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Research article

A protocol for an open-label randomized parallel group clinical study on non-alcoholic fatty liver disease (NAFLD)

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ABSTRACT

The primary objective of this study is to evaluate the efficacy of the combined effect of Agnideepan and Vyadhipratyaneek Chikitsa on the Fatty Liver Index (FLI) score in patients with Non-Alcoholic Fatty Liver Disease (NAFLD). Secondary objectives include assessing the impact of combined chikitsa on Agni, lipid profile, body weight, waist circumference, and BMI. The study also aims to evaluate the effects of Vyadhi Pratyaneekachikitsa on changes in the FLI, lipid profile, body weight, waist circumference, BMI, and Agni, as well as the impact of Agni Deepanchikitsa on these parameters. Additionally, the quality of life of NAFLD patients will be evaluated using the SF36 questionnaire. Patients diagnosed with NAFLD will be selected from the outpatient department of CARICD, now renamed the Central Ayurveda Research Institute in New Delhi. Patient information sheets and consent forms will be provided to all willing participants. Screening will be conducted, and suitable patients will be randomized using a computer-generated chart. Trial formulations will be prescribed according to a set schedule, and patients will be called for follow-up visits accordingly. It is expected that the combined treatment of Agnideepan and Vyadhipratyaneek Chikitsa will be more effective than Vyadhipratyaneek Chikitsa alone in managing NAFLD. This study aims to explore the effectiveness of Ayurveda interventions in managing NAFLD through a disease-specific approach to precisely correct RaktavahaSrotodushti with Yakrt involvement and a general approach aimed at correcting metabolism. This dual approach highlights the role of multiple therapeutic targets in disease management tailored to patient-specific factor

Keywords: NAFLD, Liver disease, Agnideepan Chikitsa, Vyadhipratyneekchikitsa, Chitrakadivatiand Ayush PTK.

INTRODUCTION

The prevalence of Non-alcoholic fatty liver disease (NAFLD) is more in affluent societies especially among obese. Global prevalence rate of NAFLD ranges from 9 to 36.9% [1].However, prevalence of NAFLD is as high as 90% among severely obese individuals and 60% among diabetics. But 20% non-obese normal people also suffer from NAFLD.There was estimation in the year 2017 that 24% of the worldwide population is affected from NAFLD [2]. In fact, Non-alcoholic fatty liver is the prime reason for chronic liver diseases. It is the second most common reason for liver transplantation. It can also occur in the individuals who have low body weight. Moreover, NAFLD commonly occurs in individuals deprived of adequate adipose depots (i.e., lip dystrophy)

In general, there are no symptoms of NAFLD in the initial stage, so the majority of the patients are diagnosed only through radiological investigations like ultrasonography or abnormal liver enzymes or during clinical examination for other reasons. Sometimes an individual complains of vague right upper quadrant abdominal pain. NAFL may be diagnosed during investigating for symptoms like pain in abdomen or flatulence of abdomen after food or rarely during abdominal surgeries for some other reason. To assess the Fatty liver

infiltration fatty liver indexed is used which is based on BMR, waist circumference, triglycerides percentage and other liver enzyme like GGT.

Fatty liver index helps physicians to suggest ultrasonography of liver and lifestyle advocacy to the suspected patients. FLI is also used by scientists to screen patients for epidemiologic studies. The score of FLI ranges from 0 to 100. If the score is < 30 (i.e. Negative likelihood ratio = 0.2) it rules out fatty liver and if it is ≥ 60 (i.e. positive likelihood ratio = 4.3) it indicates that patient suffers from fatty liver [3].

*Yakrit*mentioned in Ayurvedic texts is an organ comparable to liver as it is considered as one of the major organs, that performs all major metabolic functions and the disturbance of which may result in many "*Yakritvikaras"*. *'YakritVikara'* were first described and categorised separately by AcharyaBhavamishra in his treatise *Bhavaprakasha* [4].But, description that can clearly depict steato-hepatitis cannot be found in Ayurvedic texts. Non Alcoholic Fatty Liver disease (NAFLD) seems to be *Santarpanajanya*disease which can be correlated to *KaphajaYakritodara*as per the similarities observed in their *Nidana*, *Samprapti* and *Lakshanas*.

According to Ayurveda the pathogenesis of NAFLD can be correlated with the *samprapti* of *Santarpanajanya*disease. Initial pathology lies at *Agnivikruti* (Vitiation of digestive mechanism) which leads to the formation of *Apakva Anna Rasa* (Improperly formed digestive end product). This further vitiates *Kaphadosha*leading to deposition of *Meda* (fat tissue) in *Yakrit*. *Srotorodha* (blockage of channels) at this stage hampers the normal movement of *Vata dosha* leading to its vitiation which causes more *Agnivikruti*and this cycle repeats. This stage may be called as fatty Liver disease (*Yakritdaulyodara*). Here,consistently co-existing events in this aetio-pathogenesis are*MedodhatuDushti and DhatwagniMandya*. Considering this, correction of *Agn*i (*Agni –Deepana*) is the best treatment approach for effective management of NAFLD and its sequels. Accordingly, *Chitrakadivati* [5]. Which is *Agnideepan*formulation mentioned in Ayurvedic texts can prove beneficial.

In Ayurveda three types of treatments are mentioned for interfering in disease pathogenesis viz., *Dosha Pratyaneek, VyadhiPratyaneek* and *UbhayaPratyaneekChikitsa*. Out of these three types of treatment, *Vyadhipratyneekchikitsa* (disease specific treatment) is done after manifestation of disease (In *Sthanasamshraya, Vyakta and Bhedavastha of disease*) to avoid further progression of disease. In the current study, management of fatty liver by *Phalatrikadikasaya* [6]. Has been proposed as *Vyadhi Pratyaneekachikitsa*for the treatment of NAFL. The ingredients of this polyherbal formulation have shown hepatoprotective, hepato-cellular regeneration, antiviral and antioxidant activity in pre-clinical studies [7].

Amalaki (Emblica officinalis Gaertn.), *Haritaki* (Terminalia chebula Retz.), *Bibhitak* (Terminalia bellericaRoxb.), *Amrita* (Tinospora cordifolia Miers.), *Vasa* (AdhatodavasicaNees.), *Katuki* (Picrorrhizakurroa Royale ex Benth.), *Bhunimba* (Andrographis panniculataNees) and *Nimba* (Azadirachta indica A. Juss.) Are the major ingredients of *phaltrikadikasaya?*

Primary objective

To evaluate the efficacy of Agnideepan&vyadhipratyaneekchikitsa among patients of Non-Alcoholic Fatty in terms of change in the score of fatty liver index.

Secondary objectives

To evaluate the effect of Agnideepan & vyadhipratyaneek Chikitsa on Agni

To evaluate the effect of Agnideepan & vyadhipratyaneek Chikitsa on lipid profile, body weight, Waist circumference, BMI.

To evaluate the effect of Vyadhipratyaneek Chikitsa on percentage change in fatty liver index lipid profile, body weight, Waist circumference BMI and Agni.

To evaluate the effect of Agnideepan Chikitsa on percentage change in fatty liver index [8]. Lipid profile, body weight, Waist circumference BMI and Agni.

To evaluate the quality of life of NAFL patients in terms of SF36.

This is an exploratory parallel group clinical study with the total sample size of 80 patients randomly allocated in two groups.

Study setting it is an OPD based study which will be conducted at Central Ayurveda Research Institute (CARI) New Delhi.

MATERIALS AND METHODS

The follow up visits for the participants are 8 but due to COVID Pandemic

The participant will be advised to go for the preliminary investigations as per the protocol after that he/she will be enrolled and detailed history will be taken at baseline. Physical examination include the recording of height, weight, heart rate and blood pressure etc will be done at all follow-up visits. On the day of subsequent visits, all assessment tools will be re-administered to see the effect of the interventions and the same will compared with the baseline. Likewise, all the investigations will be done as per CRF at the baseline and at the end of the treatment to evaluate the impact of the Ayurveda drugs on various laboratory parameters. Participants will visit the investigating site 4 times during the trial. They will be advised to take trial medicine for the period of one month. Telephonic follow up will be done on weekly basis,

Eligibility criteria

Inclusion Criteria

Either gender aged between 18-65 years Diagnosed cases of drug naïve Grade- I&II of non-alcoholic fatty liver disease as evident by fatty infiltration by Ultrasound evaluation (USG Abdomen).

Participants having BMI from 18.5 to 30 Subjects of non-alcoholic fatty liver disease with their hepatic enzymes <2 times upper normal limit. Willing to provide informed consent and for the participation for 3 months in the study.

Exclusion criteria

Any other identified cause of chronic liver disease or already taking supplementary medicine for NAFLD H/o hepatitis or jaundice in the past three years. H/O habitual consumption of alcohol intake of >20g/day for women,>40g/day for men. Subjects who have a history of Cardiac disorders like Arrhythmia, Acute Coronary artery disease, acute MI, Cerebrovascular accident in the last 6 month. Known case of malignancy, concurrent kidney disorder, uncontrolled respiratory disorders like Bronchial Asthma and COPD etc, Neurological disorders, neuropsychiatric disorders, or other concurrent severe disease. Uncontrolled Diabetes Mellitus defined as HbA1C>8.

Subjects taking participation in any other clinical trial. Lactating women/Pregnant women or females of reproductive age group who are not using contraceptive or planning pregnancy in next 12 months the study. Any other condition which PI think can jeopardize.

Interventions

In group I Chitrakadivatiand the dose of 500 mg twice daily will be administered one hour after food along with the *Vyadhi Pratyanika Chikitsa* i.e. *PhalatrikadiKwatha*Dasaage form: Kasayaghanvati 2 tablets BD in empty stomach).In group II as *VyadhiPratyanikaChikitsa*: *Phalatrikadi Kwatha* Kasayaghanvati 2 tablets BD will be advised to the participants to take in empty stomach

Criteria for discontinuing or modifying allocated interventions

Supply drug Accountability

The study drugs will be stored in steal Almira with glass door and if any discrepancies occur, it would be explained to the IEC. Study participants will be encouraged to maintain the stock information about the trial formulation.

Drug Compliance

The participants who will consume more than or equal to 80% of study formulations would be continued in trial. The drug compliance will be assessed at each visit during the follow up (one-month interval) by assessing the approximate quantity of medicines consumed by the participants. The participants will be instructed to return the empty strips at the time of each follow up visit.

Concomitant Medication

All the participants will be instructed to avoid the use of any other medicine on their own for any ailment and will also be clearly instructed to consult the investigator for any symptom or complaint, or if anything unusual felt by them. If any medication(s) he/she prescribe to alleviate their ailments. Will be recorded as concomitant medication.

Rescue Medication

To address any emergency medical condition, the use of rescue medicine/therapy may be permitted.

Outcomes

The Primary outcome

Change in the % of Fatty Liver Index (FLI) at the end of study period (3months) between the two groups or it may be change in absolute score of FLI.

The secondary outcome

Number of participants with reduction in FLI from baseline in Group I.

Number of patients with reduction in FLI from baseline in Group II.

Changes in ALT, AST, GGT, Serum bilirubin, total proteins & Alkaline Phosphatase. Changes in Lipid profile.

Changes in HbA1C.

Change in BMI and waist circumference.

Change in domain of Agni questionnaire.

Adverse events and to record the number of participants with any biological intolerability or adverse event during the trial period.

Timelines for Outcome assessment:

The initial visit is screening after preliminary investigations, Patient will be enrolled after obtaining informed consent of each subject. On Baseline visit (visit 1) complete medical history will be obtained. At subsequent visits, assessment tools will be re administered to assess the effect of the therapy and will be compared with the baseline. Laboratory investigations will be done as per study schedule at visit 1, and at the end of the treatment (visit 5).

Participant timeline

Study duration is of two years; however, the enrolment period is of 9 months and the treatment duration will be 3 months. Including the follow up visits the baseline visit will be the day of enrolment then follow up visits at 30th, 60th, and 90th day. Refer table no 1 for timelines.

Sample size

On the basis of change in the values of fatty liver index, assuming that if FLI [8]. is 81.09 with a standard deviation(σ) 15 in control group(Agnideepan & vyadhipratyaneek Chikitsa) and absolute difference (d)10 is assumed in trial group (Vyadhipratyneekchikitsa) with 95% Confidence Level (α = 0.05) and 80% power ,the sample size in this study is calculated as n = (Zα/2+Zβ)2 *2*σ2 / d2, for each group is 36 and total sample size is 72,where Zα/2 is the critical value of the Normal distribution at α/2 (for a confidence level of 95%, α is 0.05 and the critical value is 1.96), Zβ is the critical value of the Normal distribution at β (for a power of 80%, β is 0.2 and the critical value is 0.84), Expecting a dropout rate of 10%, the required sample size is 72+ 7.2 =79.2 (approximately 80). That is 40 in each group.

Table 1: study schedule of enrolment, interventions, and assessments.*

		STUDY PERIOD				
		Allocation	**Post-allocation**			**Close-out**
VISITS	**Screening Visit 1**	**-**	**Baseline Visit 2**	**Treatment Period**		
				Visit 3	**Visit 4**	**Visit**
TIMEPOINT**	**-1 week**		**0 day**	***30th day***	***60th day***	***At the end of 90th day***
ENROLMENT:						
Eligibility screen	✓					
Informed consent	✓					
Allocation		✓				
INTERVENTIONS:						
Intervention Group (Ayush-HR)				◆—	—	—◆
Control group (Placebo)				◆—	—	—◆
ASSESSMENTS:						
Demographics and medical history	✓		✓			
PRIMARY OUTCOME MEASURE ASSESSMENT						
Change in the % of Fatty Liver Index (FLI)	✓					✓
SECONDARY OUTCOME MEASURE ASSESSMENT						
Assessment of ADRs						
Number of participants with reduction in FLI from baseline in Group I and group II			✓	◆—	—	—◆ ✓
Change in domain of Agni questionnaire			✓			✓
SF-36 Health Survey Questionnaire			✓			✓
ASSESSMENT OF SAFETY PARAMETERS						
Routine examination	✓					✓
Bio-chemical Investigation	✓					✓
OTHER PARAMETERS						
Concomitant Medication				✓	✓	✓
Rescue Medication				✓	✓	✓
Assessment of drug compliance				✓	✓	✓
Issue of Trial drugs			✓	✓	✓	

Recruitment

Participants will be selected as the selection criteria from the Outpatient department of the study canter. Radiologist and gastroenterologist of nearby hospitals would be contacted for referring the NAFL patients to CARI New Delhi, Other treating physicians at OPD of CARI would also be requested to refer the case. Other than this through outreach research activities of the institute if anybody have the history will also be screened.

Methods: Assignment of interventions (for controlled trials):

The allocation sequence will be done by the biostatician at CCRAS, the participants wille enrolled by the undersigned and medicine will also be dispensed by the scholar.

Blinding (masking): It is an open label study and no blinding will be done under this project.

Data collection, management, and analysis methods

The study participant's record will be collected in preapproved Case Report Forms as well as Electronic version inxls file. The personal information of all the enrolled participants will be kept confidential.

The Review committees or departmental Research committee at DMIMS Wardha, Nagpur and CCRAS statistical unit may assess the raw data and analysis report. The analysis will be done at CCRAS New Delhi.

Statistical Analysis

The data collected would be imported in MS-excel for statistical analysis by using STATA 16.1. Univariate and multivariate analysis of the data will be done by using STATA 16.1. The descriptive data will be represented as number (%), while the continuous data will be reported as mean (SD). The descriptive data will be compared using chi-square test. The continuous data will be checked for normality and will be compared using parametric tests if it follows normal distribution / non-parametric tests if it does not meet the assumption of normality Please refer Figure no 1 for study flow chart.

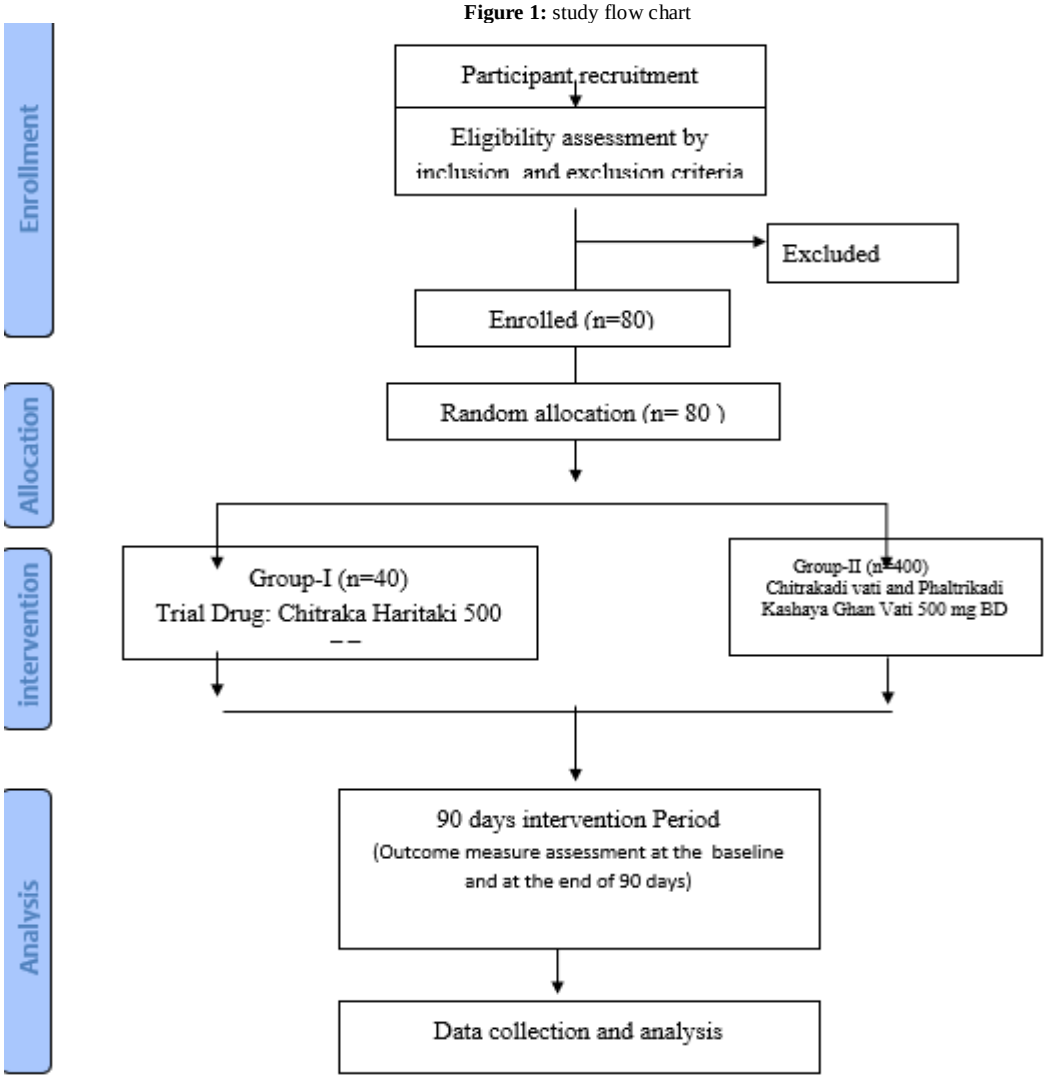
Protocol Variation

Study will be conducted per protocol. No deviation will be made in the protocol except only in that case if it became necessary to relieve an immediate risk to the trial patients. Accordingly, if any amendment required in the protocol will be reported to the IEC.

Adverse Event or Adverse Drug Reaction (AE/ADR)

Documentation of Adverse Events/Adverse Drug Reactions if any, will be recorded in the CRF along with the relatedness, severity, outcome and management done.

Figure 1: study flow chart



Ethics and dissemination

Ethics committee at Mahatma Gandhi Gov. Ayurvedic College Wardha and CARI New Delhi had approved this project. The study outcome after completion of the study will be published in terms of research article as well as thesis document.

Expected Outcomes/Results

The concept of Agni correction at both the levels (jataragni and dhatvagni) may showcase the pathway to intervene the disease at early stage i.e. fatty infiltration accordingly the liver disease burden may be reduced.

DISCUSSION

According to Ayurveda Agni-Vikruti plays important role in manifestation of gastro-intestinal disorders. This study aims to hinder the disease pathogenesis in NAFLD by correction of Agni (Agnideepan) at both the lavelsjatharagni (digestive)as well as bhutagni (metabolic) Therefore this study would also explore the effectiveness of Ayurveda intervention in the management of NAFLD through two different approaches, i.e., Disease specific approach to precisely correct Raktavaha Srotodushti with Yakrt involvement and general approach aimed at correction of metabolism which would prove the role of multiple targets in the disease and its management depending upon the patient specific aspects.

A Pre-emptive preventive regimen in the form of Agni deepana (at the level of jathara) and Vyadhipratyneekchikitsa (disease specific approach at the level of bhutagni), if proven, to be effective will highlight the role of Agni and the impact of impaired Agni in metabolism and onset of future complications.

Acknowledgment

The study is conducted in collaboration CARI- CCRAS AYUSH Ministry, Govt. of India. The authors are thankful to DMIMS Wardha and Council for support and approval to conduct this study.

Summary Box

According to Ayurveda *Agni-Vikruti* plays important role in manifestation of gastro-intestinal disorders. This study aims to hinder the disease pathogenesis in NAFLD by correction of Agni (Agniepana) at both the lavelsjatharagni as well as bhutagni therefore this study will provide evidence for role of Agni Deepana Chikitsa along with vyadhipratyaneek Chikitsa, not only in NAFLD but also for general prophylaxis against any metabolic disorder.

The study would also pinpoint the efficacy of Phalatrikadikwatha which is a convenient, affordable and effective intervention to hinder the progress of disease and also in restoring the normal echo texture of liver.

This study will give evidence for comparative effectiveness of both the therapies with vyadhipratyaneek Chikitsa only so that a standard treatment protocol may be developed considering both the aspect.

Conflict of interest: None
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REFERENCES

1. Younossi, Zubair M, Koenig, et al, 2016. Global epidemiology of nonalcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 64(1), Pages 73-84. Doi: 10.1002/hep.28431.

2. Zobair M Younossi , Aaron B Koenig ,Dinan Abdelatif, et al, Global epidemiology of nonalcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016 64(1), Pages 73-84. Doi: 10.1002/hep.28431.

3. Giorgio Bedogni , Stefano Bellentani, Lucia Miglioli et al, 2006. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol. 6, Doi: 10.1186/1471-230X-6-33

4. Bhavamishra, 2003, Bhavaprakasha with Vidyotini Hindi Commentary, Madhyama Khanda, 3rd Edition, Chaukhamba Sanskrit Series Office, Varanasi, Chapter 41, Verse 17-18, Pages. 417-418.

5. Ayurvedic Pharmacopia of India (API), 2005, PART II VOL III, Pages 107.

6. Ayurvedic formulary of India (AFI) 200, PART III, 4:19, Pages 89.

7. Nirmal Kumar, Anil Kumar Singh, 2013. Phalatrikadi Kvatha - An Ayurvedic Hepatoprotective Drug. International journal of research in pharmacy and chemistry. 3, Pages 591-594.

8. Columpsi PI, Maiocchi L2, et al, 2019, fatty liver index is a sensitive and specific marker of nonalcoholic fatty liver disease measured by transient elastography in a cohort of HIV mono-infected patients. Gastroint Hepatol Dig Dis, Doi: 10.33425/2639-9334.1031