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Trial of Liv.52 in Infectious Hepatitis in Children in Goa

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INTRODUCTION

Infectious hepatitis produces an acute inflammation of the liver which, though mild and self limiting in many cases, often runs an acute fulminating and fatal course or results in severe, chronic and irreparable hepatic damage. In India the infection seems to be more severe and its complications more frequent than in the affluent countries, probably due to malnutrition. No satisfactory specific treatment is yet available for this infection. Liv.52* has been reported by many workers[1,2,3] to be effective in the treatment of infectious hepatitis by decreasing its morbidity and the duration of jaundice as well as improving the appetite and preventing complications. Its effect on liver cell regeneration and protection against hepatotoxicity has also been described by many workers[4,5,6]. A trial was conducted in the Department of Paediatrics, Goa Medical College from July 1971 to June 1974 to assess the effects of this drug in cases of infectious hepatitis in children. The trial group of patients comprised of 50 consecutive cases admitted to the Children's Ward. The control group also had 50 children who had been likewise consecutively treated as inpatients in the ward from January 1967 to June 1971. The controls were adequately well matched with the trial group in their ages, sex, socio-economic background and severity of the condition. At the end of the trial a careful comparative evaluation was made of the results in the two groups. This paper outlines our findings.

MATERIAL AND METHODS

There were 50 children of the trial group (Table I) ranging in age from 5 months to twelve years, comprising of 30 males and 20 females. A very careful history and physical findings were recorded. Table II shows the clinical manifestations on admission in both groups of patients.

*Each ml of Liv.52 drops contains:

Extracts of:	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.

Table I: Age incidence (1967-1974)

	No. of patients		
	Control	Trial	Total
0-3	9	13	22
3-6	21	19	40
6-9	10	6	16
9-12	10	12	22

Table II: Manifestation on admission

	No. of cases		
	Control	Trial on Liv.52	Total
Fever	35	40	75
Anorexia	27	24	51
Nausea and/or vomiting	12	14	26
Abdominal pain	10	8	18
Dark urine	15	27	42
Light or clay coloured stools	–	6	6
Oedema	3	1	4
Pruritus	–	1	1

Constipation		2	1	3
Diarrhoea		–	1	1
Drowsiness and pre-coma		2	1	3
Jaundice	Nil	–	3	3
	Mild	32	31	63
	Moderate	12	10	22
	Severe	6	6	12
Enlarged Liver	Upto 3 cm	45	34	79
	More than 3 cm	5	16	21
	Tender	26	24	50
	Firm	5	8	13
Enlarged spleen		15	12	27

Since 1967, we have routinely investigated liver function tests in cases of hepatitis on admission and again at weekly or two weekly intervals depending on clinical improvement. The same schedule ws followed during the trial. The results of the tests in both groups, showing the figures on admission and after two weeks, are detailed in Table III. In both groups there were a number of patients who, for considerations other than medical, had to be sent home within two weeks of admission. They, however, followed the treatment at home and returned for their tests when required. Out of 50 patients in the control group 4 died within one week of admission. The admission L.F.T. data of these 4 patients are included (in Table III in the "Before" column) in order to give a comprehensive picture of all the patients. They are excluded from calculation of results. In every case the following investigations were done on admission: peripheral hemogram, estimations of serum bilirubin, total proteins, albumin, globulin, glutamic pyruvic transaminase, alkaline phosphatase, zinc turbidity as well as prothrombin time, urinalysis and stool examination.

Table III: Liver function tests before and after treatment

Test		No. of patients			
		Control		Trial on Liv.52	
		Before	After*	Before	After
Serum bilirubin in mg%	1-2	14	18	18	45
	2-5	27	28	21	5
	>5	9	0	11	0
Serum total proteins in g%	<4	4	0	2	0
	4.1-4.5	16	0	2	0
	4.6-5.0	8	0	15	2
	5.1-5.5	9	9	7	11
	5.6-6.0	3	8	10	17
	>6.0	10	29	14	20
Serum albumin in g%	<2	8	0	3	0
	2.1-2.5	14	12	8	0
	2.6-3.0	21	29	24	25
	3.1-3.5	2	0	9	10
	3.6-4.0	0	0	5	12
	>4.0	5	5	1	3
SGPT in IU	40	9	14	11	39
	40-100	28	32	21	11
	100-260	13	0	18	0
Alkaline phosphatase in K.A.U.	<14	4	9	16	32
	>14	46	37	34	18
Zinc turbidity units	<6	9	0	10	38
	>6	41	46	40	12
Prothrombin time	Normal	30	37	26	50
	Raised	20	9	24	0
Urine: Bile Salts, Pigments, Urobilinogen	Present	22	1	22	0
	Absent	28	45	28	50
* 4 patients in the control group died within 2 weeks of admission					

Liver function tests were repeated every week until full recovery. Liver biopsies were performed before and after treatment in five patients.

The trial group were given Liv.52 in three daily doses of 20-30 drops for infants and 40-60 drops for older children. In the ward, all patients were kept at bed rest. Older children were given a daily diet yielding 2112 calories containing 62.4 g proteins, 68.8 g fats and 297 g carbohydrates. Infants were given adequate milk according to their weights. Vitamin supplements were given to children in both groups. After the jaundice subsided, in the trial group, Liv.52 was continued for periods varying from 3 to 6 months until the patients were normal both clinically and by way of liver function tests.

Patients in the control group (30 males and 20 females) were admitted to the Children's Ward and were not given any specific treatment. The regime of bed rest, vitamin supplements and diet was the same as in the trial group.

In very severe and fulminant cases in both groups patients who were in impending hepatic coma, prednisolone and other measures were used as indicated. Care was taken to ensure that the findings in such patients did not vitiate the comparison of cases in the two groups.

Patients were followed in the out-patient's department after discharge, initially at two weekly intervals, and later, at monthly intervals for 6 months and then twice yearly.

OBSERVATIONS

Seasonal Incidence: The seasonal admission of cases of hepatitis is shown in Table IV. It was seen that the heaviest concentration of admissions was in the months of October, November, December and January. We have observed a similar high incidence of gastroenteritis and cases of enteric fever during these months. The phenomenon seems to be at variance with observations in other parts of the country where the highest incidence of these diseases is recorded during the monsoon months. Goa has an annual rainfall of 120 inches, almost entirely from mid-June to mid-September, and it is not clear why the pattern of food and water borne infections is different from other parts of the country with similar climate.

Table IV: Seasonal incidence (1967-1974)

Month	Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.
No. of cases	9	7	9	4	7	7	8	9	6	10	13	11
	October-February – 50 (Dry and Cool)				March-May – 20 (Hot)				June-September – 30 (Monsoon)			

Age and Sex Incidence: In this series males predominated over females in the ratio of 60 to 40. The youngest patients were a 6-month-old in the control group and a 5-month-old in the trial group. The largest number of patients was in the age group 3-6 years.

Clinical Manifestations: The average duration of illness before admission was 16.2 days in the control group and 13.8 days in the trial group.

The commonest symptoms on admission (Table II) were fever, anorexia and jaundice. The complaints of nausea and/or vomiting, abdominal pain and passing of dark coloured urine were next in the order of frequency. Oedema of feet was present in four cases and two of the three patients in precoma were drowsy on admission.

Liver was palpable in all cases and was tender in 50% of them. In a small number the liver was firm. Splenic enlargement was present in 27% cases on admission.

In the Liv.52 group the average duration of jaundice after admission was 10.9 days and in the control group it was 14.6 days. Appetite improved within 5 days of starting Liv.52 and in the control group after 7 days. Nausea and vomiting subsided within 3 days in the Liv.52 group and after 5 days in the control group. Tenderness of the liver persisted for 7 days in the trial group and more than 10 days in the control group. The average weight gain was 0.92 kg in 2 weeks in the Liv.52 group. In the control group there was no appreciable weight gain during the same period.

LABORATORY FINDINGS

Serum bilirubin (Maximum recorded – 8.8 mg): In the control group there were 36 patients with initial serum total bilirubin levels of more than 2 mg and after 2 weeks, in 80% of the patients these abnormal levels persisted. In the trial group 32 patients had a level of more than 2 mg initially, and after two weeks only five had levels between 2-5 mg%. In both groups there were approximately 20% of cases who had initial levels of more than 5 mg but at the end of two weeks none in either group had these levels.

Serum total proteins (Minimum recorded – 3.2 g): Almost all patients in both groups who had serum protein values of less than 5 g per 100 ml showed improvement at the end of two weeks.

Serum albumin (Minimum recorded – 1.6 g): Low serum albumin levels (less than 3 g) were seen in over 70% of cases in both groups. At the end of 2 weeks, the level remained less than 3 g% in 80% of the control group and 50% of the trial group.

SGPT (Maximum recorded – 259 units): Almost 80% of patients in both groups showed moderately raised readings initially. At the end of 2 weeks, 70% of the control group continued to have high levels of SGPT, whereas in the trial group only 22% had pathological levels. About 30% of patients in both groups had initial levels of over 100 units but after two weeks no child in either group had SGPT over 100 units.

Alkaline phosphatase (Maximum recorded – 38.4 K.A.U.): Almost 80% of all patients had pathological levels initially. At the end of 2 weeks, 80% of the control group and only 36% of the trial group had abnormal values.

Zinc turbidity (Maximum recorded – 64 units): Eighty per cent patients in both groups had levels more than 6 units. At the end of 2 weeks all 46 survivors in the control group, but only 24% in the trial group showed abnormal levels.

Prothrombin time (Maximum recorded – 64 seconds against 19 seconds for control): Between 40-50% patients in both groups had prolonged prothrombin time initially. After 2 weeks, 20% of the control group and none in the trial group continued to have this abnormal finding.

Bile salts, pigments and urobilinogen in urine: Out of all 100 cases, 56% initially showed the presence of these in the urine. After two weeks none but one in the control group showed their presence in the urine.

Corticosteroids had to be used in 5 and 6 cases respectively in the trial and control groups. These were cases of fulminant hepatitis, hepatic precoma and coma. In the control group all four patients of hepatic coma died, including the one in whom exchange transfusion was performed. In the trial group 2 cases of acute hepatitis who went into coma and 2 of prolonged fever and jaundice had grossly deranged liver function tests. Inadequate response to Liv.52 in these severe cases prompted us to use prednisolone, but Liv.52 was continued throughout the illness. Post-treatment liver biopsies in these 2 latter cases showed reversal to reparative changes (without scarring) from the

diagnostic findings of severe acute necrosis of liver cells in the earlier biopsies. All the four children recovered completely. There were no deaths in the trial group.

DISCUSSION

Clinical improvement was more rapid and symptoms subsided earlier in the patients treated with Liv.52 than in the control group. This was elicited by the early subsidence of jaundice and return of appetite, the latter being substantiated by the finding of an average weight gain of 0.92 kg. In the control group the appetite remained poor considerably longer and consequently there was hardly any weight gain during the observation period.

Tenderness of the liver seemed to persist longer in the control than in the trial group. It is difficult to conclude if the liver size regressed to "Normal" in any children, since throughout childhood, the liver is normally palpable anywhere upto 2 cm below the costal margin. We did, however, notice that excessive enlargement of more than 5 cm regressed in 4-6 weeks in the trial group, whereas in the control group it took longer.

Liver function tests have shown that Liv.52 brings down the level of serum bilirubin in a great majority of patients much earlier than in patients treated without this drug. It was seen that the rise in serum total proteins after treatment was similar in both groups but in the Liv.52 group the rise in serum albumin was seen in a larger number of patients to definitely higher levels. Lowered serum albumin level has been recognised as an index of hepatocellular damage and in as much as that, Liv.52 seems to stimulate liver cell regeneration. SGPT is the index of hepatic cell destruction and its continued presence at high levels indicates liver function impairment and that the disease has not resolved. There was a large difference in the Liv.52 and the control group of patients who showed continued high SGPT levels indicating that Liv.52 stimulates hepatic cell repair earlier. Without this treatment a number of patients seemed to continue having liver cell damage and it is conceivable that some of them might have gone on to develop further and irreparable damage.

Alkaline phosphatase and zinc turbidity tests convincing returned to normal in a larger number of patients treated with Liv.52 than in the control group. In the latter, 90 to 100% of patients continued to show abnormal levels of one or both tests at the end of 2 weeks. In the trial group this number was reduced to almost 33% indicating the beneficial effects of Liv.52 in reducing inflammation of the liver cells and promoting their regeneration, as well as decreasing bile stasis.

About half the patients in both groups had prolonged prothrombin time. Two weeks of Liv.52 reduced the time to normal in all the 50 cases, whereas in the control group, 20% of cases still showed abnormal values after two weeks, indicating a more serious prognosis.

A noteworthy case, not included in the study, was a 12 day old male infant with neonatal hepatitis who had deep jaundice and hepatosplenomegaly. His LFT were – serum bilirubin – 13 mg%, alkaline phosphatase 20 units, SGPT – 200 i.u., Zinc turbidity – 12 units and Prothrombin time – 100 seconds (19 seconds for control). Urobilinogen was present in urine initially but it disappeared after 5 days of treatment. Liv.52 effected clinical improvement in 5 days and clinical cure in 4 weeks. LFT returned to normal after six weeks. He has remained normal to date after two years of follow-up.

CONCLUSIONS

Liv.52 is beneficial in the treatment of acute infectious hepatitis. It abates the symptoms rapidly, reduces the duration of jaundice and restores appetite. It causes the return of impaired liver function tests to normal indicating its effectiveness in promoting liver cell regeneration and preventing further damage.

Prolonged use of Liv.52 is helpful in cases of severe acute hepatic necrosis by promoting liver cell regeneration.

No untoward side effects of Liv.52 therapy were noted during the course of this study.

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