SINGLE BLIND RANDOMIZED CONTROLLED CLINICAL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF SHIVAGUTIKA IN DYSLIPIDEMIA

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ABSTRACT

Objective: To evaluate the effect and safety of trial drug Shivagutika on Lipid profile and Apolipoprotein B in dyslipidemia and comparison with control drug Navaka Guggulu. Study Design: Randomized, single blind controlled clinical study of 45 days duration with pre and post test assessment. 60 patients diagnosed with dyslipidemia were randomly selected and assigned into two groups, Group A (Control) and Group B (Test), each group consisting minimum of 30 patients. Group A patients received Navaka Guggulu and Group B patients received Shiva Gutika for 45 days. Blood samples of both the groups for Lipid profile, Apolipoprotein B and Safety Assessment were evaluated before starting the treatment (0th day) and after the completion of the treatment (46th day). Results: Both Group A & Group B drugs showed significant result in reducing Lipid Profile & Apolipoprotein B in Dyslipidemia. Shivagutika had edge over Navaka guggulu in reducing the components of Lipid profile like S. Triglycerides, LDL, HDL, VLDL, Total Cholesterol and Cholesterol/HDL ratio. On Apolipoprotein B Navaka Guggulu showed better results than Shivagutika. Interpretation & Conclusion: The result obtained in this study support the hypothesis i.e trial drug is better than control drug. Hence in this study design Shivagutika when compared to Navaka guggulu has shown a better result for Dyslipidemia. The safety assessment of drugs both clinically & statistically shows a significant result, which implies that the drug of trial & control group are safe in this study design for the said interval, for the said duration & for the said dosage.

Keywords: Shiva Gutika, Navaka Guggulu, Dyslipidemia

INTRODUCTION

Hyperlipidemia, hyperlipoproteinemia or dyslipidemia is the condition of abnormally elevated level of any or all lipids and /or lipoproteins in the blood. Epidemiological studies have established a strong correlation between premature coronary artery disease (CAD) and cardiovascular disease (CVD) and serum cholesterol levels. World Health Organization (WHO) in 2002 reported that high cholesterol level is one of the main non-communicable disease-related risk factors in India. Conventional treatment principles for hypercholesterolemia aim to reduce cholesterol biosynthesis, which will lead to lower blood levels. Most of the drugs (statins) available today are inhibitors of 3-
hydroxy-3-methylglutarylcoenzyme A reductase, which is involved in cholesterol biosynthesis in the liver. Literature shows that the use of statins has a risk of chronic toxic effects including carcinogenic, teratogenic, and mutagenic changes over a lifetime of use. Other drug therapy includes resins, niacin and fibrates which give rapid relief but long term side effects such as hepatic or renal impairment, malaise, hyperglycemia, constipation, flatulence, nausea, diarrhea, gallstones, myositis and liver enzyme elevation. Most of these lipid lowering drugs are contraindicated in patients with Chronic liver disease, severe renal failure, gout and gall bladder disease. Hence there is a need for more natural methods to control cholesterol levels. Ayurveda emphasizes various dietetic regimens, panchakarma procedures, wide range of herbal and mineral drugs in the management of medoroga, which are kaphamedohara, sthoulyahara and hrudya either individually or in combination. During past few decades there has been extensive research carried out in this regard and effective treatment modalities have been found. But these treatment modalities mainly include snehapanam, vamana, virechana which are inpatient oriented, time consuming and costly. Shivagutika is one of the herbomineral drugs contexted in various ayurvedic classics for the treatment of kaphamedoja vikara like prameha, medoroga, sthoulya, granthi, gulma, arbuadh. The main ingredient of Shivagutika is shilajatu along with, karkata shungi, trikatu, chaturjataka, gomutra and honey. Shilajatu possesses rasayana (rejuvenation), vrishya properties (aphrodisiac). It is useful in the treatment of prameha (diabetes mellitus), pandu (anemia), gulma (tumor), pleeharoga (spleenic disorders), sthoulya (obesity), shotha (swelling), jvara (fever), HIV etc. It has significant anti-inflammatory, analgesic, immunomodulatory, antiviral and antioxidant activity. Experimental studies on lipid profile of hyperlipidemic albino rats, shiljatu has proven a significant effect against simvastatin. The above mentioned trial gives a potential proof to conduct human clinical trials. Hence an attempt was made to find a safe, cost-effective and a promising remedy against dyslipidemia.

MATERIALS AND METHODS

Drug Source
Shiva Gutika and Navaka Guggulu were purchased from GMP certified SDM Ayurveda Pharmacy, LN nagar, Kuthpady, Udupi, Karnataka which were prepared as per the literature reference.

Sample Source
60 patients diagnosed with Dyslipidemia were taken for the study from the OPD and IPD of the Government Ayurveda Medical College and Hospital, Mysore and from the special camps conducted for the study.

Method of collection of data
60 patients fulfilling the inclusion criteria of either sex were randomly selected. They were assigned into two groups A & B of 30 patients each.

a) Diagnostic criteria
Patients were diagnosed on the basis of the lipid profile, showing any one or more of the following criteria.
- Serum cholesterol >200 mg/dl
- Serum Triglycerides >150 mg/dl
- Serum LDL >130 mg/dl
- Serum VLDL >40 mg/dl
- Serum HDL <40 for male <30 for female
- Ratio of HDL to Cholesterol >4.5
- Apolipoprotien B >125mg/dl

b) Inclusion Criteria
- Men and women age more than 20 years and below 60 years.
- Patients fulfilling the diagnostic criteria.
- Both fresh and treated cases were included (Flush out period of 7 days was maintained for treated cases).
c) **Exclusion criteria**
- Patients having history of serious cardiac disorders like myocardial infarction, cardiac failure, etc.
- Patients having any major illness, insulin dependent diabetes mellitus, Type II diabetes mellitus that is poorly controlled
- Patients having a history of untreated thyroid disorder
- Hyperlipidemia due to drugs (e.g., glucocorticoids)
- Pregnant females and lactating mothers
- Renal insufficiency

d) **Subject withdrawal criteria**
- Occurrence of a serious adverse event
- Subject had an acute reaction (allergy, shock and so on) to the investigational product
- Detection of a systemic disease that was not discovered at the screening stage
- Unable to progress because of worsening of preexisting disease
- Subject’s withdrawal of consent
- Subject is uncooperative
- Investigator’s decision to terminate the process for the sake of the subject’s health

e) **Investigations:**

**Specific investigation –**
- Serum Lipid Profile (12 hr fasting blood sample), Apolipoprotien B was investigated as a biomarker for hyperlipidemia.
- Other Blood investigations – Hb %, TC, DC, ESR, RBS to rule out other diseases.
- Blood Urea, Serum Creatinine, Liver function test for safety assessment.
- Urine investigations - Urine Sugar, microscopic, albumin were done to rule out other systemic diseases or complications.

f) **Intervention (Drugs and posology)**

The selected patients were randomly allocated into two groups as follows:

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<tr>
<th>GROUP A</th>
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<tr>
<td>Drug</td>
<td>Tab <em>Navaka guggulu</em></td>
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<td>Dose</td>
<td>2gram per day in two equally divided doses.</td>
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<td>Duration</td>
<td>45 days</td>
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<tr>
<td>Anupana</td>
<td>Water</td>
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<tr>
<td>Route / Mode</td>
<td>Oral</td>
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<td><em>Kala</em> (Timings)</td>
<td>Morning and night- after meals</td>
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**Assessment parameter**
- Assessment was done by post test Lipid profile and Apolipoprotien B measurement.
- The assessment was done before starting the treatment i.e. 0\(^{th}\) day and after the completion of the treatment i.e. 46\(^{th}\) day.

**Assessment of safety**
- Liver function test, serum Creatinine and blood urea were done before and after intervention.

**Statistical Method**

The data was collected before & after intervention and assessed statistically by using descriptive statistics, paired sample ‘t’ test. Analysis was done by using Service product for statistical solution (SPSS) for windows software.

**OBSERVATION**

Among the 60 patients registered in the study, the incidence of Dyslipidemia was more in the age group of 51-60 yrs (48.33%), 53.33 % patients had no comorbidity of other diseases, 16.66% patients had a history of diabetes mellitus and 16.66% patients had a history of Hypertension, 10% patients had a history of both diabetes mellitus and hypertension. 76.66% patients were fresh cases and 23.33 % were treated cases. 23.33% patients had a family
history of dyslipidemia and 76.66% had no family history of dyslipidemia. 73.33% patients had mixed diet habit and 26.66% patients were vegetarians. 26.66% patients had a habit of daily walking and 65% patients were not following any Exercise Pattern. Maximum number of patients had over weight (46.66%), while 33.33% been obese, 20% had normal BMI and no one was under weight or morbidly obese.

RESULTS:
Effect on Lipid Profile & Apolipoprotein B
1. S. Triglycerides: There is significant change in mean value for group A from 242.3 to 219.3 & for group B 299.7 to 218.8. If we analyze the mean value, Group B is far better than group A.
2. S. LDL: There is significant change in mean value for group A from 116.4 to 112.4 & for group B 122.6 to 117.3. If we analyze the mean value, Group B is far better than group A.
3. S. HDL: There is significant change in mean value for group A from 45.73 to 45.70 & for group B 46.78 to 45.70. If we analyze the mean value, Group B is far better than group A.
4. S. VLDL: There is significant change in mean value for group A from 48.44 to 43.87 & for group B 59.95 to 43.77. If we analyze the mean value, Group B is far better than group A.
5. Total Cholesterol: There is significant change in mean value for group A from 206.53 to 204.84 & for group B 212.6 to 203.9. If we analyze the mean value, Group B is far better than group A.
6. T.Chol/HDL ratio: There is significant change in mean value for group A from 4.5 to 4.48 & for group B 4.54 to 4.49. If we analyze the mean value, Group A and group B drugs have similar effect on T.Chol/HDL ratio, with slightly better results in Group B.
7. Apolipoprotein –B: There is significant change in mean value for group A from 119.9 to 118.3 & for group B 116.73 to 116.8. If we analyze the mean value, Group A is better than group B.

Safety Assessment:
1. Blood Urea: In group A mean value changed from 21.86 to 21.70 & in group B from 21.7 to 21.8. If we analyze the mean value, both the drugs are safe for the said dosage, duration & intervention. Statistically the slight increase of Blood urea mean value I Group B implies that the drug of group A is less toxic than drug of Group B.
2. S. Creatinine: In group A mean value changed from 0.89 to 0.90 & in group B from 0.88 to 0.93. If we analyze the mean value, both the drugs are safe for the said dosage, duration & intervention. Mean values also interpret that both the drugs of group A & group B in a longer duration may give some toxic effects, so it is safer for the interventional duration beyond that cautious approach can be adopted.
3. Total Bilirubin: In group A mean value changed from 0.65 to 0.62 & in group B from 0.63 to 0.66. If we analyze the mean value, both the drugs are safe for the said dosage, duration & intervention. Statistically the increase of Bilirubin mean value in Group B implies that the drug of group A is less toxic than drug of Group B.
4. SGOT: In group A mean value changed from 26.46 to 25.63 & in group B from 28.9 to 26.2. If we analyze the mean value, both the drugs are safe for the said dosage, duration & intervention.
5. SGPT: In group A mean value changed from 29.26 to 27.55 & in group B from 31.76 to 30.63. If we analyze the mean value, both the drugs are safe for the said dosage, duration & intervention.
6. GGT: In group A mean value changed from 29.2 to 28.6 & in group B from 29.80 to 39.56. If we analyze the mean value, both the drugs are safe for the said dosage, duration & intervention. Statistically the increase of GGT mean value in Group B implies that the drug of group A is less toxic than drug of Group B.
7. S. Alk. Phoapate: In group A mean value changed from 70.66 to 73.66 & in group B from 70.86 to 71.60. If we analyze the mean value, both the drugs are safe for the said dosage, duration & intervention. Mean values also interpret that both the drugs of group A & group B in a longer duration may give some toxic effects, so it is safer for the interventional duration beyond that cautious approach can be adopted.

8. Serum Total Protein: In group A mean value changed from 7.003 to 7.039 & in group B from 7.21 to 6.97. If we analyze the mean value, both the drugs are safe for the said dosage, duration & intervention.

**DISCUSSION**

**Discussion on diseases Dyslipidemia:**

There is no precise term for dyslipidemia in the Ayurvedic classics. Literature shows that scholars have tried to use distinct nomenclature for dyslipidemia, e.g., Rasagata Sneha Vriddhi (increase in lipids in plasma), Rasa Raktagata Sneha Vriddhi (increase in the lipids in plasma and blood), Medovriddhi (generalized lipid increase), Medoroga or Medodosha (obesity), AAMA Medodhatu (abnormally formed adipose tissue). A detailed study of hyperlipidemia with regard to the pathophysiology reveals its similarity to Asthayi Medo Dhatu Vriddhi (abnormal increase in circulating lipids). This excessively increased circulating lipid is AAMA in nature is also termed as bahuabadha medas in the context of prameha.

Recent research on Dyslipidemia carried out at I.P.G.T and R.A, Jamnagar by Shivam et.al concluded that Dyslipidemia is Aama, Kapha, Kleda and Avaranajanya disease. The researches on dyslipidemia suggest that, Laghu, Ruksha, and Kashaya Rasa dominant formulation is more effective against serum cholesterol and S.LDL, while Laghu, Ushna, and Katu Rasa dominant formulation is effective in condition of hypertriglyceridemia.

Achieving Dhatusamyata is the main aim of treatment in Ayurveda. So the treatment of dyslipidemia should be also planned for achieving Dhatusamyata. Nidana of Dyslipidemia vitiates Jatharagni, Rasa Dhatvagni, Mamsa Dhatvagni, Meda Dhatvagni and increase Ama, Kapha, Kleda, Apakva Rasa, Abaddha Meda and Mamsa in the body. Hence, the first aim of the treatment is to correct Jatharagni, Rasa Dhatvagni, Mamsa and Meda Dhatvagni, and then to remove excessive Ama, Kapha, Kleda, Meda and Apakva Rasa from the body. It is also necessary to restore the normal function of above mentioned Agni, Dosha, and Dhatu for constant normal function.

**Discussion on Shivagutika:**

1. Shivagutika is indicated in Swasa, Kasa, Prameha, Shotha, Granthi, Slipada etc all most all these disorders have the involvement of the Kapha Dosha as a major Samprapti Ghataka. Shivagutika has Katu Tikta Rasa, Laghu Ruksha Guna, Anushna Veerya and Katu Vipaka. Dyslipidemia is mainly due to vitiation of doshas like Kledaka Kapha, Samana Vata and Pachaka Pitta and dooshyas like Rasa and Medo dhatu. Shivagutika being majorly Kapha Vatahar will helpful in the Samprapti Vighatana of the disease Dyslipidemia.

2. In Shivagutika, Shilajitu is the main ingredient which possesses Tikta, Katurasa, Kashaya Anurasa, Saraguna, Katu Vipaka, Ushna Veerya, Shoshaka, Chedana, Lekhana and rasayana properties and acts as medohara and stoolahara. Shilajitu is also used as yogavaha as it increases efficacy of many drugs. Apart from this the other drugs in shivagutika have kaphavata shamaka property.

3. The Principle of management of Avarana is Shodhana treatment and the use of Naimittika Rasayanas like Shilajitu and Guggulu. Dyslipidemia will be having Avaranajanya Samprapti. Shivagutika is also Naimittika Rasayana with Shilajitu as main ingredient, and hence helpful
in the removal of Kapha Avarana to Vata and to pacify Meda and Kleda.

**Discussion on Navaka Guggulu:**

1. *Navaka Guggulu* has Katu-Kashaya Rasa, Laghu-Ruksha-Tikshna Guna, Ushna Virya and Kapha Vata Shamaka properties which will have opposite action on Kapha Dosha as well as Meda Dhatu.13
2. All the contents of *Navaka Guggulu* have Deepana property. Majority of the drugs have Pachana and Yakridutejaka property. Most of the drugs possess the property of Ushna Virya and are being able to improve Medodhatvagnimandhya. In this Yoga, Sunthi is the best Amapachaka which improves the Medodhatvagni by removing the Aama.14
3. In Dyslipidemia, there is Sanga type of Srotodushti, produced by vitiated Kapha and Meda. Sunthi, Maricha and Haritaki possess the Srotoshodhana property which helps to clear the Sroto Sanga and regulate the function of Medovaha Srotas.

**CONCLUSION**

**Effect on Lipid profile & Apolipoprotein B:**

The overall outcome analysis shows both clinically & statistically the trial drug is better than the control drug on lipid profile & Apolipoprotein B in dyslipidemia. If we analyze component vise lipid profile analysis, both the drugs are benefited in lowering dyslipidemia but few components are better in control drug and few components are better in trial drug.

*Shivagutika* has showed comparatively greater results in lowering S. Triglycerides, LDL, HDL, VLDL, Total Cholesterol & Cholesterol/HDL ratio in comparison with *Navaka Guggulu*. On Apolipoprotein B *Navaka Guggulu* showed better results than *Shivagutika* in reducing the values.

The results obtained in this study supports the hypothesis i.e. trial drug is better than control drug. Hence *shivagutika* when compared to *navaka guggulu* has shown better result for dyslipidemia in this study design.

**Safety Assessment:**

The overall safety profile shows both the drugs are safer on long term use with more than 90% of normal values before & after intervention for LFT & RFT.

So the safety assessment both clinically & statistically shows a significant result, which implies that the drug of trial & control group are safe in this design study for the said interval, for the said duration & for the said dosage.

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