[*Indian Medical Journal* (1983): 1, 3]

The Treatment of Nonsuppurative Hepatic Amoebiasis with Liv.52 as an Adjuvant to Antiamoebic Drugs

Bose, S.L., *M.D., D.M.,* and **Rout, A.K.,** *M.B.,B.S.,*
Gastroenterology Division, Department of Medicine
S.C.B. Medical College, Cuttack, India.

Nonsuppurative hepatic amoebiasis is a diffuse lesion of the liver. Of all amoebic involvements, this condition has remained an enigma as regards the type of liver injury brought about by *Entamoeba histolytica.* However, the therapeutic efficacy of conventional antiamoebic drugs like Dehydroemetine hydrochloride, Chloroquine phosphate and Metronidazole and their side effects have been well documented. The drugs get distributed in the body and directly kill the amoebae at the site. Sometimes the toxic side effects are damaging to the patient and at times the drug has to be withdrawn before its therapeutic effect is achieved.

The beneficial role of Liv.52 (The Himalaya Drug Co.) against CCl_4-induced liver injury in experimental animals have been well established (Joglekar *et al.,* 1963 and Karandikar, 1963). The use of Liv.52 in many therapeutic regimen as an adjuvant has been evaluated by many workers with promising results (Sethi and Meratwal, 1974; Munuswamy and Gajraj, 1975). Its value as a hepatotonic substance and agent for reducing side effects of drugs has been claimed in different trials. There are few such trials has been designed to assess the efficacy of Liv.52 as an adjuvant with antiamoebic drugs in patients with nonsuppurative hepatic amoebiasis *E. histolytica* gives rise to serologically detectable specific antibodies when there is tissue invasion. Therefore the detection of these highly specific antibodies in serum of the patients with non-suppurative hepatic amoebiasis is the only method to clinch a definitive diagnosis.

MATERIAL AND METHODS

The study was conducted on 60 patients with nonsuppurative hepatic amoebiasis attending the S.C.B. Medical College Hospital, Cuttack from 1979 to 1981.

The patients were selected on the basis of clinical criteria of enlarged tender liver with present or past history of intestinal amoebiasis. The diagnosis was confirmed in each case by the detection of *E. histolytica* cysts or vegetative forms in the stool and positive serologic test. Among the various serologic tests for the diagnosis of amoebiasis the immunodiffusion technique is simple, reproducible and reliable (Powell, 1968).

Clinical data, routine investigations and liver function tests were recorded before inclusion in the study. Cases were randomised into 6 groups of 10 patients each for the purpose of treatment with three commonly used antiamoebic drugs: Dehydroemetine, Chloroquine and Metronidazole in conjunction with either Liv.52 or placebo. The following dosage schedules were laid down in the different study groups:

(i) Dehydroemetine 60 mg subcutaneously for 10 days.
(ii) Chloroquine, initially 500 mg twice daily for 21 days and thereafter 250 mg daily.

(iii) Metronidazole, initially 500 mg twice daily for 21 days and thereafter 1200 mg in divided doses for 10 days.

The total period of observation was 6 weeks in each case.

The response was assessed by subjective and objective improvement recorded at every weekend till the sixth week. Liver function tests were repeated each week until completion of treatment. The bromsulphthalein test was only repeated on completion of 6 weeks' treatment.

Stools were examined by Formol-ether concentration and ordinary saline preparation. Hemogram and Urinalysis were done by standard techniques. E.S.R. was done by Westergren Method. The liver function tests included estimation of total and conjugated serum bilirubin, serum transaminase (S.G.OT. and S.G.P.T.), serum alkaline phosphatase, serum protein and serum albumin by methods of Mulloy and Elvyn (1973), Reitman and Frankel (1957), King and Armstrong (1934), modified Biurette method of Kingsley (1972) and Doumas and Biggs (1972) respectively. Bromsulphthalein retention in serum was estimated colorometrically as its percentage of retention. The amoebic serologic test was done by immunodiffusion technique with antigen from Hoechst Pharmaceuticals, West Germany.

The response to therapy was adjudged by subjective and objective improvement during and at the end of 6 weeks of therapy. Results of the therapy were categorised as per following criteria.

I. *Complete cure*
1. Complete disappearance of symptoms,
2. Regression of liver to normal size,
3. Stools negative for *E. histolytica* cyst/vegetative form,
4. Complete biochemical recovery, and
5. Normal B.S.P. retention.

II. *Partial cure*
1. Disappearance of symptoms to a great extent,
2. Partial regression of liver size,
3. Stools negative for *E. histolytica* cyst/trophozoites,
4. Nearly complete biochemical recovery, and
5. Normal B.S.P. retention.

III. *Failure*
1. Persistency of symptoms,
2. Persistence of enlarged and tender liver,
3. Stools positive for *E. histolytica* cyst/vegetative form,
4. Persistence of biochemical abnormality, and
5. Abnormal B.S.P. retention.

Side effects to the drugs were noted.

OBSERVATIONS

Sixty patients with nonsuppurative hepatic amoebiasis in the age range of 18 to 60 years have been included in this study. Of these 60 patients, 53 were males and 7 females. Maximum incidence of the disease (61.1%) was observed in the age range of 21 to 40 years. The clinical data of the 60 patients have been depicted in Table 1.

Table 1: Clinical features of 60 patients with non-suppurative hepatic amoebiasis

Symptoms and signs	No. of patients	Percentage
Fever and pain in the right hypochondrium	30	50.00
Fever without pain	3	05.00
Referred pain over the right side of chest and shoulder	3	05.00
Abdominal mass	1	01.60
Jaundice	1	01.60
Anorexia	5	08.30
Cough	7	11.60
Flatulence	5	08.30
Dyspepsia	4	06.60
Nausea and vomiting	2	03.30
Constipation	15	25.00
Dysentery	16	26.60
Hepatomegaly: Just palpable to 3 cm	47	78.33
3 cm to 8 cm	13	21.67
More than 8 cm	–	–
Hepatic tenderness	60	100.00

The onset was insidious in all the patients. In half of the patients, a combination of fever and pain in the right hypochondrium was the outstanding symptom. Constipation in 25% and dysentery in 26.6% of patients were the major bowel symptoms. Other minor gastrointestinal symptoms included anorexia, flatulence, dyspepsia, nausea and vomiting and jaundice. Seven patients complained of cough. Mild and moderate hepatomegaly was present in 78.3% and 21.67% respectively. None had liver enlargement more than 8 cm below the costal margin. It was tender hepatomegaly in all the cases.

Table 2 shows the changes in laboratory parameters.

Microcytic hypochromic anaemia was present in all cases. E.S.R. was raised in 96.6%. Leucocytosis was present in 41.6%.

Clinical jaundice was manifest in one out of every 6 patients (10%) who had hyperbilirubinaemia. Mild rise in S.G.O.T. and S.G.P.T. level in 86.6 and 98.3% were the predominant abnormal liver function tests. Alkaline phosphatase was raised in only 18.3%. A low serum total protein and albumin was noted in 16.6% and 26.6%. Mild B.S.P. retention, suggestive of deficiency in functional capacity of liver, was observed in 71.6% of patients with nonsuppurative hepatic amoebiasis.

Table 2: Results of laboratory investigations in 60 patients with non-suppurative hepatic amoebias		
Investigations	No. of patients	Percentage
Leucocytosis (>9000/cmm)	25	41.6
Anaemia (<13g/100 ml)	60	100.0
Raised E.S.R. (>7 mm in 1st hour)	58	96.6
Raised serum bilirubin (>1 mg/100 ml)	6	10.0
Raised S.G.O.T. (>20 IU/litre)	52	86.6
Raised S.G.O.T. (>13 IU/litre)	59	98.3
Raised alkaline phosphatase (>13 K.A.U.)	11	18.3
Low serum protein (<6.8 g/100 ml)	10	16.6
Low serum albumin (<3.5 g/100 ml)	16	26.6
Abnormal B.S.P. retention (>5 per cent)	43	71.6

The results of the six groups have been shown in Table 3.

Table 3: Results of treatment in 60 patients with nonsuppurative hepatic amoebiasis with Dehydroemetine, Chloroquine and Metronidazole in combination with Liv.52 or placebo as an adjuvant				
Treatment regimen	Total No. of patients	Results of treatment after 6 weeks		
		Complete cure	Partial cure	Failure
Dehydroemetine plus Liv.52	10	8 (80%)	2 (20%)	–
Dehydroemetine plus placebo	10	4 (40%)	4 (40%)	2 (20%)
Chloroquine plus Liv.52	10	5 (50%)	2 (20%)	3 (30%)
Chloroquine plus placebo	10	3 (30%)	2 (20%)	5 (50%)
Metronidazole plus Liv.52	10	9 (90%)	–	1 (10%)
Metronidazole plus placebo	10	6 (60)	3 (30%)	1 (10%)

It is evident from the Table that patients treated with antiamoebic drugs and Liv.52 showed higher percentage of improvement than those treated with antiamoebic drugs and placebo. Eighty percent receiving Dehydroemetine, and Liv.52 had complete cure in comparison to 40% receiving dehydroemetine and placebo as per criteria adopted for assessment of results at the end of 6 weeks. Two patients receiving the latter combination failed to show improvement and 4 patients had partial cure. None failed to respond to treatment with the combination of Dehydroemetine and Liv.52. Remaining 2 patients in this group had partial cure.

The combination of Metronidazole and Liv.52 showed a slightly better result than with dehydroemetine with Liv.52. Nine out of 10 patients (90%) had complete cure and 1 failed to respond to therapy at the end of 6 weeks. Whereas only 60% had complete cure with Metronidazole and placebo combinations. Three patients (30%) had partial cure and one (10%) failed to respond at all.

The combination of Chloroquine and Liv.52 showed a power response than that with either dehydroemetine or Metronidazole. Only half of the patients received Chloroquine and Liv.52 had complete cure; among the other half, 2 patients (20%) had partial cure and 3 patients (30%) failed to respond to Chloroquine. Half of the patients (50%) failed to respond to combination of Chloroquine

and placebo. In this group 2 (20%) and 3 (30%) patients had partial and complete cure respectively. The average time for fever and pain to subside was 3 and 7 days respectively, in those receiving Liv.52 and placebo. The bowel symptoms and enlarged tender liver reduced gradually. The average time needed for complete disappearance of bowl symptoms and regression of liver to normal size with no tenderness, with Liv.52 and placebo was 14 and 21 days respectively.

The laboratory parameters including liver function tests carried out before and 6 weeks after treatment in each group of patients have been depicted in Tables 4a, 4b and 4c.

Table 4a: Findings of liver function tests with a combination of Dehydroemetine and Liv.52 or placebo (n=60)

	With Liv.52			With Placebo		
	Before therapy	After therapy	Significance	Before therapy	After therapy	Significance
Total bilirubin	0.71±0.26	0.36±0.34	S	0.36±0.34	0.41±0.26	IS
Conjugated bilirubin	0.34 ± 0.04	0.13±0.04	S	0.32±0.06	0.32±0.13	IS
SGOT	30.4±7.15	8.8±2.7	S	31±6.22	18.8±4.31	S
SGPT	36.4±15.5	7.6±4.4	S	30.8±1.93	19.1±4.34	S
Serum Alkaline Phosphatase	9.4±2.5	5.9±2.2	S	11.2±3.8	12.6±2.53	IS
Serum protein	6.94±1.42	6.75±0.20	S	6.74±1.16	6.94±0.14	IS
Serum albumin	3.46±0.45	3.03±0.45	S	3.50±0.63	3.70±1.29	IS
BSP	6.8±1.6	3.9±1.2	S	6.2±1.2	5.2±0.2	S

Table 4b: Findings of liver function tests with a combination of Chloroquine and Liv.52 or placebo (n=60)

	With Liv.52			With Placebo		
	Before therapy	After therapy	Significance	Before therapy	After therapy	Significance
Total bilirubin	0.77±0.23	0.43±0.18	S	0.82±0.35	0.73±0.36	IS
Conjugated bilirubin	0.33±0.18	0.13±0.06	S	0.33±0.28	0.24±0.11	IS
SGOT	29.30±6.90	10.40±3.50	S	31.50±8.90	20.5±5.30	S
SGPT	31.50±8.90	9.20±3.10	S	31.50±8.90	19.7±10.3	S
Serum Alkaline Phosphatase	7.55±0.79	6.88±0.20	S	7.03±0.83	7.12±0.28	IS
Serum protein	7.55±0.79	6.88±1.90	S	7.03±0.83	7.12±0.28	IS
Serum albumin	3.82±0.37	3.76±0.78	S	3.92±0.17	3.65±0.56	IS
BSP	6.50±1.40	5.00±1.80	IS	6.40±1.56	6.50±1.20	IS

Table 4c: Findings of liver function tests with a combination of Metronidazole and Liv.52 or placebo (n=60)

	With Liv.52			With Placebo		
	Before therapy	After therapy	Significance	Before therapy	After therapy	Significance
Total bilirubin	0.75±0.22	0.44±0.33	S	0.90±0.18	0.74±0.13	IS
Conjugated bilirubin	0.40±0.35	0.90±0.04	S	0.29±0.14	0.24±0.69	IS
SGOT	30.1±6.30	7.60±2.18	S	32.30±5.34	8.30±0.41	S
SGPT	22.90±8.92	14.4±4.81	S	35.50±6.86	14.30±4.51	S
Serum Alkaline Phosphatase	11.40±0.47	7.40±2.39	S	10.0±3.68	7.80±2.30	IS
Serum protein	7.38±0.83	7.62±0.51	S	7.18±0.65	6.70±0.37	IS
Serum albumin	3.83±0.33	4.92±0.40	S	3.50±0.37	3.16±0.48	S
BSP	6.00±1.80	4.20±1.48	S	7.2±0.60	5.20±1.66	S

It is observed from the Table that there was a significant fall in the serum level of total and conjugated bilirubin in patients treated with antiamoebic drugs and Liv.52 ($p<0.05$). The fall in serum bilirubin level was insignificant in placebo group ($p>0.05$). The pretreatment rise of SGOT and SGPT returned to normal with all the three antiamoebic drugs irrespective of being combined with Liv.52 or placebo. There was a significant fall of transaminase in all the groups ($p<0.05$). Though there was an insignificant reduction in the level of serum alkaline phosphatase in the

placebo group in comparison to the significant reduction in groups of those patients treated with Liv.52 as an adjuvant ($p<0.05$), the serum level of the enzyme did not have abnormal value either before or after treatment. The serum levels of protein and albumin rose significantly in patients treated with antiamoebic drugs except Metronidazole with Liv.52 as an adjuvant ($p<0.05$).

The percentage retention of B.S.P. was significantly less in patients after treatment with Dehydroemetine and Chloroquine either when combined with Lvi.52 or placebo in comparison to pretreatment values ($p<0.05$). The reduction in B.S.P. retention was insignificant in patients treated with Liv.52 or placebo, as an adjuvant to chloroquine ($p<0.05$).

The side effects to drugs in combination with Liv.52 or placebo are depicted in Table 5.

Table 5: Incidence of side effects of Dehydroemetine, Chloroquine and Metronidazole in combination with Liv.52 or placebo

Antiamoebic drug	Liv.52	Placebo	Nature of side effects
Dehydroemetine	–	2	Asthenia
Chloroquine	1	7	Headache, dizziness, asthenia, dry mouth and anorexia
Metronidazole	–	5	Anorexia, epigastric fullness nausea and unpleasant taste

Figures indicate the number of patients who had side effects.

It was observed that the side effects were not encountered when they were combined with Liv.52 except in one patient who was administered Chloroquine and Liv.52, where the therapy had to be discontinued during the second week. The side effects were more with all the three antiamoebic drugs Dehydrometine, Chloroquine and Metronidazole in 2, 7 and 5 patients respectively, when combined with placebo.

DISCUSSION

Nonsuppurative hepatic amoebiasis is a recognisable entity. The incidence of this disease is more common in this part of the country (Orissa) in comparison to amoebic liver abscess, the other manifestation of amoebic liver disease. The clinical spectrum and the abnormal laboratory findings observed in this series of 60 patients with nonsuppurative hepatic amoebiasis are almost comparable with other reported series (Banerji *et al.,* 1968, Sodeman, 1970). The predominant presenting symptoms were fever and right hypochondrial pain. The findings of tender hepatomegaly in all the cases was the clue to the diagnosis. The marked abnormality in laboratory parameters of anaemia, raised E.S.R. and mild transaminasemia correlated well with the findings of other authors (Banerji *et al.,* 1968; Jayant and Srinivas, 1970). Though not significant, the raised transaminase and abnormal retention of B.S.P. in the majority of patients of the present series indicates loss of liver function in nonsuppurative hepatic amoebiasis even in the absence of definite morphological abnormality. The condition always needs treatment, as its inevitable sequel is abscess formation. The earlier claims in the results of drug trials were conflicting. The side effects of Dehydroemetine, Chloroquine an Metronidazole are well-documented (Powell, 1959; Hendrick, 1973; Jayant and Srinivas, 1970). Liv.52 is an indigenous hepatotonic drug that has been tried as an adjuvant to potentiate the amoebicidal property and reduce the side effects of antiamoebic drugs.

Dehydroemetine has replaced emetine because of cardiotoxicity of the latter. Chloroquine is as effective as emetine but the relapse rate is higher with Chloroquine (Wilmot *et al.,* 1958). In this study, Dehydroemetine has been tried in preference to emetine. It is evident from this study that by

combining a hepatotonic agent, Liv.52 with one of the three antiamoebic drugs, Dehydroemetine, Chloroquine and Metronidazole, their therapeutic response is increased and the relapse rate is curtailed. The side effects are also minimized. The therapeutic response to Metronidazole in nonsuppurative hepatic amoebiasis reported in different series has been uniform (Banerji *et al.,* 1968; Jayant and Srinivas, 1970).

Unlike in the previous studies, the haematological improvement in the present group of patients occurred without any haematinic therapy. The liver function test values either reverted to normal or showed considerable improvement. Only one patient was considered as failure to therapy, due to persistence of abnormal B.S.P. retention at the end of 6 weeks. Three patients were termed as partially cured due to the persistence of enlarged liver at the end of therapy, though there was complete biochemical recovery as that of 6 other patients who had complete cure. The addition of Liv.52 as an adjuvant to Metronidazole improved the therapeutic efficacy of the drug, achieving complete cure in 90% and only one failure with abnormal B.S.P. retention. The usual side effects of Metronidazole were observed only in the placebo group.

SUMMARY AND CONCLUSIONS

1. In the present double blind trial, 60 patients with nonsuppurative hepatic amoebiasis were treated with a combination of one of the antiamoebic drugs – Dehydroemetine, Chloroquine, and Metronidazole with Liv.52 or its placebo to assess the adjuvant effect.

2. The clinical spectrum of the disease essentially comprised of right hypochondrial pain with or without fever, few other associated gastrointestinal symptoms and enlarged tender liver. A normocytic, hypochromic anaemia, raised E.S.R., mildly raised serum transaminases and abnormal retention of bromsulphthalein were the outstanding abnormal investigations.

3. The therapeutic response of the antiamoebic drugs could be improved by adding Liv.52 as an adjuvant to them. The cure rate achieved with Liv.52 as an adjuvant was 80% with Dehydroemetine, 50% with Chloroqiune and 90% with Metronidazole. In contrast, the cure rate was 40% with Dehydroemetine, 30% with Chloroquine and 60% with Metronidazole when given with placebo. The clinical improvement occurred earlier with the combined regimen of Liv.52 and anti-amoebic drugs than given on their own.

4. Side effects of the anti-amoebic drugs could be reduced by combining Liv.52 with them.

Liv.52 has a beneficial role as an adjuvant to anti-amoebic drugs in the treatment of nonsuppurative hepatic amoebiasis.

REFERENCES

1. Antoni, J. and Srinivas, H.V. *Am. J. Trop. Med. Hyg.* (1970): 19, 742.

2. Banerji, R.B., Lakshmipathy, N., Nag, Khanna, S.K. and Behari, V. *Ind. Practit.* (1968): 21, 749.

3. Dumas, B.T. and Biggs, H.G. Standard Methods of Clinical Chemsitry, Academic Press. (1972): 175.
4. Hendrickse, R.G. *Brit. med. J.* (1973): 1, 669.

5. Kingsley, G.R. Standard Methods of Clinical Chemistry, Academic Press, (1972): 199.

6. King, E.J. and Armstrong, A.R. *J. Canad. Med. Assoc.* (1934): 31, 376.

7. Mulloy, H.T. and Elvyn, K.A. *J. Biol. Chem.* (1973): 119, 481.

8. Powell, S.J. *Brit. Heart J.* (1959): 21, 263.

9. Reitman, S. and Frenkel, S. *Amer. J. Clin. Path.* (1957): 28, 56.

10. Sodeman, N.A. *Amer. J. Trop. Med.* (1950): 30, 141.