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AN OPEN-LABEL RANDOMIZED CONTROL TRIAL TO COMPARE THE EFFICACY OF *VIRECHANA&GOMUTRA-HARITAKI* VERSUS URSODEOXYCHOLIC ACID (UDCA) ON NAFLD FIBROSIS SCORE AMONG NAFLD PATIENTS

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ABSTRACT

The prevalence of NAFLD is persistently escalating (15% in 2005 to 25% in 2010). The current outbreak in chronic liver disease is linked to the load of Nonalcoholic fatty liver disease (NAFLD).According to Ayurvedic perspective, NAFLD may be recognized as *Yakṛuta Rog* (~liver disease). *Yakrut-dalaudar* is comprehensive term explained in Ayurveda where the expansion in dimension of Liver (*Yakruta- vrudhi*). So, in this study we have taken *Virechana*followed by *Gomutraharitaki*. *Virechana Karma* (purgation therapy) is indeedsuitable*ShodhanKarm(*~purificatory procedure*)* for the liver disorders and recommanded best treatment for *Pittaja and RaktajaRoga.* Aim of the trial is to evaluate the efficacy of *Virechan* followed by *Gomutra-haritaki* in NAFLD and objective is to evaluate the efficacy of *Virechana* followed by *Gomutra-haritaki* on NFS in NAFLD.Diagnosed patients with NAFLD will be enrolled in 02 groups having sample Size of 78 (39 each group)

Cases of either sex between age 18 to 60 years, NAFLD confirmed by NFS score with or without having symptoms like fatigue, mild discomfort in the upper quadrant of abdomen etc, NAFLDpatients who are refractive to standard drugs of treatment, willing and able to participate in study and given written informed consent, *yogya* for *Virechana*will be included.

Excessive utilization of alcohol in less than 2 years prior to first check up. Or alcohol intake more than 20g per day for female and less than 30 g per day for males, Uncontrolled systemic disease or medically unstable and

major psychological disorders, use of drugs associated with NAFLD within 3 months, taking part in any other medicinal scientific research previously in 3 months, as well asengagement in any other NAFLD clinical trials, pregnant/lactating woman (involving positive pregnancy test at the first assessment/check up), Any dysfunction of liver besides NAFLD such as viral infection induced hepatitis, ascites, portal hypertension, Hepatic cell carcinoma, Auto- immune hepatitis, Primary biliary cirrhosis, Wilsons disease, and liver transplantation or any other conditions interfering with the result of the treatment Alcoholic fatty liver disease patient &*Virechanaayogya*will be under exclusion criteria.

In Group-I,*Virechana*via*Trivritawaleha*will be given followed by *Gomuta-Hritaki*will be given orally as *Samana* with *Anupana* of *ushnodaka* with 2 tablets two times a day after taking mealfor 30 days. In **Group-II**, ursodeoxycholic acid (UDCA) will be given 300 mg/day. Total Duration of Treatment will be 60days

Total time period of the trial will be of 02 months in which regular check-ups of the registeredcaseswill be done successive 30 days for successive 2 months.

Primary outcome will be improvement in NFS (Age, Hyperglycaemia, BMI, Albumin, PLT Count, AST / ALT ratio) along with changes in clinical presentations (relief of the following symptoms like Fatigue, indigestion, epigastric discomfort, pain abdomen, diarrhea, constipation,) at baseline, 60th day and 120th day

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a morbid state that encompasses a broad extent of liver impairment. NAFLD, especially its histological constellation nonalcoholic steatohepatitis (NASH), can latently advance to liver impairment ranges from simple steatosis to steatohepatitis, complex liver disease like cirrhosis and hepatic cell carcinoma. NAFLD is persistently escalating and increased from 15% -25% in five years i.e. from 2005-2010. The current outbreak in chronic liver disease is linked to the load of NAFLD.

Worldwide prevalence of NAFLD is recently evaluated which come about 24%.[1]The prevalence of NAFLD in India is about 9% to 32%.[2]

NAFLD is possessed by metabolic syndrome(Met-S) and is analogous with increased weight, DM-II, hypertension & dyslipidemia that exists entirely as an endanger component for cardiovascular diseases (CVDs). Obesity and insulin resistance induce chronic inflammation; modify lipid digestion alongwitha pre-carcinogenic condition that stimulate HCC occurrence.[3]Additionally, above 90% of critically obese cases go through bariatric surgery posses NAFLD. Other than this, liver transplant recommendations because of NAFLD is increasing after chronic hepatitis C.Usual risk constituent identified linking NAFLD with CVDs, cardiac-assiciated dyingparticularly prime reason of end of life for NAFLD cases.[4]

The existing treatment alternatives for NAFLD incorporate weight loss, dietary and lifestyle refinement, use of insulin sensitizing, and lipid lowering drugs[5]. Moreover, collaboration of these techniques have also been endeoured for management of NASH [6,7]. At present; there are no definite medicaments for this context.

An often suggested drug in the therapy of NAFLD is Ursodeoxycholic acid (UDCA)[8], which take action via immunomodulatory and anti-apoptotic attributes by its interplay with the glucocorticoid nuclear receptor at the hepatocyte level. However, for prolonged duration with high dose of administration of drug has shown relief liver[9]

The utility of Vitamin C and Vitamin E combination for their antioxidant effect in comparison to UDCA even though the dissimilarity was not significant. There was no change in USG grades between the two groups.[10] Also due to Vitamin E, prostate enlargement in males has increased.

According to Ayurvedic perspective, NAFLD may be recognized as *Yakṛuta Rog* (~liver disease).*Yakritaudara*[11] is comprehensive terminology in Ayurveda where the expansion in dimension of Liver (*Yakrutavruddhi*). Whenever in that palce, shoot up of *Kaphadosa* give on to extension in dimension of Liver, afterwards*KaphaYakrutadaludara*arises. Subsequently it increase the *Meda* interior to the *Yakruta* open on to *Medaja Yakritdalludara*[12]

Origin of research problem –

Even Ayurveda medication in NAFLD is indecisive[13,14], and restrained to case studies[15,16,17] and literature review [18,19] . At par best of our knowledge, no clinical trial except single case study on *Panchkarmatherapy(~Virechana*) has been documented till now in NAFLD.

Till date, *Virechana*is beingconsidered for their probableeffectivecapability in various clinical trials as in avertinggenesis and advancement of dyslipidemia,[20,21] weight reducing[22,23,24], hepatoprotective actions [25,26] antioxidant effects, anti-diabetogenic effect[27-30], anti-hypertensive effects[31,32], Met S and insulin resistance in experimental models[33]

Moreover, *GomutraHaritaki* is a known for *Yakrit vikara*[34] by *Acharyas*. Also a medicine having lipid balancer effect[35-37], antiobesity[38], Liver diseases(~viral hepatitis) [39], *Bahupitta Kamala (*Jaundice)[40] anti-fibroidal/ tumour property[41,42.]

Nonalcoholic fatty liver disease is accounting as *Yakritvikaras* takes place due to *Atisantarpana* (over nutrition). NAFLD is not equivalent to any ailment in Ayurveda, but we scrutinize it as *SantarpanajanyaVyadhi* (disease generated by over nourishment) because similarity in the *Nidana* (etiology) and *Samprapti* (pathogenesis). Hence treatment planned includes *Langhana, Pachana, Deepana, MriduVirechana/ classical Virechana*. Also *Virechana Karma* (purgation therapy) is indeed suitable*ShodhanaKarma*(~purificatory procedure) for the liver disorders[43] and recommended best treatment for *Pitta and Rakta Rog.*

So, in this study we have taken *Virechana* followed by *Gomutraharitaki*. We presume that in the light of available scientific references and existing traditional usage, Ayurvedic regime would be effective in the management of NAFLD conducted to regulate liver affairsin addition to the depletion of insulin resistance. The

current clinical trial was henceoutlined to accreditpresent hypothesis with the attempt to look through a more favoured treatment having better cost-effectiveness for cases with NAFLD.

Research question-

Is there a difference in efficacy of *Virechana&Gomutra-haritaki* versus ursodeoxycholic acid (UDCA) in NAFLD?

HYPOTHESIS:

Null Hypothesis [H0]: *Virechana* followed by *GomutraHaritaki* is equally effective in comparison to UDCA in the reversal of NAFLD.

Alternative Hypothesis [H1]: *Virechana* followed by *GomutraHaritaki* is more effective in comparison to UDCA in the reversal of NAFLD.

REVIEW OF LITERATURE:

- Efficacy and safety of UDCA on fatigued patients with increased liver function tests and fatty liver: a multi-centre, randomised, double-blinded, placebo-controlled trial B. Oh, W. S. Choi, S. B. Park, B. Cho, Y. J. Yang, E. S. Lee, J. H. Lee in 2016.
- Effect of combined therapy with alpha-lipoic and ursodeoxycolic acid on NAFLD: double-blind, randomized clinical trial, VGianturco, GTroisi, A Bellomo, SBernardini, E D'Ottavio,et al in 2013.
- Efficacy of UDCA in NAFLD: An updated meta-analysis of randomized controlled trials W Zhang, YTang, J Huang , H Hu in 2020
- Efficacy of in (ald induced) - a case study NityaVirechanaUdaraNandkishor P. Umale, Swati Tikale in 2020
- Effect of Patol-katurohinyaadikwatha in kaphayakrutadaludar (NAFLD): a case study- AK Panda, JHazra in 2020.
- Effect of herbomineral compounds and *pathya(*Ayurvedic do's & don'ts) in managing *YakṛutaRoga* by P Singhal , T Nesari , GS Gupta in 2015
- Ayurveda Management of Liver Diseases -Dr. AK Panda in 2020.
- Multiherbal Regimen of Ayurveda Medicine in Hepatic Cirrhosis Complicated by Ascites: Nonrandomized, Uncontrolled, Single Group, Open-Label Observational Clinical Study by Manish V. Patel, Kalapi B. Patel, Shivenarain Gupta, Andreas Michalsen in 2015.
- Ayurvedic Intervention for Hepatobiliary Disorders: Current Scenario and Future Prospect by AK Panda, GC Bhuyan and MM Rao in 2017.
- Non Alcoholic Fatty Liver Disease- An Ayurvedic Pragmatic Approach with Its Management. International Journal of Ayurvedic and Herbal Medicine. E., Remya. (2018).

- Herbal Medicines for the Treatment of Nonalcoholic Steatohepatitis: Current Scenario and Future Prospects- RavirajsinhJadeja, Ranjitsinh V. Devkar, and Srinivas Nammi, in 2014.
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- Ayurvedic management of cirrhosis with complication: case studies by Panda A in 2017.
- Effects of Virechan in NAFLD- case study, S Sushanta in 2015
- Effect of Virechan Karmon Fructose-Induced Metabolic Syndrome by A Chaturvedi et al. in 2015
- Clinical evaluation of NityaVirechana in Hepatocellular Jaundice -Case Study. N. Milind &Parwe, Shweta. (2020).

AIM

Evaluation of the efficacy of *Virechan* followed by *Gomutra-haritaki* in NAFLD patients

OBJECTIVES:

Primary Objective

Evaluate the efficacy of *Virechan*followed by *Gomutra-haritaki* on NFS in NAFLD

Secondary Objective

• To evaluate the safety and efficacy of Ayurvedictherapy and panchkarma therapy in NAFLD.

METHODOLOGY-

Study design-

The research will be executed in three stages.

1) CONCEPTUAL STUDY:

This study will consist of evaluate assessment of correspondingtexts in Ayurvedic classics, earlierstidues&variouscontemporary medical textbooks & journals; with respect to NAFLD, *Yakritdalodar, Virechana, Gomuta-hritaki.*

2) PHARMACOGNOSTICAL AND PHARMACEUTICAL ANALYSIS:

Pharmacognostical analysis of all raw drugs used in trial and Pharmaceutical analysis of prepared drugs will be done at Pharmacognostical and Pharmaceutical laboratory of SKAU (Kurukshetra).

3) CLINICAL STUDY:

This research will be executed in the form of detailed history, physical and systemic examination and assessment of the subjects by preparing a special proforma including all the sign &symptoms of NAFLD symptoms. Standard Operative Procedure (SOP) for *Virechana*will be followed.

Research design-

- Type of trial- Interventional
- Study Design: Human Study design Randomized control trial
- Health type – NAFLD Patients
- Purpose -Treatment
- Timing -Prospective
- Masking/Blinding - Open Label
- Method of Randomization - Computer generated Random Sequence
- No. of groups- 2
- Sample Size – 78 (39 each group)- methods
- Allocation- sequentially numbered opaque envelop
- Phase of trial - 3
- Estimated total duration of trial - 4 months

Diagnostic criteria- Already diagnosed patients with NAFLD

Inclusion criteria –

- Cases of all sex having age 18 - 60 years
- NAFLD confirmed by NFS score with or without having symptoms like fatigue, mild discomfort in the upper quadrant of abdomen etc.
- NAFLD patients who are refractive to standard drugs of treatment.
- Consenting to take part in trial and given written informed consent.
- *Yogya* for *Virechana*

Exclusion criteria-

- Excessive utilization of alcohol in less than 2 years prior to first check up. Or alcohol intake more than 20g per day for female and less than 30 g per day for males
- Uncontrolled systemic disease or medically unstable and major psychological disorders*
- Use of drugs associated with NAFLD within 3 months,**

Taking part in any other medicinal scientific research previously in 3 months, as well as enrollment in any other NAFLD clinical trials.

- Pregnant/lactating woman (involving positive pregnancy test at the first assessment)
- Any dysfunction of liver besides NAFLDsuch as viral infection induced hepatitis causing parenchymal ailments, ascites, portal hypertension, Hepato-cellular carcinoma, Auto- immune hepatitis, Primary biliary cirrhosis, Wilsons disease, and liver transplantation or any other conditions interfering with the result of the treatment Alcoholic fatty liver disease patient
- *Virechanaayogya*

STUDY SETTING

Shri Krishna Government Ayurvedic College and Hospital, *Kurukshetra*. Special camps at various places will be arranged time to time.

PRIMARY OUTCOME:

1. Improvement in NFS score (Age, Hyperglycaemia, BMI, PLT Count, Albumin, AST/ALT) along with changes in clinical presentations (relief of the following symptoms like Fatigue, indigestion, epigastric discomfort, pain abdomen, diarrhea, constipation,) at baseline, 60th day and 120th day.

SECONDARY OUTCOME

1. Overall improvement in quality of life at baseline and 30th day, 60th day, 90th day and 120th day

CRITERIA OF ASSESSMENT/OUTCOME MEASURES

Parameter	**0 day**	**30th day**	**60th day**	**120th day**
NAFLD Fibrosis score	✓		✓	✓
BMI	✓	✓	✓	✓
GSRS	✓	✓	✓	✓
FSS VAS	✓	✓	✓	✓

NAFLD symptoms will be evaluated using Gastrointestinal Symptom Rating Scale (GSRS) & For Fatigue – VAS, FSS Score

Anthropometric Assessment: BMI

Biochemical Parameter Assessment Tests: Serum AST, serum ALT levels, serum triglycerides, fasting blood sugar levels, Ferritin, Platelet count, Albumin.

Radiological: USG abdomen

(Scoring system attached in Annexure)

INTERVENTION AND COMPARATOR

Intervention Arm (Group-I):

After proper *Deepana Pachana* with *Chitrakaadivati, Snehpana* with *Shatpalaghrit, Virechana* with *Trivritawaleha* will be administered followed by *Gomuta-Hritaki*will be given orally as *Samana* with *Anupana* of *ushnodaka* having dosage of two tablets two times in a day after taking foodfor 30 days.

Comparator Arm (Group-II)

In this group, ursodeoxycholic will be given 300 miligram per day.

PROCEDURES SHEDULE IN GROUP A

PROCEDURE DRUG & DOSE DURATION

Ayurvedic examination (*Kostha, agni, prakriti, mala,mutra and twak*), Vital examination (Blood pressure, Pulse rate, body Temperature etc.) & systemic examination (lungs, heart, abdomen, skin) will be examined methodically under inspection, palpation, percussion and auscultation methods. After checking the fitness of patient for *Virechana,* procedure will carried out.

Snehpana - Shatpala ghrit[44] as per *Agni &Kostha* 3-7 Days

SarvangaAbhyanga- With*TilaTaila* for 40 minutes per day in morning hours upto three Days,

BashpaSarvangSwedana – with *DashmoolaKwath*till the appearance of sweat in on forehead

Virechana - Trivritawaleha(as per *Kostha& Agni*)

SamsarjanaKrama -Plan (as per *Shuddhi*) - 3 to 7 Days

Break Day after *Samsarjan* - 10 Days

*Gomuta-Hritaki*will be given orally as *Samana* with *Anupana* of *ushnodaka*in dosage of 2 tablets twice a day after mealfor 30 days

Total Duration of Treatment 60Days

Follow-ups: Time period trial will be2 months in which consistentcheck-ups of the enrolled patients will be done succeeding 30 days for successive 02 months

PROCEDURES SHEDULE IN GROUP-B

PROCEDURE DRUG & DOSE DURATION

UDCA will be given at a dose of 300 mg/day after meal.

Total Duration of Treatment: 60days

Follow up: period trial will be 2 months in which consistent check-ups of the enrolled patients will be done succeeding 30 days for successive 02 months

RANDOMISATION

The subjectsintendedto randomize in two trial arms in 1:1 proportion.

BLINDING (MASKING)

The trial is open-label design. Still, blinding of outcome assessor will be done with respect to the trialarm allocation to the candidates.

SAMPLE SIZE

The sample size for the study is calculated assuming improvement in NFS Score with standard deviation of 10.49 based on the results of the previous studies, with 95% Confidence Level ($\alpha = 0.05$) and 80% power. The number of cases to be registered in the trial in both groups should be 39 separately. On that account, a sum of 78 cases will be registered in the trial.

Withdrawal Criteria: Participant not inclined to persue or non-conformist (less than 80% conformity) with the trial plan/method; participant results in life risking difficulties or additional critical sickness owing to other pathology that be in need of emergency treatment; Adverse effect[#]/ Adverse drug reaction [##]demanding hospital admission. Judgement to quit a case from the study will have to be informed to the IEC.

Other Medications like Concomitant/ Rescue: Participants enrolled for the study will be directed to avert the utilization of additional medications other than registered disease. If participant sense something abnormality /signs than come to investigators. The investigator will document any medication and canadvisefor relieving their complaints. For controlling of emergency situation, utilization of rescue medication will be authorizedin accordance of the discrimination of the Investigators. Whole scenario will have to be recorded in the Case proforma.

Data management:

Statistical methods:

Qualitative data in research work will be shown in number &/ percentage. Quantitative data following normal distribution will be shown as mean (SD), and data without normal distribution will be presented as median (min-max). Paired t-test for within group comparison and independent sample t-test for between group

comparison will be used in case of Parametric data. In case of non-parametric data, Wilcoxon signed rank test for within group comparison and Mann-Whitney test for between group analysis will be used.

Data Monitoring: ¼th of total cases had finished of their trial period thanan Interim analysiscan be done as needed.

Ethics Approval: After receiving approval by the institutional Ethics committees, trial will be implemented.

During the trial, principles of Declaration of Helsinki and the ICMR's National Ethical Guidelines for Research on Human Participants will be followed.

Protocol Implementation:

The research will be carried out in conformity with the protocol. If condition arrives that forces one for modifications, involving changes to interventions, assessments, data assemblage and technique of analysis than it will be informed to the IEC at the earliest with justification.

Consent: At first visit of participant, informed written consent/permission will be received by the research investigators. Subjects prospectively explained about the details of the study and an informed consent according to Schedule-Y (Amendment 20th Jan. 2005) will be obtained before recruiting the subjects for the study

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