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Clinical Trial of Liv.52 Drops in Infective Hepatitis – A comparative study with broad spectrum antibiotics and corticosteroids

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Hepatic disorders in infancy and childhood continue to pose problems in their management. Viral hepatitis in our country is frequently of prolonged duration with a predisposition to complications like post-hepatitis cirrhosis, chronic cholestasis, subacute necrosis and hepatic failure. Sometimes, though rarely, the disease is fulminant and death ensues in the acute phase. Such cases are commonly those in whom a superimposed nutritional factor increases the susceptibility of the liver cells to necrosis.

The therapy of viral hepatitis assumes immense importance as death from this disease is much more common in India due to the poor standard of nutrition though natural clinical cure occurs with or without residual liver cell damage. There have been no revolutionary advances in the therapy of viral hepatitis and pre-coma and coma, and the various modes of treatments have little effect in altering the course. The only aim of therapy is to support the failing hepatic parenchyma and help regeneration of liver cells, thus restoring liver function. A large number of workers have reported on the effect of Liv.52 (The Himalaya Drug Co.), an indigenous compound on the regeneration of liver cells and its effectiveness in acute infective hepatitis. Jaffari (1969) reports that Liv.52 clears jaundice, improves appetite and brings a sense of well-being. He postulates that it has an anti-inflammatory action and advises its use freely since Liv.52 is free from untoward side effects.

Mukherjee (1971) recommended its use in order to prevent a prolonged course of illness and residual cell damage. Dayal (1970) reported that jaundice regressed and liver function tests showed improvement. A large number of workers have reported on the effects of Liv.52, an indigenous compound, on the regeneration of liver cells and its effectiveness in acute infectious hepatitis. Each ml of Liv.52 drops contains:

Exts.	Capparis spinosa	17 mg
	Cichorium intybus	17 mg
	Solanum nigrum	8 mg
	Cassia occidentalis	4 mg
	Terminalia arjuna	8 mg
	Achillea millefolium	4 mg
	Tamarix gallica	4 mg

(Prepared in the juices and decoctions of various hepatic stimulants).

Each tablet of Liv.52 contains:

Exts.	Capparis spinosa	65 mg
	Cichorium intybus	65 mg
	Solanum nigrum	32 mg
	Cassia occidentalis	16 mg
	Terminalia arjuna	32 mg
	Achillea millefolium	16 mg
	Tamarix gallica	16 mg
	Mandur bhasma	33 mg

(Prepared in the juices and decoctions of various hepatic stimulants).

The present study was undertaken to observe the effectiveness of Liv.52 in cases of viral hepatitis as there are few studies in this respect and to compare the responses of broad spectrum antibiotics and steroids in similar cases on Liv.52.

MATERIAL AND METHODS

One hundred and twenty five cases of viral hepatitis were taken up in the Sarojini Naidu Children Hospital, Allahabad and divided into groups A and B. Group A, the study group, consisted of 100 cases and the control group B, of 25 cases. The study group were given Liv.52 in three daily doses of 20-30 drops for infants and 50-70 drops for the older children and the dosage was further increased according to the severity of the illness. The control group was given appropriate doses of broad spectrum antibiotics, i.e. 30-40 mg daily per kg body weight in 3 or 4 divided doses, and steroids, i.e. prednisolone 2 mg per kg body weight daily. Vitamin supplements were given to children in both the groups. Liv.52 was continued for periods varying from 3-6 months after the jaundice subsided.

METHODS OF STUDY

A detailed history was taken, thorough clinical examination done, and nutritional status, degree of jaundice and state of consciousness were noted in all the cases on a special *pro forma.* Socio-economic status of the family was judged by occupation, monthly income according to the classification by Government of India 1962 and Bank *et al*. 1967.

Laboratory studies included a routine haemogram, urine for bile salts and bile pigments, serum bilirubin, total serum protein and estimation of serum alkaline phosphatase; serum transaminase activity was studied only in a few cases. Liver function tests were repeated after one week initially and then in the third week.

OBSERVATIONS

The one hundred and twenty five cases ranged in age from 6 months to 12 years. There were 77 males and 48 females.

Table I: Showing the age and sex distribution in 125 cases

Age	6 mths - 3 yrs.	3-6 yrs.	6-9 yrs.	9-12 yrs.
No. of cases	28	30	35	32
Male	20	18	17	22
Female	8	12	18	10

Socio-Economic Status: It was divided into four broad groups according to the classification given by the Government of India 1962 (Bank *et al*. 1967). Seventy per cent of the patients belonged to class IV, 20% to class III and 10% to class II strata of society. Thus it was observed that the maximum number of cases belonged to class IV stratum of society.

The nutritional status was assessed according to Gomez' classification (1955) and grade two type of malnutrition was common.

PRESENTING FEATURES

The commonest symptoms were jaundice, anorexia, dark urine, fever, nausea/vomiting. The complaints of abdominal pain and clay coloured stools were next in order of frequency. Oedema of feet was present in 25 cases and generalised oedema was observed in 10 cases. Fifteen cases were having marked drowsiness as well. Liver was palpable in all the cases and was tender in 70%. In 10% cases the liver was firm, splenic enlargement was present in 20 cases.

Enlarged liver

Upto 3 cm	3–6 cm	Beyond 6 cm
75	30	20

LABORATORY FINDINGS

In the study group A, 55 cases had serum bilirubin in the range of 1–5 mg% and 45 cases had above 6 mg% as observed from table III. Ninety five per cent had serum bilirubin below 1 mg% in the third week and 5% had the bilirubin in the range of 1-5 mg%.

Table II: Symptoms observed in 125 cases

	Symptoms	No. of cases
1.	Jaundice	125
2.	Anorexia	88
3.	Dark coloured urine	76
4.	Fever	90
5.	Nausea/vomiting	85
6.	Abdominal pain	46
7.	Stools: clay coloured	15
8.	Oedema	25
9.	Pruritis	15
10.	Constipation	10
11.	Diarrhoea	25
12.	Drowsiness	15

Table III: Liver function tests before and after treatment: Showing the values of serum bilirubin initially and at the end of 3 weeks in cases of infective hepatitis cases

Serum bilirubin		Liv.52				Control			
		Before	1st wk	3rd wk	%	Before	1st wk	3rd wk	%
1.	Less than 1 mg%	–	40	95	95%	–	3	20	80%
2.	1–5 mg%	55	45	5	5%	5	17	5	20%
3.	6–10 mg%	20	10	–		10	5	–	
4.	11 and above	25	5	–		10	–	–	

In the control group 5 cases had serum bilirubin in the range of 1–5 mg% and 20 cases above 6 mg%. When serum bilirubin was repeated in the third week 80% had serum bilirubin below 1 mg% and 20% had bilirubin in the range of 1–5 mg%.

Improvement in the total serum protein was observed in the third week in all patients in both the groups as observed from table IV.

Table IV: Showing serum protein values initially and in the 3rd week in cases of infective hepatitis

Serum protein in gm%		Liv.52		Control group	
		Initially	3rd week	Initially	3rd week
1.	3–4 gm%	14	–	2	–
2.	4.1–5 gm%	34	4	12	5
3.	5.1–6 gm%	40	70	6	11
4.	Above 6 gm%	12	26	5	9

In the trial group 64% cases had normal levels of serum alkaline phosphatase. In the third week only 20% showed pathological levels. In the control group 68% had pathological levels of alkaline phosphatase initially and in the third week 52% still had abnormal values, (Table V).

Table V: Showing Alkaline Phosphatase values initially and at the end of the 3rd week in cases of infective hepatitis

Alkaline phosphatase K.A.U.		Liv.52		Control group	
		Initially	3rd week	Initially	3rd week
1.	Less than 14	36	80	8	12
2.	Above 14	64	20	17	13

Out of 100 cases in the study group 68 cases initially showed the presence of bile salts, bile pigments and urobilinogen in urine whereas in the control group 15 cased showed their presence. In the third week urine was clear in all the cases undergoing Liv.52 therapy whereas only one case in the control group still continued to show their presence in the third week. (Table VI).

Table VI

Urine bile salts, pigments, urobilinogen		Liv.52		Control group	
		Initially	3rd week	Initially	3rd week
1.	Present	68	–	14	1
2.	Absent	32	100	11	24

Serum transaminase was estimated in 25 cases including 15 cases of study group and ten cases of control group as seen from table VII. It is observed that 80% of study group cases had levels between 40-100 units while in the control group only 40% had levels between 0-40 units in the third week and 60% were still having S.G.O.T. between 40-100 units.

Table VII: Showing serum transaminase values initially and at the end of the third week in cases of infective hepatitis

Serum transaminase in 25 cases	Liv.52		Control group	
	Initially	3rd week	Initially	3rd week
Less than 40 units	–	12	–	4
40 – 100 units	10	3	6	6
Above 100 units	5	–	4	–

Table VIII: Improvement in symptomatology in number of days

Symptoms	Liv.52	Control	% of less time taken in Liv.52 group in regression of various symptoms
Jaundice	8	12	33%
Anorexia	5	8	40%
Nausea/vomiting	3	5	40%
Dark coloured urine	9	14	36%
Fever	3	5	40%
Abdominal pain	4	7	43.2%
Drowsiness	3	5	40%

DISCUSSION

A few interesting facts emerge from the above observations. Clinical improvement in Group A cases were seen much earlier as assessed by various symptoms e.g. Jaundice which regressed at least 33% earlier compared to Group B. Similarly other symptoms like anorexia 40%, nausea/vomiting 40%, dark coloured urine 36%, fever 40%, abdominal pain 43.2% and drowsiness 40%. All regressed earlier indicating the superiority of Liv.52 therapy in cases of uncomplicated infective hepatitis. However, it is difficult to say whether the liver size regressed to normal in any of the cases because the liver may normally be palpable throughout childhood upto 2 cms below the subcostal margin. Liver function tests have shown that Liv.52 brings down the level of serum bilirubin in most of the cases much earlier than in the patients treated with antibiotics and steroids. The rise in total serum proteins after treatment was the same in both the groups. A considerable difference was observed in the Liv.52 group and the control group patients who continued to show high levels of serum transaminases even after 3 weeks, indicating that Liv.52 stimulates much earlier hepatic cell repair.

CONCLUSION

In the present study although no histological tests (liver biopsy) were performed it is quite evident from the clinical and biochemical assessment that Liv.52 accelerates the rate of recovery in cases of

infective hepatitis as compared to the effect observed in cases who were given broad spectrum antibiotics and steroids only. The drug is free from any untoward effects.

HIGHLIGHTS FROM SOME INTERESTING CASE REPORTS OF PRECOMA CASES

CASE NO. 1

A ten-year-old male child presented with history of severe jaundice, violent behaviour and incoherent speech; associated symptoms noted were marked anorexia, nausea and black stools of a couple of days' duration. Examination revealed a well nourished boy of average build with severe jaundice and clouding of consciousness. Temperature was 102°F and liver was 5 cm enlarged below the costal margin. Spleen was just palpable. No other positive findings were noted. Laboratory investigations revealed serum bilirubin of 18 mg%, S.G.O.T. and S.G.P.T. over 100 units initially. He was put on Liv.52 drops three teaspoonfuls three times a day, vitamin B complex, glucose orally and Neomycin 50 mg/kg was given orally.

After a week

There was dramatic improvement clinically as shown by a marked fall in serum bilirubin to 8 mg%.

Second week

The general condition of the patient became normal. He still had mild icterus, serum bilirubin was 5.6 mg%.

Third and fourth weeks

The child was apparently normal with no evidence of jaundice clinically, liver was one finger enlarged and serum bilirubin was only 2 mg%, S.G.O.T. and S.G.P.T. had come to normal. He was discharged with the advice to continue Liv.52 in heavy doses for six months and to come for check-up every fortnight in the O.P.D.

CASE NO. 2

A male child of 12 years presented with severe jaundice, violent behaviour irrelevant speech, high fever associated with marked anorexia, nausea, bleeding tendency of 3 days' duration. Physical examination revealed a semicomatose, severely jaundiced patient with temperature of 103.4°F. and rapid respiration. Liver could not be felt under subcostal margin. The upper border of the liver was in the 6^{th} intercostal space on the right side. Serum bilirubin was 22 mg% and S.G.O.T. and S.G.P.T. were raised considerably over 100 units. He was put on Liv.52 drops 3 teaspoonfuls four times a day and vitamin B complex in the usual doses.

After the first week

He showed no improvement and the liver dullness disappeared completely. Coma deepened.

After the second week

The child showed signs of recovery. Mental state and consciousness came towards normal, jaundice also decreased, appetite returned and the liver could be felt 3 cm below the subcostal margin. Serum bilirubin came down to 12 mg%, other liver function tests and S.G.O.T. and S.G.P.T. showed improvement.

After the third and fourth weeks

The mental condition became normal, appetite was normal, jaundice decreased, liver 1 cm below the subcostal margin and serum bilirubin was lowered to 6 mg% by the end of the 4^{th} week. Thus he was discharged with advice to continue the treatment with Liv.52 drops and to attend the O.P.D. fortnightly.

After the fortnight that followed after his discharge, his serum bilirubin was only 2 mg%, LFT's and S.G.O.T., S.G.P.T. had come to normal and the child was apparently normal. He was again seen after 6 months and was absolutely normal.

CASE NO. 3

A 7-year-old female child was admitted with post-primary pulmonary tuberculosis. While on anti-tubercular treatment she developed deep jaundice, anorexia and hepatomegaly. The jaundice was thought to be unrelated to the tubercular lesion or therapy and was due to viral hepatitis and her general condition deteriorated in no time. Liv.52 therapy was instituted, she remained delirious for two days after which she gradually improved. The clinical improvement was observed within a week's time whereas biochemical improvement was observed in two weeks' time. In four week's time she was completely relieved of her illness relating to liver disease. She was advised to continue Liv.52 therapy for six months.

CASE NO. 4

A one-year-old child having icterus since one month, liver was 6 cms in epigastrium, spleen was 3 cms enlarged. He was admitted in the stage of prehepatic coma. Serum bilirubin was 32.5% mg%. He was given steroids, Liv.52 drops and broad spectrum therapy. The child's condition deteriorated and ultimately he succumbed to the illness on the 5^{th} day of admission. He was a case of fulminant viral hepatitis and did not respond to even combined therapy.

CASE NO. 5

A male child of 8 years of age presented with fever, anorexia, malaise, nausea and diarrhoea since 12 days, jaundice 10 days, behavioural disturbances of 2 days. Physical examination revealed liver 6 cms (firm in consistency), non-tender, smooth and margins well-defined. Spleen just palpable.

He had been given broad spectrum antibiotics and vitamin B-complex and glucose along with very small doses of Liv.52 drops by a general practitioner. But no improvement was observed even after a week and the child's condition was deteriorating (behavioural disturbances) (precoma stage). When admitted in the hospital he was put on Liv.52 drops 3 teaspoonfuls three times a day along with B-complex, glucose and broad spectrum antibiotics were continued for another week. The general condition of the child improved within 4 to 6 days. Liver became soft and was only 3 cms. below subcostal margin and liver function test showed improvement after 2 weeks' time. Serum bilirubin normalised within 4 weeks' time, whereas S.G.O.T. and S.G.P.T. took six weeks to come to normal.

Thus in this case it was observed that when the dose of Liv.52 drops was increased, the condition of the patient started improving, showing thereby that the effect was due to Liv.52 as all other therapy was the same as before.

CASE NO. 6

A female child aged five years who had been taking anti-tubercular therapy for a year or so developed marked icterus with gross liver enlargement (9 cms) and splenic enlargement of 3 cms firm and slightly tender. There were marked associated symptoms of malaise, extreme degree of anorexia, nausea and vomiting, fever of moderate degree along with loss of weight. She was probably a case of serum hepatitis since she had received 90 injections of streptomycin in the past. She was put on Liv.52 drops along with a broad spectrum antibiotic, multivitamins and plenty of glucose. The serum bilirubin level was initially 15mg%, S.G.O.T. and S.G.P.T. were found to be raised. The urine contained both bile pigments and bile salts. The bleeding and clotting time was

prolonged and the prothrombin time was also prolonged. After Liv.52 treatment was started the appetite of the child and the feeling of well-being returned within a week's time.

The size of the liver started gradually receding in the second week (7 cms). Clinically, signs of mild icterus were observed.

The serum bilirubin level had considerably lowered but there was not much improvement in the S.G.O.T. and S.G.P.T. values. The liver size had receded to 5 cms, soft in consistency and not tender, spleen was just palpable. In the fourth week the serum bilirubin became 2 mg% and S.G.O.T. and S.G.P.T. values had considerably lowered but not yet touched normal levels. The liver size had reduced to 3 cms and spleen was not palpable. Side by side she was also being given antitubercular treatment. She was discharged free of symptoms and with advice to continue Liv.52 for six months and to attend O.P.D. every 2 weeks. At her last visit when seen she was absolutely normal.

NOTE

There were five other cases (age group 6 months to 2 years) who were admitted in the hospital in the pre-coma and coma state.

The duration of illness had been over a month. In spite of all possible treatment given, they all expired within a few hours of hospitalisation. No assessment of treatment could be done in such cases. Hence they have not been included in this report.