Protocol of Comparative Evaluation of Efficacy of Kulattha Gutika with Atorvastatin in the Management of Dyslipidemia (Medoroga)

Abstract:

Introduction: The term *'Dyslipidemia'* can be referred to Medoroga included under santarpanajanyavyadhi as per Ayurveda. In *Dyslipidemia* there is involvement of *Tridosha* with *kapha*dominance. Intake of unhealthy food, alcohol, cigarette smoking, stress and lack of physical activity are the main etiological factors of Dyslipidemia. According to *Ayurveda Guru, Madhur, Sheet, Snigdha, Kapha Meda Vardhaka Ahar, Avyayam, Diwaswapa, Achinta* and *Bijadosha* are the main causative factors for *medoroga*.

Aim and objectives: Comprarative evaluation of Efficacy of *Kulattha Gutika* and Atoravastatin in the management of Dyslipidemia (*Medoroga*).

Material and Methods: The study will recruit 60 patients with dyslipidemia and they will be divided into two equal groups (containing 30 patients each). Group A (Interventional) patients will be treated with *Kulattha Gutika* 1gm thrice a day after meal with warm water for 45 days and Group B (Experimental group) will be given Atorvastatin tablets 10mg at bedtime with warm water for 45 days. Objective parameters including BMI, lipid profile and fasting blood sugar will be assessed before and after treatment. Incidence of dyslipidemia as per prakriti will be assessed by analysing prakriti of each patient.

Discussion: Kulttha is indicated for the treatment of medoroga in Bhavprakash due to its kaphamedohar property which may help in improving the objective parameters.

Result: Subjective and objectives outcomes will be statistically analysed by appropriate method.

Conclusion: Conclusion will be drawn from result obtained.

Keywords: Dyslipidemia, *Medoroga, Kulattha Gutika*, Atorvastatin, Santarpanajanya vyadhi.

Introduction:

In terms of food, living standards, and the environment, human life is rapidly changing. The majority of the population suffers from metabolic diseases as a result of changes in eating habits and a sedentary lifestyle. Metabolic diseases are caused by changes in normal metabolic processes caused by aberrant chemical interactions in the body. Dyslipidemia is defined as a group of metabolic diseases involving lipoprotein metabolism, evidenced by increase in total cholesterol, triglycerides (TGs), or both, or a reduction in high density lipoprotein levels, or all three, and all can lead to atherosclerosis at any age. [1,2] According to the ICMR-INDIAB study, hypercholesterolemia was prevalent in 13.9 percent of the population, hypertriglyceridemia was prevalent in 29.5 percent, low HDL-C was prevalent in 72.3 percent, and high LDL-C levels were prevalent in 11.8 percent. Ayurvedic texts do not provide any descriptions of dyslipidemia. As a result, it cannot be compared to any specific

condition in Ayurveda. However, it falls under the category of *SantarpanjanyaVyadhi* due to similarities in their etiopathogenesis and clinical featuresm such as *Shonitabhishyandana*, *RasagataSnehaVriddhi* (raised plasma lipid levels), *RasaRaktagata Sneha Vriddhi* (raised plasma and blood lipid levels), *Medovriddhi* (elevation of generalised fat), *Medoroga* (obesity), and *AamMedodhatu* (abnormal). The main etiological causes of dyslipidemia are poor eating habits, a sedentary lifestyle, family history of dyslipidemia, alcohol consumption, cigarette smoking, and stress.[3,4] According to Ayurveda the main causes of *Medoroga* are *Guru,Madhur*, *Sheet*, *Snigdha*, *KaphaMeda Vardhaka Ahar*, *Avyayam*, *Diwaswapa*, *Achinta*, and *Bijadosha*.[5] All of these *Hetus* aggravate the *kapha* and *Meda*, resulting in *Strotorodha*. The regular movement of *Vayu* is obstructed due to *Stotorodha*. This obstructed *Vayu* enters the *Koshtha*, causing *Jatharagni sandhukshana* (increased digestive capacity), which causes early digestion of ingested food, resulting in insatiable appetite and a desire for huge amounts of food. *Agnimandya* and *Ama* production, according to *Dalhan*, are to be blamed for the situation. The effective functioning of *Agni* is essential for all metabolic activity in the organism.[6] Food digestion is hampered by *Agnimandya*, which creates *Ama*. *Ama* is thought to be a crucial element in the aetiology of metabolic problems in Ayurveda. This ama obstructs the *Strotas* (metabolic process channels), resulting in disease development. Excess fat accumulates in the blood and adipose tissue due to a malfunction in fat metabolism. The creation of aberrant *Poshaka Medodathu* in huge quantities is caused by *Medodhatwagnimandya*. This improperly produced *Poshaka Medodathu* accumulates in vast quantities in *Rasadhatu*. The accumulation of *Poshaka Medodhatu* leads to the development of a condition known as *Dhamanipratichaya*. *Dhamanipratichaya* is one of *KaphaDosha's* 20 *NanatmajaVyadhis*.[7] *MedorogaSamprapti* begins with inflamed *Kapha* and *Medas* accumulating in the various *Strotasa*, resulting in *Strotorodha*. *Shonitabhishyandana* is a condition in which there is an excessive concentration of *Kapha* and *Medas* in the *Rasadhatu* (plasma) and *Raktadhatu* (blood, and blood vessels).[8,9] It adheres to the *Upalepa* and forms within the *dhamani's* walls. [10]. *Acharya Charak* prescribes *karshana* and *kaphamedanashanachikitsa* in Ayurveda to eradicate the *KaphaMedaApatarpanaupalepa*. *Kulattha* is mentioned in *Bhavprakash*[11] for the management of *Medoroga* which helps in *Sampraptivighatana*. *Kulatha* possesses *Laghu*, *Ruksha* and *Tikshnaguna*, *KashayaRasa* and due to its *Ushna* potency, it exhibits *Vata-Kaphanashak Karma* and *Lekhan Karma*, it also exhibits *Medohar* quality[12]. As, Atoravastin is a standard drug used in the treatment of dyslipidemia, it is therefore going to be use in this study in the control group.

Research Gaps Analysis: Animal studies conducted on *Kulattha* showed its antihyperlipidemic, nephrolithic and antioxidant activity. Also, *Kulattha* is mentioned to exhibit *medohar* quality by its *Lekhankarma*. There are large numbers of research studies available on dyslipidemia. *Shodhanachikitsa* like *Vamana*, *Virechana* and *Basti* (*LekhanaBasti*) showed good results in improving lipid levels [13,14]. But not all patients will be willing to undergo procedures of *Shodhanachikitsa*. This is because it is expensive; patients have to visit the hospital frequently, and have to be followed up pre and post operatively. In addition, *Shodhanachikitsa* cannot be used in patients contraindicated for it. In such patients *Shamanachikitsa* can be given. In *Shamanachikitsa* most of the formulations have guggul as main ingredient. In *BhavaprakashSamhita* it is mentioned to avoid long term consumption of *guggul*. The long term consumption has adverse effects like abdominal discomfort [15], and impotency [16]. The *Lekhana* drugs available for dyslipidemia can also cause abdominal irritation in some patients. The patients having intolerance to *Guggul* and *Lekhana* drugs cannot consume it for a long duration. *Kulattha* is described in *Dhanyavarga* so it can safely be used for long duration. It is cost effective and easily available. Therefore,

the aim of the present study is to evaluate efficacy of *Kulattha* in the management of dyslipidemia in human subjects.

Trial plan: The study design is Double arm Randomized Standard controlled single blinded clinical trial. It is an interventional study having 1:1 ratio on both parallel groups.

Research Question: Is *KulatthaGutika* as effective as Atorvastatin in the management of dyslipidemia?

Hypothesis

Null hypothesis (H0):

• *KulatthaGutika* is not as effective as Atorvastatin in the management of dyslipidemia.

Alternate hypothesis (H1):

• *KulatthaGutika* is as effective as Atorvastatin in the management of dyslipidemia.

Aim and objectives

Aim: Comparative evaluation of Efficacy of *KulatthaGutika* and Atoravastatin in the management of dyslipidemia (*Medoroga*).

Objective: 1. To assess the efficacy of *KulatthaGutika*on as a remedy for the lowering of the levels of Total cholesterol, Triglyceride, HDL, LDL, VLDL & BMI in dyslipidemic human subjects..

2. To assess the efficacy of Atorvastatin as a remedy for the lowering of the levels of Total cholesterol, Triglyceride, HDL, LDL,VLDL & BMI dyslipidemic human subjects.

3. To compare the efficacies of *KulatthaGutika* and Atorvastatin as a remedy for the lowering of the levels of Total cholesterol, Triglyceride, HDL, LDL, VLDL & BMI in human subjects.

4. To determine the incidence of dyslipidemia as per *prakruti*.

Methodology:

Type of trial: The trial is a parallel-group, randomized, single-blind, standard - controlled trial that will include, a 45 days treatment period, and a 15^{th}, 30^{th} 45^{th} day week follow-up period.

Allocation ratio: A total of 60 patients will be selected for the study and will then be equally divided into two groups. Group A (experimental group) whereas Group B (standard control).

Drug collection / authentication: The raw material will be procured from reliable source and will be authenticated at the Department of *Dravayguna* of Mahatma Gandhi Ayurved College, Hospital & Research Centre, Salod (H), Wardha.

Formulations: Preparation of Material (*KulatthaGutika*) :- The *kulatthaGutika*, will be prepare as per the standard operating procedures, mentioned in Sharangdhar Samhita, *MadhyamKhand*[17] .

Table 1. Preparation of *KulatthaGutika*

Sn. No.	**Ingredient**	**Botanical Name**	**Part Used**	**Quantity**
1.	*Kulatthi*	*Dolichos biflorus* Linn.	Grains	1 Part

Table: 2. Drug Properties[18]

Sr. No	Drug	Rasa	Guna	Virya	Vipak	Karma
1.	*KulatthaGutika*	*Kashaya*	*Laghu, Ruksha, Tiksna*	*Ushan*	*Katu*	*KaphavataSamakaMedohara*

Study setting:

Selection of patients will be done from outpatient department (Room No. 30) and IPD of Department. of Kayachikitsa, Mahatma Gandhi Ayurved College, Hospital & Research Centre, Salod (H), Wardha. Also patients will be selected from various specialized peripheral camps.

Diagnostic criteria: Diagnostic Criteria[19] [ATP-III National cholesterol education program(NCEP) criteria]:

- Serum Total Cholesterol ≥200 mg/dL & or
- Serum Triglycerides = 150-499 mg/dL & or
- Serum HDL (HIGH DENSITY LIPID) < 40 mg/dL & or
- Serum LDL Cholesterol (LOW DENSITY LIPID) = 130 -189 mg/dL

Assessment criteria: The patients will be assessed by objective parameters like lipid profile (Total cholesterol, Triglycerides, Low density lipoproteins, High density lipoproteins and Very low density lipoproteins), fasting blood sugar level and body mass index.

Prakruti will be assessed as per software application AYUVYA to study the incidence of dyslipidemia as per *prakruti*.

Eligibility criteria: Selection of patients will include both gender and will be among persons between the age group of 30– 60 yrs irrespective of the *SharirikPrakruti* status. Patients fulfilling the diagnostic criteria of dyslipidemia will be included in the study. Patients pre-diagnosed with major illness such as cardiovascular disorder, diabetes mellitus and renal disorders, patients taking the medication like glucocorticoids and those that are pregnant and lactating will be excluded.

Randomization: An independent statistician will create a block randomization sequence. Selected individuals will be randomly assigned to either the experimental group or the conventional controlled group in a 1:1 ratio, with randomization stratified by site. A remote and web-based randomization system will be used by the researchers to assess the treatment allocation for each eligible participant. A total of 60 patients will be selected for the study which will then be divided into two groups. Group A is experimental group where as Group B is standard controlled.

Blinding: Treatment allocations will be kept a secret from participants, the researcher will apply for a randomised assignment for each qualified patient by Random Sampling Computerized table method and will enrol him in study or control group. The blinding will not be broken during the trial and will be kept strictly confidential.

Interventions:

Group A (Experimental)**:** *KulatthiGutika* 500 mg 2 tablets thrice a day before meal with warm water for 45 days.

Group B (Standard Control): Tablet Atorvastatin 10 mg once a day at bed time with warm water for 45 days.

Screening investigations (base line): Lipid profile, fasting blood sugar level.

Investigation during treatment: Not applicable.

Investigation (end line): Lipid profile, fasting blood sugar level.

Criteria for discontinuing or modifying allocated interventions: During the study if any unwarranted incidence, evidence of drug sensitivity or any other disease or problem arises, subject will be withdrawn and free treatment will be offered to the subject till the condition subsides. We will measure quantity of *Gutika* for the consumption of appropriate dose for assessment and to check drug adherence during treatment the subject will be followed up.

Follow up: Patients will be followed up on15th day, 30th day and 45th day during the period of treatment. Patient will be advised to take normal routine activity and routine diet and no any specific precautions for food intake will be prescribed.

Primary Outcomes: The primary outcome of the trial is to evaluate the efficacy of interventional drug (Kulattha Gutika) on serum levels of Total cholesterol, Triglyceride, HDL, LDL, VLDL & BMI

Secondary Outcomes: The secondary outcome of the trial is to study the incidence of dyslipidemia as per prakruti.

Relief and relapse incidents- Relapse is defined as a rise in lipid levels, blood sugar levels, or body mass index in patients with dyslipidemia (*Medoroga*) who had responded to the initial treatment. When the patient's symptoms disappear, it signifies the treatment has been successful. The time until relief, time until first relapse, and total relapse times are the relief and relapse incident outcomes. The time between patients obtaining therapy and experiencing therapeutic success is referred to as the time until relief. The time of first relapse refers to the period of time between a patient's treatment success and the reappearance of elevated cholesterol, sugar levels, or BMI. The sum of relapse times during both the treatment and follow-up periods is the total relapse time.

Long-term effectiveness: Long-term effectiveness responders are those who show adequate relief on a weekly basis for at least 45 days throughout the follow-up period.

Statistical analysis: A statistically significant level of type I error is 5% (two-sided). Data of prakriti analysis will be analysed with the help of Wilcoxon test. Paired as well as unpaired t-test will be used to analyse the data having objective criteria. The McNamara's test will be used to analyse the data with subjective criteria.

Total follow up: Patient will be followed-up thrice during the trial, First on 15^{th} day after initiating the treatment, second on 30^{th} day after initiating the treatment, and third on 45^{th} day i.e. after completion of the treatment.

Follow up time: The assessment of the patients will be done before and after completion of treatment.

Enrolment and interventions time schedule: Drugs will be given from 0 to 45 days with follow up on day 15^{th}, day 30^{th} and day 45^{th} to check adherence to the drug.

Recruitment: By computerized random chart sampling method, 60 patient will be recruited (30 in each group)

Implementation: Principal investigator will enrol and allocate the patients.

Methods: Data collection, analysis and management.

Data collection method:

Objectives: Serum levels of Total cholesterol, LDL, HDL, VLDL, triglycerides, and BMI (Body Mass Index).

Prakriti Assessment: Prakruti will be assessed as per software application AYUVYA to study the incidence of dyslipidemia as per prakruti.

Plan to promote participants retention and complete follow up: We will stay in touch with the patient by obtaining his/her contact number and offer to them timely advice on proper medication practices and follow up and the data regarding follow up will be stored in the documentation with valid reasons.

Data management: The data will be collected from patients by assessor by doing investigations and assessment after taking written consent form from the patient. Prakriti will be assessed with the help of software application AYUVYA will be collected using structured questionnaire filled during interview of the patient. Data will be entered in master sheet and analysed by using appropriate statistical technique and data coding will be done by principal investigator.

Safety assessment-

On a consent form, details about adverse events will be noted, and on case sheet other details of patients will be noted. If there are any major adverse events, they must be reported to the principal investigator and the ethics committee within 24 hours, and any necessary therapy will be given as quickly as possible. All major adverse occurrences will be investigated and tracked until they are remedied.

Ethics and dissemination:

Research Ethics Approval: Approval for the trial from research ethics committee has been obtained; Ref. No. MGACHRC / IEC / July – 2021/ 339.

Consent or assent: Written consent will be taken before starting the study from the patient. During the study the confidentiality of each patient will be properly maintained.

Dissemination policy: The data will be disseminated by paper presentation and publication.

Any intended use and authorship will involve eligibility guidelines of professional writers.

Informed consent materials: The participants will be given model consent form and all other related documentation with providing all information.

Result: Expected outcome result in control group with intervention. *Kulattha Gutik*as per oral is potentially added effectual in improving the serum lipid levels or anti-lipidemic.

Discussion:

In modern science, some health behaviours have been demonstrated to have an impact on lipid levels. Excess use of alcohol and tobacco, unhealthy food habits, lack of physical activity and obesity are all are risk factors for causing dyslipidemia. Lack adequate intake of fruits, nuts/seeds, and vegetables, as well as a high consumption of saturated fats, are all nutritional risk factors. Genetic abnormalities in addition, might potentially induce dyslipidemia. Autosomal dominant mutations in LDL receptors cause the majority of cases of familial hypercholesterolemia, resulting in a rise in LDL-C levels. Other mutations in the cholesterol pathway have been reported, but they are less common.[20, 21]

In Ayurveda, the main etiological factors which bring vitiation in *medoroga* are lack of physical exercise, day sleep, excessive intake of fatty foods, excess drinking of *Varuni* (a kind of wine).[22] *Medovaha Srotodushti* occurs due to vitiation of *Kapha* dosha and decreased functioning of *medo Dhatvagni*. This leads to excessive *Meda* and eventually to dyslipidemia.[23,24] Dyslipidemia is one of the major causes of cardiovascular and cerebrovascular diseases. Many research works have been conducted on it, but none of these

studies showed complete cure. In modern medicine, various classes of drugs like Atorvastatin are used but there are some limitations. Long term use of it leads to nephrotoxicity and hepatotoxicity[25, 26]. Animal studies conducted on *Kulattha* showed its antihyperlipidemic activity[27] but no studies are conducted on human beings. *Kulattha* is included in *AnnaVarga*. It is safe, cost effective and easily available [28-30].

In this study we will evaluate how *Kulatthi Gutika* helps in effectively improving serum lipid levels in dyslipidemia. *Kulatthi Gutika* consists exclusively of kulattha which has properties like *Laghu*, *Ruksha* and *Tikshnaguna,KashayaRasa*and *Ushna* potency. The ushna, *teekshnaguna* will ignite the *medodhatvagni* and also act against the vitiated *Kapha*dosha. Due to exhibition of *LekhanKarma*, it will scrap the excessively accumulated *Meda*. Thus, it may also exhibit *Medohar* quality. The following *guna-karma* will do the *Samprapti-Vighatan* and help in arresting the disease in that stage.

By assessing the *Medohar* effect of *Kulatha Gutika*, we will study the changes in Lipid Profile, BMI (Body Mass Index) of the subjects [31-38]. Since, the disorder involves *Kaphadosha* we will assess the *prakriti* of subjects so that a conclusion can be made on which subjects are more prone to dyslipidemia.

Conclusion: *Kulatthi* Gutika may prove more efficacious in improving serum lipid levels in dyslipidemia *(Medoroga)*as compared to the tablet Atorvastatin with minimum side effects.

NOTE:

The study highlights the efficacy of "Ayurveda" which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable.

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