: GROUP-I I (Guggulu group)

Parameter	Before	After
SERUM CHOLESTEROL	219	205
LDL-C	145	135
HDL-C	42	41

DISCUSSION

This study was specifically designed to compare the safety and efficacy of guggulu against Atorvastatin. Across the dose ranges, Atorvastatin 20 mg and Guggulu 250 mg were selected for this study. Atorvastatin was selected due to its high safety and efficacy when compared with other statins like simvastatin, pravastatin, lovastatin, fluvastatin. NCEP, ATP-III suggested that the use of lower doses in initial stages of treatment for the hyperlipidemics

ISSN (O): 2687-5365; ISSN (P): 2753-6556

gives better results basing on that we selected the dose of Atorvastatin 20mg for the study. Studies like "Hyperlipidemic and Antioxidant effects of Commiphora Wightii as an adjunct to dietary therapy in patients with hypercholesterolemia'' done by sing RB, Niaz MN et al. "Guggululipid for the treatment of hypercholesterolemia randomized controlled trial" done by Szapary PO, Wolfe ML, Bleodon LT et al. shown guggulu 250mg dose was effective in hypercholesterolemia patients. Graphical representation of effect of Atorvastatin and Guggulu Lipid profile of Atorvastatin(Group-I) and Guggulu (Group-II) before and after treatment were given in the Tables 1and 2 respectively. Reports produced by the Guggulu group were not matching with previous researches. May be this is due to small population and small duration of study.

Hyperlipidemia and hypercholesterolemia are reportedly the major risk factors in lifestyle-related diseases such as atherosclerosis and related cardiovascular complications inclu by targeting the hyperlipidemia and hypercholesterolemia through diet and/or drug administration.[6] Atorvastatin only group appeared more potent in preventing the rise in TC, TG, LDL, and VLDL as compared to the gugulipid only group. However, atorvastatin and gugulipid combination group was more potent in preventing the elevation of the lipid parameters as compared to atorvastatin or gugulipid alone excepting HDL which was significantly high in comparison to gugulipid alone. Hence, it can be said that the combination has a possible synergistic effect in controlling the hyperlipidemia and thus may have a role in the clinical use. Considering the fact that chronic use of atorvastatin in higher dose has some adverse effects such as rhabdomyolysis, proximal myopathy, and hepatotoxicity, the possible synergistic effect can help us to reduce the dose of atorvastatin without compromising the therapeutic effect which was evidenced in the Phase 2 part of the study. In that phase, we have studied this combination with different dose level of atorvastatin with ding cerebral stroke and myocardial infarction.[10,11] Prevention or treatment of such disorders can be achieved a standard dose of gugulipid to find out the optimally effective and safe dose regimen which was not explored earlier. Atorvastatin 7.2 mg/kgbw and gugulipid 6.75 mg/kgbw in combination appeared superior in preventing the rise of TC and TG, whereas atorvastatin 3.6 mg/kgbw and gugulipid 6.75 mg/kgbw appeared as an optimally effective acceptable combination to start with, in preventing the rise of TC, TG, and LDL also catalyzing the rise of HDL with reduced chance of statin-induced toxicity.

As per available literature, gugulipid appears to be as a safe hypolipidemic agent that possesses an immense potential to be combined with a reduced dose of atorvastatin for long-term therapeutic use in humans.[8] A recently published study on diet-induced hyperlipidemic rat model observed coadministration of guggulipid extract with rosuvastatin enhanced the antihyperlipidemic activity of the latter at least partly by enhancing its bioavailability; rosuvastatin is metabolized by CYP2C9 and CYP2C19 enzymes and gugulipid inhibits CYP2C19 which might be the reason of increased serum level of the former.[11] Thus, the result of the present study necessitates further pharmacokinetic and pharmacodynamic exploration for any possible interaction between atorvastatin and gugulipid when used in combination. A number of clinical trials had been conducted using gugulipid with majority showing favorable results in reducing TC, TG, and a few with not so impressive effect.[2,3,10] In those studies, gugulipid was used as a monotherapy versus placebo in majority or clofibrate in one and none with statin. However, in overall pooled analysis of four studies, gugulipid was found to have a comparable magnitude of hypolipidemic effect similar to the available drugs in modern medicine.[11] Noteworthy, though of short duration, those studies documented favorable safety profile of gugulipid with a low incidence of dyspepsia and mild skin rash.

CONCLUSION

Atorvastatin is superior to Guggulu in lowering LDL-C and raising HDL-C, but it is better to use guggulu in patients having liver disease or hypersensitive to statins. We only observed a possible pharmacodynamic drug synergism between gugulipid and atorvastatin with different dosage schedule which was not done earlier. In addition, considering the high efficacy but potential adverse effect of statins, a well-designed clinical safety and efficacy study with different dosage regimen of atorvastatin or any other statin in combination with gugulipid is the need of the hour.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556

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ISSN (O): 2687-5365; ISSN (P): 2753-6556