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MANAGEMENT OF CHRONIC HEPATITIS B WITH NEW LIVFIT® IN END STAGE RENAL DISEASE

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Abstract : New Livfit® (NLF) is a standardized, poly-herbal formulation that has been found useful in the management of hepatitis. The aim of this placebo-controlled study was to evaluate its usefulness against hepatitis B virus in the patients of end stage renal disease (ESRD). Patients were regularly evaluated at 6, 12, 24 and 36 weeks of therapy. With 36 weeks of treatment of NLF, there was rapid clearing of HBV- DNA in a significant number of patients. Significant seroconversion of the other markers of hepatitis B and restoration of the raised levels of ALT and AST was observed. The study suggests the potential usefulness of NLF in the control of HBV infection in the patients of ESRD prior to renal transplant.

Key words : hepatitis B, end stage renal disease, hemodialysis, hepatoprotective

INTRODUCTION

Patients with end stage renal disease (ESRD) are more susceptible to hepatitis B virus (HBV) infection and the risk increases with the number of hemodialysis (HD) received. The defective immune response associated with chronic uremia favors HBV replication and once infected there is a high rate of progression to chronicity. The majority of long-term studies have reported reduced patient compliance

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for renal transplant in the patients with chronic hepatitis (1). Further, post-renal transplantation clinical course of a HBV infected renal transplant recipient (RTR) is also very different, with exacerbations, rapid progression to liver cirrhosis and an increased risk of death from liver failure. There is, therefore, a need for a therapy to reduce the duration of HBV illness so as to enable the renal transplant at the earliest possible.

New Livfit® (NLF) is a standardized, poly-herbal formulation consisting of the aqueous extracts of 11 herbs commonly used in ayurveda for various disorders of liver and hepatoprotection. Several of these herbs have shown significant activity against HBV in clinical and experimental studies. *Eclipta alba, Phyllanthus niruri, Rheum emodi, Tephrosia purpurea and Cinchorium intybus* are its major ingredients (2, 3, 4). Six weeks treatment in cases of acute hepatitis B infection reduces the duration of active disease and a rapid clearance of HBsAg makes it useful in healthy carriers of hepatitis B (5). The present clinical study was planned to evaluate the usefulness of New Livfit® in ESRD patients who are infected with HBV.

METHODS

Study design

A randomized, double blind, placebo controlled, parallel designed, prospective, clinical study was conducted to evaluate the efficacy of New Livfit® against HBV infection in ESRD patients.

Subjects

Subjects of the study were enrolled from the Nephrology unit of Belleuve Clinic, Kolkata, India. Patients of end stage renal failure with chronic hepatitis as diagnosed by HBsAg positivity for more than six months duration, were eligible to enter the study. Children below the age of 10 years and pregnant females were not included in the study.

The exclusion criteria included the patients of liver disease other than hepatitis (diagnosed at baseline or subsequent follow-up) as well as hepatitis other than HBV (diagnosed at baseline or subsequent follow-up). Also excluded were the patients with established cirrhosis, carcinomas, risk of portal hypertension and other life threatening ailments due to their underlying chronic renal disease as well as those suffering from other systemic disorders like hormonal dysfunction, diabetes, hyperlipidaemias and tuberculosis.

The patients who developed any form of medical complication were not included in final analysis. Also the patients who could not complete all the four follow- ups were excluded from the final analysis. The patients were explained the nature and scope of the study before registration and an informed consent was obtained from each patient prior to their participation in the study.

Test drug

For preparing the test drug, the individual herbs were collected from their

natural habitats from various geographical locations of India. These herbs included *Eclipta alba* (aerial parts), whole plant of *Phyllanthus niruri, Tephrosia purpurea, Andographis paniculata* and *Fumaria officinalis, Cinchorium intybus* (seeds), *Terminalia chebula* (fruits) and underground parts of *Boerhavia diffusa, Rheum emodi* and *Picrorrhiza kurroa.* The voucher specimens of herbs have been submitted with the Agro Bio tech department of Dabur Research Foundation, Sahibabad. The plant parts used were dried in shade, powdered and subjected to extraction with water in a particular ratio. The extract was spray dried and used for manufacturing the tablets.

All the batches of New Livfit are standardized by a standard procedure of fingerprint HPTLC conforming the presence of known marker compounds in its ingredients.

Identical looking tablets of the test drug and placebo were packed in identical plastic containers labeled with appropriate codes. Each container had 120 tablets. As soon as the patients were enrolled in the trial, they were instructed to take 2 tablets twice a day before meals. The drug was continued for 36 weeks. The samples required for the study were provided by Dabur Research Foundation, India. The placebo tablets contained starch, calcium carbonate, microcrystalline cellulose, talcum and magnesium stearate.

Methodology

After registration the patients were assigned to the groups, A or B, with the help of random number tables. All the patients in test group, Group A received NLF 2 tablets B.D. for 36 weeks, while Group B, the control group received placebo tablets. The periodical assessment of patients was done each time at the end of 6, 12, 24 and 36 weeks of therapy. During each follow up visits, the effects of NLF were evaluated by liver function tests and serological tests specific for hepatitis B virus. Biochemical investigations were regularly done to evaluate the progression of renal pathology and screening tests were carried out to exclude the concomitant infections.

Statistics: The data was analyzed by using SPSS software. The Cochrane's statistics was used to assess the significance of dichotomous parameters at different treatment time intervals. For quantitative parameters, the Repeated Measures Analysis was performed of General Linear Model. All the values are presented as Mean±S.D. The probability level of $P=0.05$ was taken as the limit of significance.

RESULTS

Twenty-five patients of ESRD who were positive for HBsAg were enrolled for the study. Of these 3 patients could not complete the study and are not included in the final analysis. Thus, twenty -two patients, 10 in the New Livfit treated group and 12 in the placebo group could complete the study. At the start of the study, both the groups were comparable with respect to the age (NLF–43.5±12.7 years; placebo: 49.7±8.0 years) and base line disease characteristics, like duration of HbsAg positivity before inclusion (NLF: 9.10±8.6 months; Placebo: 10.67±9.6 months),

TABLE I: Effect of New Livfit® on liver function tests.

	ALT		*AST*		*Total Bilirubin*		*S. albumin*		*Globulin*	
	NLF (N=8)	*Placebo (N=8)*	*NLF (N=8)*	*Placebo (N=8)*	*NLF (N=8)*	*Placebo (N=8)*	*NLF (N=8)*	*Placebo (N=8)*	*NLF (N=8)*	*Placebo (N=8)*
Baseline	153.3±114.6	92.9±68.8	130.13±120.11	46.25±45.77	0.56±0.16	1.21±0.9	3.11±0.50	3.14±0.36	3.72±0.88	3.30±1.03
24 wks	96.9±63.6	84.1±54.6	63.86±58.22	62.71±68.71	1.0±0.4	1.21±0.45	3.33±1.22	3.30±0.75	4.13±0.71	3.58±0.69
36 wks	55.0±42.0^{+}	83.7±55.9	59.40±50.0^{+}	39.0±58.22	1.11±0.91	1.17±0.58	3.20±1.25	3.30±1.12	4.03±0.84	3.46±1.03

Values are mean±S.D.
$^{+}$P<0.05; as compared with the baseline.

duration of end stage renal disease (NLF: 15.9±10.8 months; Placebo: 15.33±14.5 months) and the number of hemodialysis received (NLF: 76.9±24.5; Placebo: 62.42±18.1).

ALT levels tend to return towards normal in the treatment group. At the end of 36 weeks of treatment, in NLF treated group, the ALT levels were significantly lower ($P<0.05$) as compared to the baseline. After 36 weeks of therapy, AST levels were also significantly lowered in the treatment group as compared to control, however, for serum albumin, globulin and bilirubin, no significant difference could be observed between the two groups (Table–I).

As the Table–II shows, there was no significant difference between the two groups, for any of the renal function tests at any stage, thereby, indicating that treatment with NLF has no effect on the kidneys in the patients of end stage renal disease.

The effects of NLF were also evaluated by measuring the serological markers of hepatitis. Four patients were negative for HBV DNA and another two acquired HCV infection. The effects of treatment on the serological markers of hepatitis in the remaining 16 patients (8 in each group) have been shown in Table–III.

A definite improvement in various parameters of hepatitis was seen in NLF group at the end of 36 weeks as a higher fraction of patients became negative in comparison to the control group. With NLF therapy, 62.5% of cases (5 of 8) became negative for HBV- DNA, 25% (1 of 4) became negative for Anti HBc IgM and Anti HBeAg.

TABLE II: Effect of New Livfit® on renal function tests.

	Blood urea		*Serum creatinine*		*Serum potassium*	
	NLF (N=10)	*Placebo (N=12)*	*NLF (N=10)*	*Placebo (N=12)*	*NLF (N=10)*	*Placebo (N=12)*
Baseline	117.76±26.67	149.92±53.21	11.4±4.77	8.94±2.92	4.95±1.01	4.92±0.98
6 weeks	138.37±39.24	131.24±34.46	11.12±4.93	9.70±2.83	4.97±0.79	5.80±1.57
12 wks	166.81±31.10	121.15±28.64	13.02±3.40	9.04±2.36	5.64±1.57	5.29±1.13
24 wks	134.90±23.33	128.13±39.71	11.16±3.59	9.74±3.68	5.09±1.22	5.29±1.13
36 wks	162.26±50.20	128.81±39.99	12.42±3.90	10.11±3.27	5.54±1.10	5.28±0.98

All values represent Mean±S.D.

TABLE III: Effect of New Livfit® on the serological markers of HBV.

Parameter		*New Livfit®*			*Placebo*		
		Baseline	*24 wk*	*36 wk*	*Baseline*	*24 wk*	*36 wk*
HBsAg	Positive	8	7	7	8	8	8
	Negative	0	1	1	0	0	0
HBV DNA	Positive	8	4	3^{+}	8	7	7
	Negative	0	4	5*	0	1	1
HBeAg	Positive	6	2	2^{*+}	6	5	4
	Negative	2	6	6	2	3	4
Anti HBc IgM	Positive	4	2	1*	2	2	2
	Negative	4	6	7	6	6	6
Anti HBeAg	Positive	4	1	1*	2	2	2
	Negative	4	7	7	6	6	6
AST		132.6±92.2	53.1±31.9	50.5±30.6	81.9±66.3	70.9±35.1	75.4±40.7
ALT		153.3±114.6	66.6±51.5	47.4±22.9	99.9±68.8	82.0±47.4	80.7±46.9

*$P<0.05$; compared with control group.
$^{+}P<0.05$; compared with baseline.
Values represent the number of patients found positive or negative for that particular marker.

On the other hand, in control group, only 1 out of 8 patients became negative for HBV DNA and no improvement was seen for Anti HBc IgM and Anti HBeAg. The results are significantly different. Better improvement in NLF group was also evident for HBsAg and HBeAg, the differences are, however, not statistically significant.

DISCUSSION

Controlling the spread of HBV infections in dialysis units has been one of the most important aspects of the management of ESRD patients and includes segregation, universal precautions, vaccination, reduced blood transfusions, and screening of organs before transplantation. Although these measures result in a reduction of HBV spread within dialysis centers, some isolated outbreaks continue to occur in developed countries and the prevalence of chronic HBsAg positivity varies from 7.6% to 21.6% in developing countries (1).

Recognizing that HBV infection is a major health problem in dialysis dependent end stage renal failure patients, hepatitis B virus vaccination has now become a routine procedure. Unfortunately, the sero-conversion rate after recombinant HB vaccine in ESRF patient is poor due to depressed cell mediated immunity. Immunomodulators like levamisole and granulocyte macrophage colony stimulating factor (GM-CSF) are being used along with the vaccination with variable response rate.

As seen in the previous trials of NLF, the raised levels of hepatic enzymes were restored towards normal. A significant reduction was observed in the ALT and AST levels and this was also significantly different from the placebo.

Further, HBV-DNA was cleared in a significant number of patients on New Livfit®, indicating the control of HBV infection.

Before treatment, 75% of patients in each group were positive for HBeAg. Seroconversion occurred in 4 patients in the treatment group and in 2 patients of placebo group. As the presence of HBeAg indicates a high level of replication and infectivity, the higher seroconversion in the treatment group indicates towards the effectiveness of NLF in controlling viral replication and infectivity.

Anti-HBc (IgM) that indicates acute/ recent HBV infection was found positive in 4 patients of NLF and 2 of placebo group. In three patients of treatment group, Anti HBc (IgM) became negative, indicating a rapid control of the disease. On the other hand, no change was seen in placebo group. The differences have been found to be significant.

No difference was seen in any of the renal function tests between the treatment and placebo group, indicating that treatment with New Livfit does not affect the end stage renal disease.

Thus, New Livfit® when given to the patients of ESRD with hepatitis B infection was found to improve the serological markers and a significant reduction was observed in the levels of hepatic enzymes. This study, thus, suggests that NLF is an effective adjuvant to control HBV infection in patients on maintenance hemodialysis prior to renal transplant in the patients of ESRD.

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