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Original Research Paper

Toxicology

COMPARATIVE CLINICAL STUDY ON BILWADI AGADA (AYURVEDA FORMULA) ON ALCOHOLIC LIVER DISEASE

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ABSTRACT Alcoholic liver disease, a most common cause of cirrhosis and leads from simple steatosis to hepatocellular carcinoma. Toxicity role of the alcohol is ongoing medical challenge but effective intervention is pending. In alcoholic liver diseases, aspartate aminotransferase (AST) levels are <300 U/L and AST/ALT ratio is typically >2 with elevated Alkaline phosphatase and gamma glutamine transferase. Antioxidants are vital factor in repairing body tissues due to poisonous damage. System of Indian medicine is rich source that having number of detoxifying measures, via current randomized clinical study with Bilwadi Agada and Phaltrikadi Kwath Vati, between group comparison showed significant improvements in Symptomatic relief and parameters of liver function test ($p < 0.001$). Within group assessment showed significant ($p < 0.001$) improvement in liver function tests and symptoms of alcholic liver disease.

KEYWORDS : Alcoholic liver disease, Bilwadi Agada, Ayurveda formula, liver damage

INTRODUCTION

Prevention is better than cure is a universal saying and Ayurveda is the highest example for that had giving solution in scientifically and practically. Though the index of education and technology are high in world, disease free survival is decreasing day by day. Therefore, reinstalling better health in spiritually, socially, mentally and physically is quite challengeable in present era with single discipline. Ayurveda incorporates all forms of lifestyle in therapy. Thus yoga, aroma, meditation, gems, amulets, color, astrology, diet, herbs, and surgery etc. are used in a comprehensive manner in treating patients.

Ethanol is naturally present in carbohydrate rich fruits after reaching post-maturity. Ethanol is a water-soluble compound that rapidly crosses cell membranes, resulting in ready equilibration between intra- and extra-cellular concentrations (K. G. Marco CA, 1990) Alcohol metabolism is attained by both oxidative pathways, which either add oxygen or remove hydrogen, and nonoxidative pathways. Liver is the major site of alcohol metabolism, and it is one of the major targets for alcohol-induced organ damage. Ethanol can act as a toxic and create harmful effects to body. Absorption of the alcohol takes part in intestine and go through the liver for metabolism and liver is the most vulnerable organ in alcohol toxicity. Alcohol liver diseases (ALD) are accounting from liver steatosis, steatohepatitis, cirrhosis and hepatocellular carcinoma: among these, alcoholic liver steatosis is the earliest stage and is developed in 90% of heavy drinkers or with chronic ethanol consumption. Liver is vital organ in human and normal liver function is essential in healthy living.

Though the liver is vibrant hepatoprotective drugs are very limited in modern medicine. Nevertheless, in ayurveda number of hepatoprotective formula in text and has to introduce to common medical platform. Bilwadi agada (BA) is ancient formula that described to indication of detoxification due to chemical induce toxicity. The formula consists of 14 ingredients and containing detoxification property.

MATERIAL AND METHODS

The patient attending to Toxicology clinic at outpatient department of the institute were recruited for the study as per the CONSORT statement guidelines. The study was randomized, parallel group comparative clinical trial. The patients were allocated in two intervention groups in 1:1 ratio. Sample size was 15 patients in each group and all the patients (n=30) were randomly divided into two groups: Group A and Group B. Single formula: Group A (n=15) received Phaltrikadi Kwath Vati (PKV) 1g trice a day for 45 days. Combined formula: Group B (n=15), received Bilwadi Agada 1g thrice a day and Phaltrikadi Kwath Vati 1g a day for 45 days. All interventions were administered with normal water after meal. PKV and BA are the formulations from the classical text books of Ayurveda. Preparation of PKV was carried out at Pharmacy at national Institute of Ayurveda Jaipur and Bilwadi Agada (Gutika) was provided by GMP certified Shree Dhootapapeshwar Limited Khetwadi, Mumbai. Duration of intervention was 45 days with follow-up on every 15th day.

Screening was carried out by principal investigators and personally attended with patients meet pre-defined inclusion criteria: both male and female patient with alcohol consuming history more than 2 years. Patients (n=40) meeting the liver steatosis with fatty liver grade I, II and III by USG abdomen were screen and 32 patients were recruited. Recruited patients were educated with the study details and informed consent was obtained. Out comes were evaluated by using chronic liver disease symptom release scale (CLDSRS) and Clinical Nutrition and Simplified and Clinical Nutritional Assessment Questionnaire Score (SCNAQS) and Liver enzymes, (Liver Function test) blood parameters (Complete Blood Count) at pre and post interventions. All the statistical analysis were carried out in SPSS 29.0.2.0 (20) version.

RESULTS

Total patients recruited were 32 and 29 completed the study. Group A 14 patients and 15 patients in Group B. Mean age of the patients was 45.5 years and 97.7 was male. 70% of patients were from urban area of the Rajasthan and 30% from rural area. Middle socio -economic status 42.2 % and 37.7% were completed secondary level education. 62.2% patients had a 10-15 years of alcohol consuming history and 41.9% were grade II fatty liver. All subjective parameters like age, weight, diet pattern and education level and biochemical parameters like SGOT, SGPT, ALP, GGT, total protein and level of bilirubin level, hematological parameters: Hb% RBC, WBC: DC was comparable in both groups at beginning.

On 30th day primary outcomes on CLDSRS and SCNAQS showed significant improvement in both groups. In group A and group B were compared subjective parameters: anorexia ($p=0.01$), weight loss ($p=0.03$), malaise ($p=<0.001$), nausea/vomiting($p=0.12$) and abdominal pain ($p=0.05$) No any difference in body weight in both groups after 30 days. (TABLE-1)

Table -1

Sr no	Parameter	Gp A- PT B- PT+Bi	0day+SD	30thday+SD	Deference day0 & day30	P value	Remark
1	Anorexia	A	3.16±1.43	1.76+1.45	1.4	0.01	S
		B	0.55±1.76	0.1±2.05	0.46	0.015	S
2	Weight loss	A	2.66±0.25	2.66±0.21	00	00	NS
		B	2.66±0.87	2.16±0.2	0.5	0.126	NS
3	Malaise	A	6.22±0.32	0.61±0.05	5.61	<0.001	HS
		B	6.32±0.93	0.57±0.51	5.75	0.01	S
4	Nausea /Vomiting	A	2.30±0.56	0.60±0.91	1.7	0.002	S
		B	1.3±0.23	0.60±0.68	0.7	0.06	NS
5	Abdominal pain	A	4.88±0.23	3.10±0.16	1.78	0.010	S
		B	4.88±0.36	3.78±1.26	1.10	0.03	S

Table- 2

Sr no	Parameter	Gp A- PKV B- PKV +BA	0day+SD	45thday+SD	Deference day0&day30	P value	Remark
1	SGOT	A	138.93±5.94	113.46+5.13	25.46±10.29	<0.001	HS
		B	124.61±7.59	54.6±2.83	69.93±14.4	<0.001	HS
2	SGPT	A	106.26±4.35	89.20±3.35	17.06±9.92	<0.001	HS
		B	111.93±4.57	51.72±3.73	60.27±9.92	<0.001	HS
3	ALP	A	126.13±45.3	105.6±12.28	20.53±15.25	0.012	S
		B	132.06±40.6	82.33±28.1	49.73±15.2	<0.001	HS
4	Total Protein	A	5.70±1.02	5.21±0.84	0.48±0.12	0.002	S
		B	6.32±0.67	6.97±0.68	0.65±0.14	<0.001	HS
5	GGT	A	175.73±11.7	92.53±3.07	83.20±29.2	0.010	S
		B	239.2±28.1	101.3±28.26	137.86±29.7	0.016	S
6	Total Bilirubin	A	0.78±0.31	0.76±0.03	0.15±0.06	0.011	S
		B	0.61±0.54	0.72±0.08	0.144±0.06	<0.001	HS

Assessments of the parameters of liver function test: Aspartate aminotransferase, Alanine aminotransferase, Alkaline phosphatase, Total protein, Gammaglutaminetransferase and total Bilirubin were significantly reduced after 45 days in both groups. Within group comparison both groups were indicated significance reduction and between groups comparison of liver function test group B was showed highly significance reduction than group A with less value in mean, remarkable mean difference and P value <0.001. All haematological parameters such as haemoglobin, total red blood cell and white blood cell count, differential count and platelets count were in normal range after treatment in both groups.

DISCUSSION

The present study showed, Ayurveda formulas (Bilwadi Agada and Phaltrikadi Kawath Vati) had positive role in the management of Alcoholic Liver Disease. In spite these Ayurveda interventions had beneficial out comes in symptoms of chronic liver disease. All the patients were chronic heavy drinkers with liver cell steatosis in abdominal ultra sound scanning and more than 3time elevated level in hepatic enzymes. Patients were newly diagnosed and medicated for 1st time. Patients had shown fatty filtration and found with fatty liver grade I to Grade III. Malise severity was reduced up to mild state and appetite was improved as normal. Liver function test parameters were reduced in both groups other than the total bilirubin. How ever total bilirubin level is in normal values before and after treatment. Both groups hadn't any change in body weight in qualitative assessment as per CANQ scale.

Phaltrikadi Kwath Vati and Bilwadi Agada have number of ingredients that proven hepatoprotective activity. Triphala (TP): Terminalia chebula, Terminalia bellirica and Embilica officinalis is common ingredients in both drug and rich in polyphenols, Vitamin C and flavonoids. TP has proved favorable action on superoxide dismutase and glutathione peroxidase activity and providing hepatoprotection. Further ultrasonic extract of Triphala was most effective, suggesting that hepatoprotection may be related to the larger tannins via activation of Nrf-2signaling (Wei X, 2021). Other than the TP contains of PKV include Andrographis paniculata and Tinospora cordifolia with high amount of antioxidant. Deoxyribose by hydroxyl radical generated from Fe3+-ascorbate-EDTA-H2O2 system was found to be inhibited by Andrographis paniculata extract in pre- clinical studies (Sheeja, 2006) and its aqueous extract has greater antioxidant activity and inhibits the formation of oxygen derived free radicals, including superoxide, hydroxyl radicals, lipid peroxidation, and nitric oxide (Mussard E, 2019).

In Bilwadi Agada contains more ingredients than PKV including Ocimum sanctum, Aegle marmeolos, Valerina jatamansi Piper nigrum, Piper longum and Zingiber officinalis. Bioactive compounds rutin, ellagic acid and kaempferol were found out in Ocimum sanctum leaf extract and has showed significant hepatoprotective activity against the CCl_4 toxicity (Lahon, 2021). Piperine are chemical compound that found in piper and Aegle. marmelos in combination with piperine had showed significant reversal of hepatotoxicity (Rathee D, 2018). Additionally, Aegle marmelos ethanolic fruit pulp extract there has shown significant reduction in the SGPT, SGOT and ALP levels in comparisons to the DMBA in cancer study (Akhouri, 2020). Valeriana jatamansi, has proven hepatoprotective activity and extract of the plant's rhizomes protected liver damage thioacetamide induced hepatotoxicity. The extract lowered SGOT and SGPT and alkaline phosphatase levels, and increased survival rate (Prasad R, 2010) on rates and hepatic injury with liver cirrhosis (Shakir Ali, 2000). BA contain Zingiber officinalis and it is rich in various chemical constituents, including phenolic compounds, terpenes, polysaccharides, lipids, and organic acids. Gingerols and shogaols are compounds in ginger and can provide good health benefits including antioxidant, anti-inflammatory, and anticancer and leading to protection of hepatocytes (Mao QQ, 2019). Liver histopathological examinations confirmed the protective effect against abnormalities (Fahmi A, 2019). Hence BA has number of ingredients having antioxidant, anti- inflammatory and free radical scavengers' activity than PKV.

Review on Bilwadi Agada has mentioned that it is the specific drug of having detoxification effects. Commonly this drug is used as prominent first line drug in several toxic pathological conditions Sarpa damsha (Snake bite), Loota Visha, (insect bite) Visuchika, Ajeerna, (Diarrhea, indigestion) and Gara Visha (chemical poison) in Ayurveda medicine. PKV is indicated to jaundice and disease in liver. Further, in

Ayurveda, the group of disease caused by the improper use of alcohol are known as Madatyaya and it is common and direct term for alcohol intoxication the effects of improper usage of alcohol and its associated health issues. Similarly, alcohol or Madya consider as kind of artificial or chemical poison (Brahmanandtripathi., 1998). BA is the Vishagna (detoxifying) medication which is mentioned to treat chemical poisoning. As well, the hepatotoxicity of ethanol is associated with its metabolism (RKN Priyangika, 2024) through the pathways of cytochrome P450 2E1 (CYP2E1) and alcohol dehydrogenase, which leads to the generation of poisonous acetaldehyde (Roehrs, 2001). Furthermore, the reduced form of nicotinamide adenine dinucleotide (NADH), produced by alcohol dehydrogenase-mediated ethanol metabolism, stimulates the production of fatty acids and inhibits their oxidation, hence promoting steatosis of liver cell (Jen Kuei Peng, 2018).

Both medicines used in this trial are mentioned as hepatoprotective in different ways in Ayurveda text. In modern science all ingredients had been proved for antioxidant, anti-inflammatory (Prasad, 2024), free radical scavenges and reducing blood cholesterol and glucose activity (Ravishankar.K, 2023). Hence the afore said detoxifying and hepatoprotective quality can be formed due to result of these actions. Hence combination of these two drugs were significantly worked on liver cell damage due to alcohol toxicity and had shown satisfactory reduction of hepatic enzymes. Further each and every parameter in liver function test didn't reach value of normal level and 90 days duration study would have given more clarity of the drug action and double- blind large scale clinical trial at multi centric studies with advanced biological assessments can be considered in future.

CONCLUSION

Study demonstrated that Ayurveda interventions with Bilwadi Agada and Phaltrikadi Kwath Vati had a beneficial role in the management of ALD. It showed hepatoprotective activity and symptom relief of chronic liver disease index. Had no adverse effects on haematological parameters noted. Advantages of Ayurveda medicine in both symptomatic and biochemical in hepatotoxicity was remarked.

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Conflict Of Interest: NIL

Study was registered at Indian Clinical Trial Registry under CTRI/2023/0957507.

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