

A Cross Over Trial Evaluating Combined Effect of Ruksha Virechana, Lashuna Erandadi Kashaya and Patolamooladi Kashaya in Diagnosed Patients of Non-Alcoholic Steatohepatitis

Shirvadkar Divyashree M¹, Dr. Prashanth A S²

¹Final Year MD Scholar, ²Principal, Head and Professor

Department of Kayachikitsa,

Ayurveda Mahavidyalaya and hospital Hubli, Karnataka, India

Abstract:- The change in living habits due to increasing popularity of fast foods, sedentary lifestyle have given rise to *lifestyle disorders* and Non Alcoholic Steatohepatitis is one among them. *Non Alcoholic Steatohepatitis* (NASH) is a spectrum of Non Alcoholic Fatty Liver Disease (NAFLD) characterized by the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis. There is no direct reference to NASH in Ayurvedic literature but based on the etiopathogenesis, signs and symptoms it can be correlated to *Yakritodara*. NASH has no FDA approved therapeutics, so, it is need of the hour to search an effective hepatoprotective remedy from Ayurvedic treasure of therapeutics. Hence, the present study was designed as cross over single blind clinical study with the objectives of evaluating the combined efficacy of *Amapachana, Ruksha virechana* and *Shamanoushadhi* with *Lashuna Erandadi Kashaya* and *Patolamooladi Kashaya* in the management of NASH. Overall study showed marked improvement in 60% of cases and Moderate improvement in 26.66%. Hence, it can be concluded that the combined effect of therapy with *Amapachana, Ruksha virechana* and *Shamanoushadhis (Lashuna Erandadi Kashaya and Patolamooladi Kashaya)* has shown a significant role in relieving the signs and symptoms of subjects diagnosed with Non Alcoholic Steatohepatitis.

Keywords:- *Lifestyle disorders, NASH, Yakritodara, Virechana, Lashuna Erandadi Kashaya, Patolamooladi Kashaya.*

I. INTRODUCTION

Ayurveda is an eternal science of healthy living treasures which deals with physical, psychological and spiritual well-being of the human being and covers all the aspects of human life. The secret of good health is optimum metabolism. Due to the advanced technology, busy schedule and sedentary lifestyle, there is increased popularity of fast foods leading to the impairment of metabolism in an individual making him prone to a series of disorders called as "*lifestyle disorders*".

Liver is an organ of the human body that performs an array of functions that help support metabolism of carbohydrates, proteins, fats; immunity, digestion, detoxification, vitamin storage among other functions. It is intertwined with nearly every system in the body; hence, it is prone to a variety of pathologies.

The term "Non Alcoholic Steatohepatitis" (NASH) was first coined by Dr. Ludwig et al in 1980 to describe a unique entity characterized by fatty changes with lobular hepatitis.^[1] "Non-Alcoholic Steatohepatitis" (NASH) represents a part of a wide spectrum of Non-Alcoholic Fatty Liver Disease (NAFLD), which ranges from simple steatosis and steato-hepatitis to advanced Fibrosis and Cirrhosis.^[2] The occurrence of Fatty Liver in Type 2 Diabetics, Obese and Hypertriglyceridemics is exceedingly high. Also, the risk of severe Liver Disease goes up with increasing features of "Metabolic Syndrome".^[3] Epidemiological studies suggest the prevalence of NAFLD is around 9% to 32% of general population in India with a higher prevalence in those with Obesity and Diabetes.^[4]

There is no direct reference available in Ayurvedic classics correlating to Non Alcoholic Steatohepatitis. NASH can be considered as a *Santarpanjanya Vyadhi* and can be correlated to *Yakritodara*.

Liver is compared with *Yakrit* in Ayurvedic classics. *Yakrit* is derived from the *Matruja Bhava*^[5] and is the *Mulasthan* of *Raktavaha Srotas*^[6] which transforms *Rasa Dhatu* to *Rakta Dhatu* and plays an important role in *Dhatu Parinama*. *Acharya Bhavamishra* was the first to introduce the term "*Yakritvikara*" with its classification in his treatise *Bhavaprakasha*.^[7]

In *Charaka Samhita*, a reference is available regarding *Yakritodara* in *Ashtodariya Adhyaya* and *Udara Chikitsa Adhyaya* enumerating 8 types of *Udara Roga* and the *nidana, samprapti, lakshana* and *chikitsa* of *Yakritodara* are similar to that of *Pleehodara*. As per the Ayurvedic concept, the consumption of *Pitta-Kaphavardhaka -Vidahi* and *Abhishyandi Ahara* and *Vihara* are responsible for the *Dushti* of *Annavaha, Udakavaha, Rasavaha, Raktavaha, Medovaha* and *Pureeshavaha Srotas*. *Ajirna, Sthoulya* and

Prameha acts as *Nidanarthakara Rogas* which may result in the manifestation of *Yakritodara*.

Initial pathology lies at *Agnivikruti* which leads to the formation of *Apakva Anna Rasa* which in turn leads to *Kapha Dosha Dushti* and unequal formation and deposition of *Meda* in *Yakrit*. This condition is called as Fatty Liver. Vitiating *Kapha* and *Meda* results in *Sroto avrodha* which provokes *Vata*. Vitiating *Vata* again results in *Agnivikruti* and this cycle repeats. When *Pitta* gets involved in the pathogenesis, hepatocytes have inflammatory changes and the disease progresses to the next stage i.e. NASH. When *Vata* gets involved, Fibrosis occurs and the condition may progress to its drastic end stages Cirrhosis, Ascites, Hepato cellular Carcinoma and also pave way to other metabolic complications. Major factors responsible for the etiopathogenesis of NASH include vitiation of *Samanavayu*, *Apanavayu*, *Pachakapitta*, *Ranjakapitta*, *Kledaka Kapha*, *Rasa*, *Rakta*, *Medo Dhatu* and *Pureesha*. It will manifest symptoms like *Dourbalya*, *Arochaka*, *Avipaka*, *Mala-Mutragraha*, *Angamarda*, *Chardi* etc.

The pathogenesis of NASH is explained by-‘Two Hit Hypothesis’. The ‘first hit’ results in steatosis (fatty liver) which is only complicated by inflammation. If a ‘second hit’ occurs, Leptin, which is an appetite reducer and a fibrogenic in vitro, is probably then needed to cause hepatic fibrosis. The components of first hit includes the release of free fatty acids from central adipose tissue, along with adipokines, drain into the portal vein as well as causing insulin resistance. These processes result in reduced hepatic fatty acid oxidation and increased fatty acid synthesis.^[8]

Virechana is the most suitable *Shodhana Karma* for *Pittaja* and *Raktaja Vikara* and *Yakrit* being the *Moolasthan* of *Raktavaha Srotas*, *Virechana* is the *Sreshtha Chikitsa*. It is indicated in *Bahudoshavastha* and *Sroto avrodha*. *Agnideepana*, *Rookshana* and *Virechana* should be administered.

NASH has no FDA (Food & Drug Administrative agency) approved therapeutics.^[9] In spite of the tremendous advances made in modern medicine, still there is need of effective and safe hepatoprotective medicines. Hence, in this study, an effort was made to assess the efficacy of *Amapachana* with *Ajamodadi Churna*^[10] and *Ruksha Virechana* with *Dashamoola Panchakoladi Kashaya*^[11] in both the Groups, followed by *Shamanoushadhi –Lashuna Erandadi Kashaya*^[12] in Group A and *Patolamooladi Kashaya*^[13] in Group B.

❖ Objectives

➤ Aim of the Study:

To formulate effective easily available formulations in the management of Non alcoholic Steatohepatitis (NASH) aiming at good health maintenance and prevention of complications.

➤ Objectives of the Study:

- To assess the efficacy of *Ruksha Virechana* in the subjects of NASH.
- To evaluate and compare the efficacy of *Lashuna Erandadi Kashaya* and *Patolamooladi Kashaya* in NASH.
- To formulate effective easily available formulations in the management of Non-alcoholic Steatohepatitis (NASH) aiming at good health maintenance and prevention of complications.
- To study the concept of Non-alcoholic Steatohepatitis in Ayurveda.

II. MATERIALS AND METHODS

Study Design: Cross over single blind clinical study.

Study Population : A minimum of 20 subjects diagnosed with NASH fulfilling the diagnostic and inclusion criteria were selected for the study.

➤ Plan of work

The entire study was designed to be conducted in three phases.

● PHASE I

- ✓ Detailed literature review, done extensively using tertiary resources, secondary resources, primary resources.
- ✓ Procure the necessary documentation: Designing of data entry form, informed consent document, patient information sheet.
- ✓ Ethical committee approval: Ethical clearance was obtained from the Institutional Ethics Committee of Ayurveda Mahavidyalaya Hubli.

● PHASE II

- ✓ The sample size was collected which comes under the inclusion and exclusion criteria at the time of enrolment.
- ✓ Data was collected using data entry form after explaining patient information sheet and signing informed consent document.

● PHASE III

- ✓ Reports were analyzed using various statistical tools.
- ✓ Reporting of results and presentation.

➤ Sources of data:

Patient interview and patients case records which contain the patient’s demographics, history, laboratory investigation reports and prescribed drugs.

➤ *Study criteria*

Patients were selected based on the following

❖ *Inclusion Criteria*

- Non-alcoholic individuals, between the age group of 20-60 years, irrespective of either sex.
- Patients with raised Liver Function test (LFT) and Fatty Liver Disease on Abdominal Ultrasonography (Patients with Grade 1 and Grade 2).
- Patients fit for Ruksha virechana.

❖ *Exclusion Criteria*

- History of alcohol abuse.
- Patients with uncontrolled DM/HTN.
- Patients with Grade 3 Fatty Liver on Abdominal Ultrasonography.
- Patients with T.B., HIV, HBsAg, Obstructive jaundice, Viral hepatitis, Drug induced Hepatitis and other systemic disorders.
- Evidence of moderate to severe Ascites, Fibrosis, Cirrhosis, Splenomegaly, Jaundice, Hepatic Encephalopathy, etc.

➤ *Diagnostic criteria*

Diagnosis was entirely based on subjective and objective findings of Non Alcoholic Steatohepatitis and Yakritodara.

➤ *Parameters of the study*

Following subjective and objective criterias were considered for the study.

➤ *Subjective Parameters*

- Loss of appetite
- Nausea
- Vomiting
- Abdominal pain/dull aching pain in the right Hypochondriac region.
- Yellowish discoloration of skin, urine and sclera (IF ANY).

➤ *Objective Parameters*

- Fatty liver on USG gradings.
- Appropriate investigations were done if necessary.

➤ *Assessment Criteria*

Overall assessment was done based on the improvement in Subjective and Objective Parameters before and after treatment which was subjected to Statistical Analysis.

- Marked Relief - Above 75 % Improvement
- Moderate Relief -50 to 75 % Improvement
- Mild Relief -25 to 50 % Improvement
- No Relief - Below 25% Improvement

➤ *Intervention*

A minimum of 20 subjects fulfilling the inclusion criteria were selected for the study in Group A and intervention was carried out. After a proper washout period of 15 days, the same 20 subjects were posted in Group B as the idea of study design was a clinical Cross over study.

Aamapachana	
<i>Ajamodadi Churna</i> - 3-5grams (twice a day) with <i>Ushna Jala</i> before food till <i>Nirama lakshanas</i> were seen.	
Virechana (Ruksha Virechana)	
<i>Dashamoola Panchakoladi Kashaya</i> 30-45ml (As per the <i>koshta</i> and <i>agni bala</i> of the patient)	
Shamanoushadhi	
<i>Lashuna Erandadi Kashaya</i>	<i>Matra</i> - 15 ml (twice a day) <i>Anupana</i> - <i>Ushna Jala</i> Duration - 45 days
Follow up during treatment: Once in 15 days.	
Total duration of the study: 60 days.	

Table 1:- Intervention in Group A

Aamapachana	
<i>Ajamodadi Churna</i> - 3-5grams (twice a day) with <i>Ushna Jala</i> before food till <i>Nirama lakshanas</i> were seen.	
Virechana (Ruksha Virechana)	
<i>Dashamoola Panchakoladi Kashaya</i> 30-45ml (As per the <i>koshta</i> and <i>agni bala</i> of the patient)	
Shamanoushadhi	
<i>Patolamooladi Kashaya</i>	<i>Matra</i> - 15 ml (twice a day) <i>Anupana</i> - <i>Ushna Jala</i> Duration - 45 days
Follow up during treatment: Once in 15 days.	
Total duration of the study: 60 days.	

Table 2:- Intervention in Group b

III. RESULTS

Subjects screened	Withdrawal	Group	Included	Drop out	Completed
28	2	A	26	03	23
		B	23	02	21

Table 3:- Study Chart

➤ *Effect of Therapies*

26 subjects were registered in this clinical trial in Group A with 3 dropouts. So in Group A, 23 subjects completed the first intervention. As per the Cross over study design, after a washout period of 15 days, the same 23 subjects were posted to the second intervention in Group B with 2 dropouts. So, in total 21 subjects completed the study. The cardinal symptoms were considered for statistical analysis and were assessed twice before and after the completion of treatment of 120 days. Along with the symptomatology, the fatty liver gradings on USG were also assessed by comparing the changes before and after treatment.

All the symptoms were scored on self-prepared scale and those scores were analyzed with statistical analyzing software.

Wilcoxon signed rank test was applied to interpret the observations within the group. Mann-Whitney U test was applied to compare the effectiveness in both groups.

Wilcoxon signed-rank test											
Parameter	NEGATIVE RANKS			POSITIVE RANKS			TIES	TOTAL	Z value	P value	REMARKS
	N	MR	SR	N	MR	SR					
Loss of appetite	20	10.50	210.00	0	0.00	0.00	3	23	-4.130	0.0001	HS
Nausea	23	12.00	276.00	0	0.00	0.00	0	23	-4.508	0.0001	HS
Vomiting	11	6.00	66.00	0	0.00	0.00	0	11	-3.207	0.001	S
Dull aching right hypochondriac pain	16	8.50	136.00	0	0.00	0.00	6	22	-3.619	0.0001	HS
Yellowish discolouration	8	4.50	36.00	0	0.00	0.00	7	15	-2.828	0.005	NS

Table 4:- Effect of Therapy on Subjective Parameters of Group A

MR-Mean Rank, SR-Sum of Ranks, HS - Statistically Highly significant, S - Statistically significant, NS- Statistically Not Significant

Wilcoxon signed-rank test											
Parameter	NEGATIVE RANKS			POSITIVE RANKS			TIES	TOTAL	Z value	P value	REMARKS
	N	MR	SR	N	MR	SR					
Loss of appetite	21	11.00	231.00	0	0.00	0.00	0	21	-4.144	0.0001	HS
Nausea	21	11.00	231.00	0	0.00	0.00	0	21	-4.144	0.0001	HS
Vomiting	10	5.50	55.00	0	0.00	0.00	0	10	-2.972	0.003	S
Dull aching right hypochondriac pain	13	7.00	91.00	0	0.00	0.00	1	14	-3.500	0.0001	HS
Yellowish discolouration	12	6.50	78.00	0	0.00	0.00	1	13	-3.646	0.001	S

Table 5:- Effect of Therapy on Subjective Parameters of Group B

MR-Mean Rank, SR-Sum of Ranks, HS - Statistically Highly significant, S - Statistically significant

Wilcoxon signed-rank test											
USG Grading of fatty liver	NEGATIVE RANKS			POSITIVE RANKS			TIES	TOTAL	Z value	P value	REMARKS
	N	MR	SR	N	MR	SR					
Group A	14	7.50	105.00	0	0.00	0.00	9	23	-3.742	0.0001	HS
Group B	21	11.00	231.00	0	0.00	0.00	0	21	-4.583	0.0001	HS

Table 6:- Effect of Therapy on Objective Parameter of Group A & Group B

MR-Mean Rank, SR-Sum of Ranks, HS- Statistically Highly Significant

➤ *Comparison of Effect of Therapy on Subjective Parameter*

Mann Whitney U Test								
Loss of appetite	N	MR	SR	Mann Whitney U Value	Z value	P value	REMARKS	
Group A	23	32.83	755.00	4.000	-6.019	0.0001	HS	
Group B	21	11.19	235.00					

Table 7:- Comparison of Effect of Therapy on Loss of Appetite

MR-Mean Rank, SR-Sum of Ranks, HS - Statistically Highly significant

Mann Whitney U Test							
Nausea	N	MR	SR	Mann Whitney U Value	Z value	P value	REMARKS
Group A	23	29.80	685.50	73.500	-4.571	0.0001	HS
Group B	21	14.50	304.50				

Table 8:- Comparison of Effect of Therapy on Nausea

MR-Mean Rank, SR-Sum of Ranks, HS - Statistically Highly significant

Mann Whitney U Test							
Vomiting	N	MR	SR	Mann Whitney U Value	Z value	P value	REMARKS
Group A	12	12.57	153.00	45.000	-1.662	0.096	NS
Group B	10	10.00	100.00				

Table 9:- Comparison of Effect of Therapy on Vomiting

MR-Mean Rank, SR-Sum of Ranks, NS- Statistically Not Significant.

Mann Whitney U Test							
Dull aching right hypochondriac pain	N	MR	SR	Mann Whitney U Value	Z value	P value	REMARKS
Group A	22	21.77	479.00	82.000	-2.532	0.011	S
Group B	14	13.36	187.00				

Table 10:- Comparison of Effect of Therapy on Dull Aching Pain

MR-Mean Rank, SR-Sum of Ranks, S - Statistically significant

Mann Whitney U Test							
Yellowish discolouration	N	MR	SR	Mann Whitney U Value	Z value	P value	REMARKS
Group A	15	17.03	255.50	59.500	-2.236	0.025	S
Group B	13	11.58	150.50				

Table 11:- Comparison of Effect of Therapy on Yellowish Discolouration

MR-Mean Rank, SR-Sum of Ranks, S - Statistically significant

Mann Whitney U Test							
USG Gradings of fatty liver	N	MR	SR	Mann Whitney U Value	Z value	P value	REMARKS
Group A	23	30.61	704.00	55.000	-4.737	0.0001	HS
Group B	21	13.62	286.00				

Table 12:- Comparison of Effect of Therapy on Objective Parameter

MR-Mean Rank, SR-Sum of Ranks, HS - Statistically Highly significant

Parameter	Mean		Percentage of Relief
	BT	AT	
Loss of appetite	2.0	0.3	85 %
Nausea	1.70	0.20	88.23%
Vomiting	2.3	0.2	91.30%
Dull aching right hypochondriac pain	1.68	0.34	79.76%
Yellowish discolouration of skin,urine and sclera	0.933	0.06	93.56%
USG gradings of fatty liver	1.66	0.366	77.99%

Table 13:- Effect of Therapy on Subjective and Objective Parameters of the Study

Sl. NO	Percentage of Relief	Remarks
1	60%	Moderate relief
2	84.61%	Marked Relief
3	78.50%	Marked Relief
4	72.22%	Moderate relief
5	63.63%	Moderate relief
6	100%	Marked Relief
7	94.11%	Marked Relief
8	89.47	Marked Relief
9	90%	Marked Relief
10	100%	Marked Relief
11	100%	Marked Relief
12	81.25%	Marked Relief
13	90.90%	Marked Relief
14	100%	Marked Relief
15	100%	Marked Relief
16	82.14%	Marked Relief
17	60%	Moderate relief
18	72.72%	Moderate relief
19	91.53%	Marked Relief
20	26.19%	Mild relief
21	100%	Marked Relief

Table 14:- Showing Effect of Therapy on Individual Subjects

Relief	No. of subjects	Percentage	Remarks
Above 75%	15	71.42%	Marked relief
51% to 75%	5	23.80%	Moderate relief
26% to 50%	1	4.76%	Mild relief
Less than 25%	0	0	No relief

Table 15:- Distribution of Subjects According to Overall Assessment of the Result

IV. DISCUSSION

In this study, “*Ajamodadi churna*” was selected for *Amapachana* which has *deepana*, *pachana*, *vata kaphahara* effect and along with it, possesses *vatanulomaka* property. *Virechana* is the most suitable *Shodhana Karma* for *Pittaja* and *Raktaja Vikara*. *Yakrit* is the *Moolasthan* of *Raktavaha*

Srotas and hence, *Virechana* is the *sreshta chikitsa*. *Ruksha Virechana* was adopted in the present study on NASH as it is a *Santarpana janya vyadhi*. If *Snigdha Virechana* is given, then *doshas* will get adhered in the other *Srotas* instead of being expelled out.

Ruksha virechana was administered with *Dashamoola Panchakoladi Kashaya* main ingredients are *Trivrit* and *Danti*. *Trivrit* is one among the *bhedaniya mahakashaya*, *tridosha hara* and has *rechaka* property. *Danti* acts as *deepana*, *pachana*, *sramsani*, *srusthavinmutra*, *rechaka*, *adhobhagahara* and *bhedana*.

The *shamanoushadhi* i.e. *Lashuna Erandadi and Patolamooladi kashaya* acts as *Amapachaka*, *Agni Dipaka*, *Vatakaphahara*, *Mridurechaka*, *Shophahara* and *Shulahara* that helps in disintegrating the pathogenesis of NASH. The *shamanoushadhi*'s are dominant in *Tikta rasa* which has *Raktashodhaka* and *Raktaprasadaka* properties. Because of its *Yakrit Uttejaka karma* and *Pitta saraka* properties, it stimulates liver, reduces the engorgement in liver. Thus, the congestion in liver and parenchyma is subsided. This is essential for *samprapti vighatana* of *kaphaja yakrit roga*. Hence, the above mentioned formulations have *pitta rechaka*, *raktashodhaka*, *yakrituttejaka* properties.

The liver damage becomes irreversible as it progresses to Fibrosis and Cirrhosis, hence steps should be taken to treat the disease at the initial stages and to stop it from progressing to irreversible condition. Hence, it is the need of the hour to search an effective and safe Hepatoprotective ideal remedy from Ayurvedic treasure of therapeutics for the welfare of mankind.

V. CONCLUSION

NASH, a lifestyle disorder, is emerging as the second leading cause for Liver Transplantation worldwide. There is no direct reference of NASH in Ayurvedic classics. The etiopathogenesis of NASH and *Yakritodara* simulate. Hence, we can correlate it with *Yakritodara*. NASH is a *Santarpanajanya vyadhi*. The cross over study design proved that along with the relief of symptoms, there was significant reduction in the grades of fatty liver on USG among the subjects of NASH. Overall study showed marked improvement in 60% of cases and Moderate improvement in 26.66%. Hence, it can be concluded that the combined effect of therapy with *Amapachana*, *Ruksha virechana* and *Shamanoushadhi*'s (*Lashuna Erandadi Kashaya* and *Patolamooladi Kashaya*) has shown a significant role in relieving the signs and symptoms of subjects diagnosed with Non Alcoholic Steatohepatitis.

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