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Full Length Research paper

Efficacy and safety of Livwin (polyherbal formulation) in patients with acute viral hepatitis: A controlled clinical trial

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The study was planned to evaluate the efficacy and safety of Livwin (polyherbal formulation) in acute viral hepatitis. In this study, there were 29 patients in each group, receiving either Livwin or placebo. Livwin capsules contains *Terminalia arjuna* - 100 mg, *Withania somnifera* – 100 mg, *Phyllanthus niruri* - 100 mg, *Berberis aristata* – 50 mg, *Tinospora cordofolia* – 75 mg, *Picrorhiza kurroa* – 50 mg, *Boerhaavia diffusa* – 50 mg. Placebo capsules contains lactose 500 mg. Both drugs were given orally, two capsules 2 times a day for 8 weeks followed by treatment free period of 4 weeks. Recovery of patients assessed by clinical parameters: fever, weakness, icterus and tender, enlarged liver and by biochemical parameters: serum bilirubin, SGOT (Serum glutamate oxaloacetate transaminase), SGPT (Serum glutamate pyruvate transaminase), serum alkaline phosphatase at baseline, 2 weeks, 4 weeks, 8 weeks and 12 weeks. Significant clinical recovery was observed in the form of icterus and weakness with Livwin as compared to placebo at 2 and 4 weeks (P < 0.001). There was significant reduction in mean levels of serum bilirubin, SGOT and SGPT at 2 weeks, 4 weeks, and 8 weeks with Livwin as compared with placebo (P < 0.001). Significant reduction in mean levels of serum alkaline phosphatase with Livwin at 2 weeks (P < 0.01) and 4 weeks (P < 0.05) as compared with placebo. Mean serum bilirubin reduced by 6.72 mg/dl with Livwin and with placebo reduced by 3.64 mg/dl at 2 weeks (P < 0.001). Mean SGOT reduced by 609.11 IU/ L with Livwin and with placebo reduced by 240.34 IU/L at 2 weeks (P < 0.001). Mean SGPT reduced by 920.65 IU/L with Livwin and with placebo reduced by 326.96 IU/L at 2 weeks (P < 0.001). Livwin had shown good efficacy in patients of acute viral hepatitis. Adverse events like epigastric pain and diarrhoea were recorded with Livwin treatment and were not significant as compared to placebo.

Key words: Acute hepatitis, liver function test, *Phyllanthus niruri*, *Tinospora cordofolia.*

INTRODUCTION

Viral hepatitis is a global public health problem that occurs endemically and sporadically throughout the world. There has been a numerous outbreak and epide-mics reported from various parts of India (Park, 2005).

The therapy for viral hepatitis assumes immense importance as death from this disease is much more common in India due to poor standard of nutrition than it is in the West, though natural cure may occur with or without residual liver cell damage. Hence, problem of therapy for viral hepatitis demands an ideal drug with essential requisite of quicker recovery and convale-scence without residual liver disease. At present, there are no established drugs for hepatitis A, E and G (Dienstag and Isselbacher, 2005). Therefore, early renor-malization of hepatic functions with symptomatic and clinical recovery is the primary goals in the management of acute hepatitis.

Polyherbal formulations in various studies (Antarkar et al., 1980; Talib et al., 1988; Kolhapure and Mitra, 2004) reduced mean period required for clinical and biochemical recovery in the form of liver function test

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(LFT) and there were no reported or observed significant adverse events. With this background, the present study was planned with the following aims and objectives: 1) to evaluate the efficacy of Livwin in patients of acute viral hepatitis by clinical and biochemical parameters .2) to compare the efficacy of Livwin with placebo by clinical and biochemical parameters .3) to know the adverse events during the study period.

MATERIALS AND METHODS

This prospective, double blind, randomized, placebo controlled, clinical trial was carried out on 58 patients from July 2004 to September 2005. Patients were recruited from the Medicine OPD, Indira Gandhi Government Medical College Nagpur. Institutional ethic committee of Indira Gandhi Government Medical College approved the study.

Inclusion criteria

Patients with diagnosis of symptomatic acute viral hepatitis (less than 6 months) (Dienstag and Isselbacher, 2005).

Exclusion criteria

Age < 15 years , pregnancy , patient of viral hepatitis associated with complications, hepatocellular failure, hepatic encephalopathy, portal hypertension ascitis, patient with chronic hepatitis (more than 6 months), bleeding tendencies, sickle cell disease/thalassemia major (haemolytic anaemia),obstructive jaundice, alcoholic hepatitis and drug induced hepatitis.

Material

Livwin is polyherbal formulation that contains extracts of seven medicinal plants as follows: *Terminalia arjuna*-100 mg, *Withania somnifera* -100 mg, *Phyllanthus niruri* -100 mg, *Berberis aristata*-50 mg, *Tinospora cordofolia*-75 mg, *Picrorhiza kurroa*-50 mg, *Boerhaavia diffusa*-50 mg. Placebo consists of lactose 500 mg. Both Livwin and Placebo were given orally, 2 capsules 2 times a day for 8 weeks followed by drug treatment free period of 4 weeks. The formulations were packed in inert gelatin capsule of same colour. Codes were given as drug A for Livwin and drug B for Placebo. The Codes to drugs were given to person's not related to trial. Both the investigators and patient were unaware of treatment. The assessing physicians are also unaware of codes of drugs. The codes were broken only on completion of the study as no patient developed serious adverse reactions during the study period. Baidhyanath research foundation, Nagpur, provided active drug and placebo. The diagnosis of acute viral hepatitis was made by physician based on clinical criteria such as jaundice, yellow urine, fever, nausea, vomiting, weakness, tender hepatomegaly and biochemical criteria like raised serum bilirubin, SGOT (Serum glutamate oxaloacetate transaminase), (SGPT serum glutamate pyruvate transaminase) and serum alkaline phosphatase (Antarkar et al., 1980; Sama et al., 1976). A written informed consent was taken from each patient.

Clinical recovery in patients of acute viral hepatitis was evaluated by recovery of symptoms and sign like fever, weakness (fatigue, malaise and myalgia) icterus and tender and enlarged liver. Fever is assessed by its absence or presence during the period of follow-ups. Weakness is assessed on the basis of presence or absence of fatigue, malaise and myalgia during the period of follow-ups. Icterus and tender and enlarged liver were evaluated objectively at the time of follow-ups. All these clinical parameters were subjectively assessed by qualified physician. Biochemical recovery was evaluated by measuring serum bilirubin and activity of enzymes SGOT, SGPT and serum alkaline phosphatase at baseline, 2, 4, 8 and 12 weeks.

No other therapy was given to patients during the study period. Vigilant follow up of patients for adverse drug reactions was done and recorded in the case report form.

Statistical analysis of data

At the level of significance $\alpha = 5\%$ and power 90%, the sample size of 29 for each group was calculated by statistician using pilot study data of 10 patients in each group. Mean values of Serum bilirubin, SGOT, SGPT and Serum alkaline phosphatase at 2, 4, 8 and 12 weeks were used for calculation of sample size. Randomization of 58 patients was done with the help of randomization number table. Mean values (at baseline, 2, 4, 8 and 12 weeks) were compared between two groups by using unpaired 't' test. Fisher s exact test was used for the statistical comparison of clinical features between the two groups. $P < 0.05$ was considered as statistically significant.

RESULTS

There was significant clinical recovery of fever, weakness, icterus and tender and enlarged liver at 2 weeks with Livwin as compared to placebo (Table 2). Clinical recovery of fever, icterus, weakness and tender and enlarged liver was observed in Livwin treated patients at 4 weeks whereas placebo treated patients were not recovered until 8 weeks. There was significant reduction in levels of serum bilirubin, SGOT, SGPT, and serum alkaline phosphatase at 2 weeks, 4 weeks, and 8 weeks with Livwin as compared with placebo. At the end of 4 weeks, serum bilirubin, SGOT, SGPT and serum alkaline phosphatase were in normal range with Livwin treatment whereas with placebo treatment all these biochemical parameters were above normal range (Table 3). Significant difference with Livwin as compared to placebo was observed with Serum bilibubin, SGOT, SGPT even after drug free period (Table 3). 6.89% of patients reported epigastric pain and 3.44% reported diarrhoea as adverse event with Livwin treatment whereas 6.89% patients reported epigastric pain as adverse event with placebo treatment (Table 4).

DISCUSSION

Both groups were comparable in age, sex and duration of illness (Table 1). The polyherbal formulations like Liv.52 (Sama et al., 1976), Liv.52DS (Baijal et al., 2004), Hepax (Dange et al., 1989), Kamalahar forte (Dange et al., 1989), Arogyawardhini (Antarkar et al., 1980), Valiliv (Dange et al., 1989) and Valiliv forte (Talib et al., 1988) have got two or more similar contents as that of Livwin such as *P. kurroa*, *T. arjuna*, *B. aristata*, *B. diffusa*, *T. cordofolia, P. niruri* and *W. somnifera*. Therefore, the efficacy of these previous formulations was reviewed in

Table 1. Demographic characteristics of patients.

Group	Livwin	Placebo
Number of patients	29	29
Age (yrs)	29.93 ± 2.70 (Range 16 - 73)	33.37 ± 2.43 (Range 15 - 65)
Sex		
Male (no.)	22	25
Female (no.)	7	4
History: duration of illness (days)	11.55 ± 0.95	10.41 ± 1.01

Values are given as mean ± S.E.M. where appropriate.

Table 2. No of patient recovered of fever, weakness, icterus and tenders and enlarged liver at baseline, 2, 4, 8 and 12 weeks with Livwin and Placebo treatment.

Symptom/sign	Group	Baseline	2 weeks	4 weeks	8 weeks	12 weeks
Fever	A	0(0)	29 (100)***	29 (100)	29 (100)	29 (100)
	B	0(0)	11 (37.93)	28 (96.55)	28 (96.55)	29 (100)
Weakness	A	0 (0)	22 (75.86)***	29 (100)***	29 (100)*	29 (100)
	B	0 (0)	1(3.44)	5 (17.24)	25 (86.20)	27 (93)
Icterus	A	0 (0)	24 (82.75)***	28 (96.55)***	29 (100)***	29 (100)
	B	0 (0)	1 (3.44)	14 (48.27)	20(68.96)	29 (100)
Tender and enlarged liver	A	3 (10)	24 (83)**	29 (100)**	29 (100)	29 (100)
	B	4 (14)	14 (48)	23 (79)	28 (96.55)	29 (100)

*P < 0.05, **P< 0.01, *** P < 0.001, Group A – Livwin, n =29, Group B – Placebo, n = 29.

the light of observation of present study. These polyherbal formulations have more components ranging from 9 to 19 and contain components other than herbal (Dange et al., 1989). Livwin has seven components and all are herbal.

In present study, there was significant earlier recovery of fever, icterus, weakness and tender and enlarged liver in Livwin group as compared to placebo group (Table 2). Dange et al. (1989) in a study of five different polyherbal formulations also observed that significantly, early clinical recovery was evident with Arogyawardhini, Hepax, Valiliv, Kamalahar forte and Liv.52 as compared to placebo. Baijal et al. (2004) also observed that there was significant improvement of jaundice and weakness in Liv.52 DS group over a period of 1 month.

Livwin contains Ashwagandha which is used as general tonic, useful in debility, nervous exhaustion especially due to the liver disease or other problems as stress (Ministry of Health and Family Welfare, 1996; Kokate et al., 2002). Weakness might also be improved due to the anti stress action of *P. kurroa* (Indian Herbal Pharmacopoeia, 2002). Livwin contain *B. aristata* (Ministry of Health and Family Welfare, 1996). *P. kurroa* (Kokate et al., 2002; Indian Herbal Pharmacopoeia, 2002). *T. cordofolia* (Indian Herbal Pharmacopoeia, 2002). *T. arjuna* (Ministry of Health and Family Welfare, 1996) which has antipyretic action and this resulted in amelioration of fever earlier. Mean values of serum bilirubin, SGOT, SGPT and serum alkaline phosphatases were decreased significantly in Livwin group as compared to placebo group (Table 3).

Dange et al. (1989) in a study of five polyherbal formulations observed that biochemical recovery (serum bilirubin, SGOT, SGPT) significantly in less days with Arogyawardhini, Hepax and Valiliv as compared to placebo .The results of present study are comparable with these studies. Clinical improvement of icterus and raised serum bilirubin with Livwin treatment can be explained on the basis that as the cause of is failure of liver to secrete bile at the rate at which it is formed in the body. Livwin contains *P. kurroa* and *B. diffusa* which helps in recovery of icterus and raised serum bilirubin by virtue of their cholerectic action. Shukla et al. (1991) observed cholerectic action of *P. kurroa* in animal

Table 3. Mean values of Serum bilirubin (total), SGOT, SGPT, Serum alkaline phosphatase at baseline, 2, 4, 8 and 12 weeks with Livwin and Placebo treatment.

Parameter	Group	Baseline	2 weeks	4 weeks	8 weeks	12 weeks
Serum total bilirubin (mg/dl) (Mean ± S.E.M.)	A	8.66 ± 0.86	1.94 ± 0.31***	1.24 ± 0.11***	0.83 ± 0.05***	0.84 ± 0.05***
	B	7.79 ± 0.73	4.15 ± 0.35	2.76 ± 0.17	1.98 ± 0.11	1.32 ± 0.80
SGOT (IU/L) (Mean ± S.E.M.)	A	685.86 ± 76.35	76.75± 10.22***	43.24 ± 3.00***	38.75± 2.78***	34.00 ± 2.06***
	B	432.20 ± 62.39	191.86 ± 27.15	110.34 ± 10.94	78.79 ± 9.24	50.72 ± 3.60
SGPT (IU/L) (Mean ± S.E.M.)	A	989.75 ± 88.70	69.10 ± 9.81***	27.31 ± 2.00***	21.68± 1.34***	19 ± 1.18***
	B	558.37 ± 64.78	231.41 ± 26.66	126.85 ± 13.23	69.62 ± 5.85	42.93 ± 3.26
Serum alkaline phosphatase (IU/L) (Mean ± S.E.M.)	A	203.20 ± 23.09	109.31 ± 5.87**	88.86 ± 6.10*	85.48 ± 4.11	83.20 ± 3.36
	B	235.48 ± 23.76	147.37 ± 11.17	108.00 ± 5.70	96.10 ± 4.54	91.20 ± 4.68

*P < 0.05, **P< 0.01, *** P < 0.001, Group A – Livwin, n = 29, Group B – Placebo, n = 2.

Table 4. Adverse events reported during study period in group A and group B.

Adverse events	Group A	Group B
Epigastric pain	2 (6.89%)	2 (6.89%)
Diarrhoea	1 (3.44%)	_

Group A – Livwin, n =29, Group B – Placebo, n = 29.

studies. Chandan et al. (1991) in animal studies observed cholerectic action to *B. diffusa*. Raised serum bilirubin in acute viral hepatitis presumably results from intrahepatic obstruction of biliary canaliculi, the obstruction is direct consequence of cellular inflammation. Begum et al. (1988) observed anti-inflammatory action of *W. somnifera*. Pandey et al. (1989) observed anti-inflammatory action of *P. kurroa*. Livwin contains *P. niruri* that has activity against hepatitis B virus. In present study, number of hepatitis B positive patients were less (Livwin-1, placebo-1) . Venkateswaren et al. (1987) observed that *P. niruri* had antiviral action against Hepatitis B virus *in vitro*. To prove the efficacy of Livwin in hepatitis B virus positive patients needs further evaluation.

Adverse events such as epigastric pain and diarrhea were reported by 10.37% patients in this study and are not significant as compared to placebo. Adverse events such as epigastric pain, diarrhea and skin rash were observed with Arogyawardhini in 10% patients, with Valiliv in 17.39% patients and with Liv.52 in 8.82% patients (Dange et al., 1989). Adverse events observed with Livwin are comparable to adverse events with these polyherbal formulations.

Conclusions

Livwin caused significant earlier clinical and biochemical recovery as compared to placebo. Biochemical parameters with Livwin treatment at the end of 4 weeks were recovered almost in normal range. Adverse events reported with Livwin were epigastric pain and diarrhoea. Livwin needs further evaluation in treatment of hepatitis B virus infection.

REFERENCES

Antarkar DS, Vaidya AB, Joshi JC, Athavale AV, Vinchoo KS, Natekar MR (1980). A double-blind clinical trial of Arogya-wardhani Ayurvedic drug-in acute viral hepatitis.Ind. J. Med. Res. 72: 588-593.

Baijal R, Patel N, Kolhapure SA (2004). Evaluation of efficacy and safety of Liv 52 DS tablets in acute viral hepatitis: A prospective, double-blind, randomized, placebo-controlled, phase III clinical trial.Medicine Update 12(5): 41-53.

Begum V, Hazeena SJ (1988). Long Term Effect of Herbal Drug Withania somnifera on adjuvant induced arthritis in rats.Indian J. Exp. Biol. 26: 877-882.

Chandan BK, Sharma AK, Anand KK (1991). Boerhaavia Diffusa: A study of its Hepatoprotective Activity. J. Ethnopharmacol. 21: 299-307.

Dange SV, Patki PS, Pawar SS, Phadke SA, Shrotri DS (1989). Comparative Efficacy of Five Indigenous Compound Formulations in Patients of Acute Viral Hepatitis.Maharashtra Med. J. 36(5): 75-80.

Dienstag JL, Isselbacher KJ (2005). Acute viral hepatitis. In:Harrison′s Principles of Internal Medicine, sixteenth edition, Kasper , Braunwald, Fauci, Hauser, Longo, Jameson, editors, Mc Graw Hill, New York pp. 1822-1838.

Indian Herbal Pharmacopoeia (2002). Revised new edition, Indian Drug Manufacturers Association, Mumbai.

Kokate CK, Purohit P, Gokhale SB (2002). Pharmacognosy, twentieth edition, Nirali Prakashan,Pune, 2002.

Kolhapure SA, Mitra SK (2004). Meta-analysis of 50 phase III clinical

trials in evaluation of efficacy and safety of Liv.52 infective hepatitis.Medicine update 12(2): 51-61.
Pandey BL, Das PK (1989). Immunopharmacological studies on Picrorhiza kurroa Royle-ex-Benth Part IV: cellular mechanisms of anti-inflammatory action. Int. J. Physiol. Pharm. 33(1): 28-30.
Park K (2005). Park ′s Textbook of Preventive and Social Medicine, eighteen edition, Banarsidas Bhanot Publishers, Jabalpur Pharmacological Investigation of Certain Medicinal Plants and Compound formulations used in Ayurveda and Siddha. Ministry of Health and Family Welfare, first edition Govt. of India, New Delhi, 1996.
Sama SK, Krishnamurthy L, Ramachandran K, Krishnan L (1976). Efficacy of an Indigenous Compound Preparation Liv 52 in Acute Viral Hepatitis – A Double Blind Study. Ind. J. Med. Res. 5: 738-741.
Shukla B, Visen PKS, Patnaik GK, Dhawan BN (1991). Cholerectic Effect of Picroliv, the Hepatoprotective Principle of Picrorhiza Kurroa. Planta Med. 57: 29-33.
Talib VH, Aggarwal MP, Khurana SR, Haldar SN, Taneja DK (1988). Valiliv in Hepatic Disorders with special Reference to SERUM Hepatitis. Curr. Med. Prac. 32(8): 197-202.
Venkateswaren PS, Millman I, Blumberg BS (1987). Effects of an extract from phyllanthus niruri on hepatitis B and woodchuck hepatitis viruses: *In vitro* and *in vivo* studies. Proc. Natl. Acad. Sci. USA 84: 274-278.