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A Clinico-pathological Study of Hepatomegaly with Special Reference to Liv.52 Therapy

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The liver holds a position of singular importance in the system, performing numerous metabolic functions. Diseases of the liver throw the entire system out of gear, while many systemic diseases are responsible for affections of the liver. Liver problems in our country in the paediatric age group are many; their treatment expensive and often not rewarding. Therefore, in quest of a new therapy, we thought of a trial on Liv.52 (The Himalaya Drug Co.) which is a combination of indigenous drugs and has much published data on its favourable action on liver diseases.

Review of Literature

Liv.52 has been tried in various hepatic disorders for more than a decade by many workers. Patrao (1957), found Liv.52 to be very useful and recommended its use for the treatment of severe hepatic damage. Mathur (1957), reported that the cases of infantile cirrhosis responded very well to Liv.52. Sule and Sathe (1957), observed marked clinical improvement, as well as improvement in liver function tests brought about by Liv.52 in cases of severe hepatic damage.

Vyas (1960), noted a decrease in cellular infiltration and necrotic changes in some cases of infantile cirrhosis. Sheth *et al.* (1960), showed that Liv.52 afforded quite considerable protection against hepatic damage caused by carbon tetrachloride in rats. Similar observations have been made by Joglekar *et al.* (1963), Patel and Sadre (1963) and Karandikar *et al.* (1963). Damle and Deshpande (1963), tried Liv.52 in cases of failure to gain weight and found good clinical response. Sheth *et al.* (1963), tried the drug in cases of anorexia and observed response in 68 per cent cases. Paulose (1963), reported considerable clinical improvement in cases of infantile cirrhosis by Liv.52, Sheth (1968), noted good response to Liv.52 in cases of infantile cirrhosis and observed a definite decrease in fibrosis as well as change in the architecture of the liver in some cases. *Arora* (1969), added Liv.52 to the usual treatment of infective hepatitis and reported that it adds "materially to the patients' comfort and accelerates the recovery." Jaffari and Shyamaraj (1969), tried Liv.52 in cases of infective hepatitis and observed good response clinically as well as in liver function tests. According to Prasad and Tripathi (1969), the addition of Liv.52 to the therapy brought about an immense increase in appetite and power to assimilate without bowel disturbance in all cases of malnutrition and infective hepatitis.

Plan of study

The present trial on Liv.52 has been carried out in 55 cases of hepatomegaly to assess its therapeutic response. In all these cases, Liv.52 was used as an adjunct to the treatment for specific disease entities.

A detailed history of each case was taken regarding past illnesses, dietetic, milestones, immunisation and history of specific illness in the family. A thorough clinical examination of each case was done, followed by systemic examination. The liver and spleen were examined for their size, consistency and surface.

Laboratory tests included the following investigations:

1. Urine for bile pigments and bile salts.
2. Haemoglobin percentage.
3. Total and differential white blood cell count.
4. Total serum protein, albumin and globulin.
5. Thymol-turbidity, flocculation and $ZnSO_4$ turbidity.
6. Serum bilirubin.
7. Vandenbergh reaction.
8. Icteric index.
9. Serum alkaline phosphatase.
10. Liver biopsy.

A detailed examination of each case and all the investigations were repeated every 2-3 weeks, while liver biopsy was repeated after 4-6 weeks. Skiagram of chest and Mantoux test were done wherever indicated. Liv.52 drops and tablets were used in recommended doses.

OBSERVATIONS

1. *Malnutrition*:- The present study comprised 31 cases of malnutrition. The male:female ratio was 1.2:1. The distribution of the cases according to age has been presented in Table 1:

Table I: Age distribution

Age	Malnutrition	Cirrhosis	Infective Hepatitis
Up to 1 year	9	4	–
1 – 2 years	9	5	–
2 – 5 years	4	4	5
5 – 10 years	7	3	–
10 – 15 years	2	1	2
Total	31	17	7

The common presenting symptoms were fever in 22 cases, loss of appetite in 12, cough in eight and distention of abdomen in five cases. There was a past history of measles, broachopneumonia, diarrhoea and pertussis in 13, 4, 10 and 2 cases respectively. History of underfeeding could be detected in 28 cases. Developmental milestones were delayed in 14 cases. Eighty three per cent cases belonged to poor socio-economic groups. Family history of tuberculosis was available in four cases. Pallor was observed in 28 and lymphadenopathy in five cases, ten cases proved to have primary complex. Liver function tests showed deranged liver function in 28 cases (Table No. V).

Out of the 25 cases who could be followed up, improvement in the general condition, return of appetite and weight gain were observed in 22 cases. Diminution of the size of the liver was appreciable in 11 cases. A rise in total haemoglobin percentage was observed in 20 cases. A rise in total serum proteins was present in 18 cases. The rise in the albumin fraction was more than in the globulin. Thymol turbidity and zinc sulphate turbidity improved in 15 cases. No significant change was observed in serum alkaline phosphatase levels.

Liver biopsy revealed protein depletion in 26 cases with fatty changes in 12, mononuclear cell infiltration in eight, periportal fibrosis in seven and focal necrosis in five cases. Biopsy was repeated in six cases. There was improvement in the histopathological picture in the form of repletion of cytoplasmic proteins and diminution of fatty infiltration in five of them after a period of one month.

Table II: Presenting symptoms				
Symptom	Malnutrition	Cirrhosis	Infective hepatitis	Total
Fever	22	12	6	40
Loss of appetite	12	8	6	26
Distention of abdomen	–	15	4	19
Yellow discoloration of skin	–	13	7	20
Cough	8	5	–	13

2. *Infective hepatitis*:- There were seven cases of infective hepatitis in the present series. The common presenting features were yellow discoloration of skin, fever, loss of appetite, passage of dark coloured urine and distention of the abdomen. There was past history of bronchopnueumonia in two cases, while that of measles in one case only. History of underfeeding could be obtained in three cases. There was no history of jaundice in the recent past in the family. The common signs observed were jaundice in all the seven cases and underweight in one case only.

Liv.52 therapy was administered along with broad-spectrum antibiotics. An improvement in the general condition, return of appetite and weight gain were observed in all the cases. Jaundice regressed and was clear by three weeks. Diminution of the size of the liver could be appreciated in six cases who could be followed up and the spleen also regressed in three cases where it was palpable before treatment. A rise in haemoglobin percentage was noted. Liver function tests also showed improved.

Histopathologically initial liver biopsy revealed mononuclear cell-infiltration in six cases, periportal fibrosis in five, focal necrosis in four and protein depletion in four cases. Out of the five cases where biopsy could be repeated after four weeks of Liv.52 therapy, protein depletion was reduced in three cases, fatty infiltration reduced in two cases, while mononuclear cell-infiltration was reduced in all the five cases.

3. *Cirrhosis of the Liver:*- The present series included 17 cases of cirrhosis of the liver. Out of them, 12 were male and five were female. The common presenting symptoms were distention of abdomen in 15 cases, yellow discoloration of skin in 15 cases, fever in 12, loss of appetite in eight cases and cough in five cases only. History of underfeeding could be detected in eight cases. Developmental milestones were delayed in three cases. Family history of tuberculosis was obtained in three cases. History of cirrhosis of the liver in another sibling could be obtained in one case only. The general condition was low in seven cases. Jaundice was detected in all the 17 cases, while oedema and lymphadenopathy in four and six cases, respectively. Four cases had primary complex. Histopathologically, post-necrotic cirrhosis was detected in nine cases, early infantile cirrhosis in five cases and diffuse hepatic cirrhosis in three cases.

Out of 17 cases of cirrhosis, 15 could be followed up. An improvement in the general condition and return of appetite could be seen after two-three weeks of therapy. There was regression of jaundice and a sense of well-being. A rise in haemoglobin was appreciated in seven cases. Total serum proteins became normal in 11 cases. Liver function tests showed improvement. However, these changes were very transient as they became worse when these cases reported again with deep jaundice, nasal bleeding and hepatic failure after 6-8 weeks. Diminution of the size of liver which become more firm was observed in five cases. Progression of the disease was evident in all the 9 cases histopathologically, in the second or third biopsy.

Table III: Socio-Economical Status					
S.-E. Status	Income per capita	Malnutrition	Cirrhosis	Infective Hepatitis	Total
Low	Less than Rs. 50/0 p.m.	25	3	3	31
Middle	Rs. 50 - 100/- p.m.	5	10	2	17
High	More than Rs.100/- p.m.	1	4	2	7

Table IV: Various Signs					
Sign		Malnutrition	Cirrhosis	Infective Hepatitis	Total
1.	Underweight	31	14	1	46
2.	Pallor	28	11	–	39
3.	Jaundice	–	11	7	18
4.	Lymphadenopathy	5	4	–	9
5.	Oedema	1	4	–	5

Table V: Results of Liv.52 Therapy									
Total number of follow-up cases	Infective Hepatitis 6			Cirrhosis 15			Malnutrition 25		
	Improve-ment	Deterio-ration	No change	*Improve-ment	Deterio-ration	No change	Improve-ment	Deterio-ration	No change
General condition	6	–	–	9	3	3	22	1	2
Weight gain	6	–	–	9	3	3	22	1	2
Appetite	6	–	–	9	3	3	22	1	2
Jaundice	6	–	–	9*	9	–	–	–	–
Liver size	6	–	–	4*	12	3	11	–	14
Liver consistency	6	–	–	–	4	11	7	–	18
Spleen	3	–	–	–	9	6	–	–	–
Out of 3 cases									
Total protein	4	2	–	11	4	–	18	7	–
Thymol turbidity	4	1	1	9	4	2	15	4	6
Thymol flocculation	3	–	3	7	4	4	12	3	10
$ZnSO_4$ turbidity	4	1	1	9	4	2	15	4	6
Serum Bilirubin	6	–	–	9*	9	–	–	–	–
Vandenbergh	6	–	–	9*	9	–	–	–	–
Icterus index	6	–	–	9*	9	–	–	–	–
Alkaline Phosphatase	4	1	1	3	9	3	8	8	9
* Transient regression of the symptoms and Liver Function Tests in cases of Indian Childhood Cirrhosis									

Table VI: No. of Cases in various Sub-groups of Liver Function Tests

Time	Disease	Serum proteins in gm%					Serum albumin gm%				Thymol turbidity in units					Thymol Flocculation				$ZnSO_4$ Turbidity in units						Serum Bilirubin in mg%				Alkaline phosphatase in units					
		Upto 4	4 - 5	5 - 6	6 - 7	Over 7	1 - 2	2 - 3	3 - 4	Over 4	1 - 5	5 - 10	10 - 15	15 - 20	Over 20	—	+	‡	‡‡	5 - 10	10 - 15	15 - 20	20 - 25	25 - 30	Over 30	Upto 2	2 - 5	5 - 10	Over 10	Upto 15	15 - 16	16 - 17	17 - 18	18 - 20	Over 20
Initial	Malnutrition	1	2	8	14	6	4	14	13	–	5	13	8	4	1	12	13	4	2	1	8	9	7	3	3	27	3	1	–	22	3	3	2	–	1
After 2 weeks	"	–	–	1	9	12	–	5	15	2	8	8	3	3	–	11	7	2	2	2	10	3	3	1	3	22	–	–	–	14	5	2	–	1	–
After 4 weeks	"	–	–	–	3	2	–	–	5	–	4	–	–	–	1	4	1	–	–	1	3	1	–	–	–	5	–	–	–	4	1	–	–	–	–
After 6 weeks	"	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Initial	Cirrhosis	1	2	5	6	3	2	10	5	–	–	5	8	4	–	1	10	4	2	–	–	3	4	3	7	6	7	4	–	2	–	4	–	1	1
After 2 weeks	"	–	–	–	7	6	–	6	7	–	2	6	2	3	–	2	8	2	1	–	2	4	4	1	2	2	1	1	–	4	6	–	1	2	–
After 4 weeks	"	–	–	–	2	6	–	3	4	1	2	3	3	–	–	3	4	1	–	–	3	2	1	–	2	6	1	1	–	1	1	3	1	1	1
After 6 weeks	"	–	–	–	1	2	–	1	2	–	–	2	1	–	–	1	1	1	–	–	2	–	–	–	1	2	–	1	–	–	1	–	1	–	1
Initial	Infective Hepatitis	–	–	–	5	2	1	3	3	–	–	2	1	2	2	–	3	3	1	–	–	–	2	1	4	–	4	2	1	4	–	1	1	–	1
After 2 weeks	"	–	–	–	1	5	1	–	5	–	2	3	–	–	1	2	2	2	–	1	–	–	1	2	2	5	1	–	–	2	2	2	–	–	–
After 4 weeks	"	–	–	–	1	2	1	–	2	–	1	1	–	–	1	2	–	1	–	–	1	1	–	–	1	3	–	–	–	3	–	–	–	–	–
After 6 weeks	"	–	–	–	–	1	–	–	1	–	–	–	–	1	–	–	1	–	–	–	–	–	1	–	–	1	–	–	–	1	–	–	–	–	–

Table VII-A: Histopathological Changes in Liver after Liv.52 Therapy						
Case no.	Clinical Diagnosis	1st Liver Function Test	1st Biopsy	2nd Liver Function Test	2nd Biopsy	Time interval (weeks)
12	Malnutrition	Deranged	Marked prot. Dep.	Deranged	Mild prot. Dep. Increased peri. Fib.	4
13	Malnutrition	Deranged	Mild prot. Dep.	Deranged	Prot. Dep. Less. Dilat. of sinusoids	4
26	Malnutrition	Deranged	Prot. Dep., fatty change, Mononuc. Cell infiltration	Deranged	Prot. Dep., fatty changes, Mononuc. Cell infiltration	6
34	Malnutrition	Deranged	Prot. Dep., fatty change	Improved	Prot. Dep. Less	4
41	Malnutrition	Deranged	Prot. Dep., peri. Fib.	Improved	Prot. Dep. Less. Fib. Less	4
6	Infective Hepatitis	Deranged	Subacute inf. Hepat.	Improved	Mod. fatty changes, peri. Fib. Cell infilitration	4
8	Infective Hepatitis	Deranged	Marked fatty change, prot. Dep., peri. Fib. Cell infiltration.	Improved	Mild prot. Dep., focal areas of cell infiltration	4
33	Infective Hepatitis	Deranged	Prot. Dep., increased peri fib. Cellular infiltration	Improved	Mild prot. Dep., peri. Fib. Cell infiltration less	4
42	Infective Hepatitis	Deranged	Tissue badly preserved	Improved	Mild prot. Dep. And cell infiltration	4
45	Infective Hepatitis	Deranged	Peri. Fib., focal necr. Cell infiltration	Improved	Cell infiltration less	5
51	Infective Hepatitis	Deranged	Focal-necrosis, cell infiltration	Improved	Cell infiltration less	5

Table VII-B: Histopathological Changes after Liv.52 Therapy						
Case no.	Clinical Diagnosis	1st LFT	1st Biopsy	2nd LFT	2nd Biopsy	Time interval (weeks)
4	Cirrhosis	Deranged	Early inf. Cirrh.	Deranged	Inf. Cirrh.	4
20	Cirrhosis	Deranged	Early inf. Cirrh.	Deranged	Inf. Cirrh.	8
28	Cirrhosis	Deranged	Early diffuse hepatic cirrhosis	Deranged	Same changes	4
44	Cirrhosis	Deranged	Diffuse hepatic Cirrh.	Deranged	No improvement	8
37	Cirrhosis	Deranged	Post-necrotic Cirrh.	Deranged	Inflammatory changes less	4
46	Cirrhosis	Deranged	Post-necrotic Cirrh.	Deranged	Infantile cirrhosis	6
30	Cirrhosis	Deranged	Early post-necrotic cirrhosis	Deranged	Post-necrotic cirrhosis	8
54	Cirrhosis	Deranged	Early post-necrotic cirrhosis	Deranged	Post-necrotic cirrhosis	12
48	Cirrhosis	Deranged	Post-necrotic cirrhosis	Deranged	Post-necrotic cirrhosis and infiltration	12

Abbreviations used in Tables VII-A and VII-B:	
LFT = Liver function test.	Cell infil. = Mononuclear cell infiltration.
Prot. Dep. = Protein depletion.	Focal neer. = Focal necrosis.
Peri. Fib. = Periportal fibrosis.	Inf. Cirrh. = Infantile cirrhosis.
Infec. Hepat. = Infective Hepatitis.	

DISCUSSION

Malnutrition: In a study of cases of malnutrition on Liv.52, Sheth *et al.* (1963) observed improvement of deranged liver function tests and return of normal appetite and gain in weight. Similar observations were made by Damle and Deshpande (1966), and Prasad and Tripathi (1969). In the present series of 31 cases, there was improvement in the general condition and gain in weight. Total serum proteins and liver function tests showed improvement after two to four weeks of therapy. Histopathological changes on second biopsy showed regression. There was repletion of cytoplasmic proteins and fatty infiltration also diminished. While the recovery was due partially to the improved diet, there is no doubt that Liv.52 was also responsible for the improvement.

Infective Hepatitis: Arora (1969) reported that Liv.52 adds "materially to the patients' comfort and accelerates recovery." According to Jaffari and Shyamraj (1969), Liv.52 clears jaundice earlier,

improves appetite and gives a sense of well being. In the present study of seven cases, there was improvement in all the cases within two weeks of therapy. There was increase in appetite and gain in weight. Jaundice regressed and liver size was reduced. Liver function tests also improved. Histopathological examination of liver tissue on second biopsy revealed that the infiltration by inflammatory cells was less. The recovery of cases on Liv.52 was quicker as compared to cases treated as control.

Infantile Cirrhosis: Sheth, *et al.* (1960) Joglekar *et al.* (1963) Patel and Sadre (1963) and Karandikar *et al.* (1963) observed the significant protection to liver cells by Liv.52 in experimental animals. The hepatic damage caused by carbon tetrachloride showed improvement after Liv.52 therapy. In view of these observations, the drug was tried in cases of infantile cirrhosis. Paulose *et al.* (1963) and Sheth *et al.* (1968), reported a decrease in the size of the liver and change in its consistency in cases who were put on Liv.52. Sathe and Sule (1967), observed an increase in total proteins and return of liver function tests in such cases. Sheth *et al*. (1968) reported that early and intermediate cases showed clinical improvements — anorexia, nausea, fever, ascites, jaundice, oedema, abdominal distension were relieved. In the improved group liver function tests also returned to normal as evidenced by an increase in serum proteins and improvement in serum alkaline phosphates. Histopathologically there was definite decrease in fibrosis and a change in the architecture of liver indicating improvement in some cases.

Out of 17 cases of the present series, follow-up was possible in 15 cases. There was regression of jaundice after two weeks of therapy. Liver function tests showed transient improvement in 2/3rd of the cases after three weeks, but these later became worse when these cases reported again in hepatic failure. Histopathologically there was progression of the disease in all the nine cases where biopsy was repeated. Eight out 17 cases of our series have already expired.

Cirrhosis of the liver once fully established is an irreversible condition. No medicines are known to convert fibrous tissue into parenchymatous tissue. However, in these cases it is clinically very difficult to find out the liver function still available after damage. Sometimes the quantum is such that administration of therapy might turn the balance in favour of the patient by improving liver function through its action on partially damaged and some normally functioning cells. With this hope we put our patients of Indian Childhood Cirrhosis on Liv.52. The results show that most of our cases were of advance, established cirrhosis, thus confirming the hypothesis based on available knowledge.

To sum up, we feel that Liv.52 deserves further trial on a larger scale. It would also be better if the indigenous substances used are further analysed, so that ultimately we can lay our hands on the effective ingredient.

SUMMARY AND CONCLUSION

A clinical trial of Liv.52 was carried out in 55 cases of hepatomegaly. The series comprised 31 cases of malnutrition, 17 cases of cirrhosis of the liver and seven cases of infective hepatitis. Liv.52 was used as an adjunct to the therapy for the respective disease entity.

In cases of malnutrition, return of appetite and weight gain was observed in 22 cases. Liver function tests and histopathology of liver showed improvement.

An improvement in general condition was noticed in all the cases of infective hepatitis. Jaundice regressed and liver function tests showed improvement. Infiltration of inflammatory cells in the liver tissue was less after Liv.52 therapy and recovery was quicker.

In cases of confirmed Infantile Cirrhosis, there appeared initial transient improvement in the general condition with regression of jaundice, but later, these cases relapsed. There was progression of the disease clinically as well as histopathologically. Thus Liv.52 has hardly any role in proven cases of Indian Childhood Cirrhosis. Its role in pre-cirrhotic and early cases of Indian Childhood Cirrhosis is under study.

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