[***Probe*** (1973): (XII), 3, 129-137]

A Clinical Study of the Therapeutic Efficacy of Liv.52 as an Adjuvant in the Treatment of Hepatic Amoebiasis

Prof. Sethi, J.P., *M.D., M.A.M.S., F.C.A.I.,*
and
Suresh Meratwal, *M.B.B.S.,*
Department of Medicine, S.M.S. Medical College and Attached Hospital, Jaipur, India.

INTRODUCTION

The incidence and the relative problems of amoebiasis are of considerable magnitude throughout the nation. Though a large number of antiamoebic drugs have enriched our therapeutic armamentarium, yet there is hardly any ideal amoebicide available. The problem is further complicated by relapses and reinfection so characteristically associated with the disease. The difficulty is further enhanced by the inherent side effects of the antiamoebic drugs themselves. Moreover, the involvement of the liver so commonly associated with amoebiasis affects the entire metabolism. All these, plus the chronic, relapsing and recurring nature of the illness, results in great morbidity manifesting as loss of appetite, tiredness, easy fatigue, vague aches and diminished mental alacrity in addition to the conventional typical manifestations of the disease.

Any drug, therefore, which has a protective action on the liver and due effect on metabolism will be a great asset in the management of amoebiasis, especially in cases associated with hepatic complications. This may shorten the period of therapy with conventional antiamoebic drugs, lessening the incidence of their side effects, ameliorating the symptoms earlier, resulting in quick recovery and also lessening the associated morbidity.

In the past, lipotropic agents and corticosteroids have been used as adjuvants, but their efficacy *in vivo* is yet to be established. However, lately, certain indigenous drugs have been tried as hepatotonics and the most promising of them has been Liv.52, as this drug affords reasonably good protection against the hepatotoxic effects of carbon tetrachloride (CCl_4). Moreover, its anabolic effect on the general metabolism and appetite is an added advantage.

Since the adjuvant efficacy of this drug has been reported in certain liver disorders, e.g. infective hepatitis, infantile cirrhosis, fatty liver etc., it was thought worthwhile to assess its therapeutic efficacy as an adjuvant, also in the management of hepatic amoebiasis.

MATERIAL AND METHODS

The study was conducted in S.M.S. Medical College and Hospital, Jaipur on 30 selected patients of heaptic amoebiasis, who were admitted in the medical wards.

Criteria of Selection

The criteria of selection were as follows:

1. History of previous attacks of dysentery or diarrhoea, constipation, vague abdominal pain, weakness and fatigue, with or without low grade fever.
2. Presence of *E. histolytica* (EH) cyst or trophozoites in stools.
3. Presence of enlarged, tender liver.
4. Presence of EH cysts or trophozoites on rectal scrapings.
5. Presence of amoebic ulcers on sigmoidoscopic examination.
6. Presence of hepatic involvement on histopathological examination.

The presence of at least three or more parameters with enlarged, tender liver was essential to label a case as hepatic amoebiasis.

All the cases suggestive of hepatic amoebiasis were evaluated thoroughly by clinical history, physical examination and general laboratory investigations. Repeated clinical examination and relevant laboratory investigations were done on the 3rd, 7th, 10th, 12th and 15th day of therapy.

Drug Administration and Dosage Schedule

Nivembin (M&B) consisting of di-iodohydroxyquinoline (300 mg) and chloroquine (65 mg) per tablet was given as a standard antiamoebic drug in a dosage schedule of two tablets three times daily, for 15 days.

Liv.52 or placebo tablets were given in a dosage of two tablets three times a day for the same duration.

Placebo tablets were identical to Liv.52 tablets in shape, size and colour, so that the study used a double-blind technique. Two groups on drugs were formed: one on Nivembin plus Liv.52 tablets; and, the other, on Nivembin plus placebo tablets. The two drugs groups were labelled as A and B, respectively.

The patients were put on drug groups A and B alternately for a period of 15 days and follow-up was made on the 3rd, 7th, 10th, 12th and 15th day.

After completion of 15 days' combined therapy on either of the drug groups, a further course of Liv.52 tablets alone was given for one month to those patients who did not show the desired response.

Criteria for Improvement

The response to therapy was adjudged by observing subjective and objective improvement.

Subjective: Amelioration of pain in abdomen, constipation, flatulence, dyspepsia, nausea, vomiting, loose motions and an improvement in the appetite.

Objective: 1 - Absence of colonic and liver tenderness.
2 - Regression of liver to normal size.
3 - No EH or trophozoites in stool.
4 - Disappearance of ulcers as visualised on sigmoidoscopy.

Results of the therapy were categorised according to the follow criteria:

I. *Complete Cure*
   1. Complete disappearance of symptoms.
   2. Regression of liver.
   3. Return of normal mucosal appearance on sigmoidoscopy.
   4. Stool free from EH cysts or trophozoites.
   5. Normal histological appearance of liver tissue.

II. *Partial Cure*
   1. Disappearance of the symptoms to a great extent.
   2. Partial regression of the liver size.
   3. No EH cyst or trophozoites in stools.
   4. Partial improvement in the rectal mucosal appearance as visualised on sigmoidoscopic examination.

5. Partial improvement in histological appearance of liver tissue.

III. *Failure*

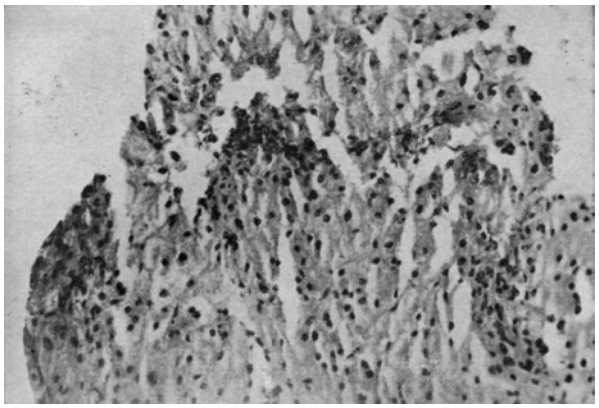
1. Persistence of symptoms.
2. Persistence of enlarged, tender liver.
3. Persistence of rectal mucosal changes.
4. Presence of EH cyst or trophozoites in stools.
5. No change in histological appearance of liver tissue.

OBSERVATIONS AND RESULTS

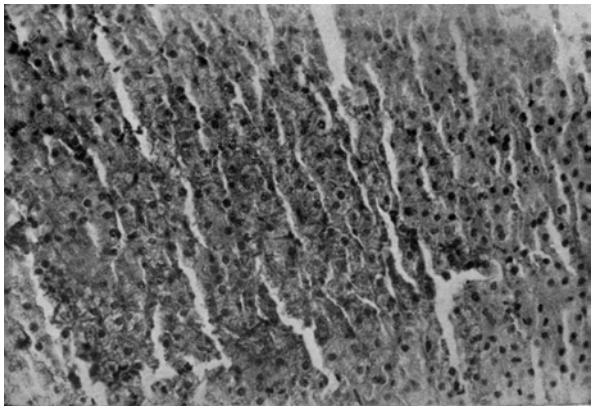
Thirty cases between 15 and 52 years of age, satisfying the criteria of hepatic amoebiasis were selected. Of the 30 patients, 28 were male and 2 female. Maximum incidence (66.6%) of the disease was observed in the age group 21-40 years.

Fifteen patients received drugs belonging to Group A and the same number of patients were treated with drugs of Group B.

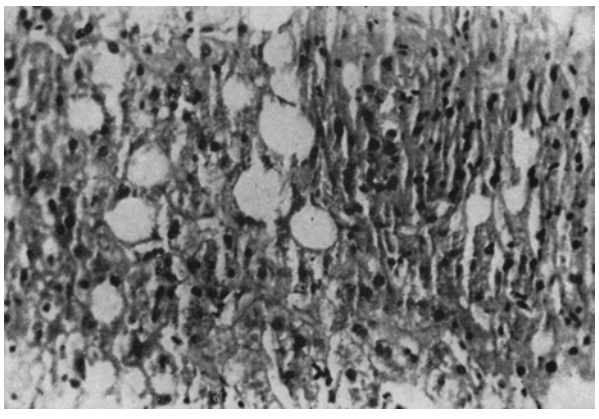
Of 30 patients, 22 gave a history of having loose motions before the present illness. Their duration varied from less than a month to 10 years.



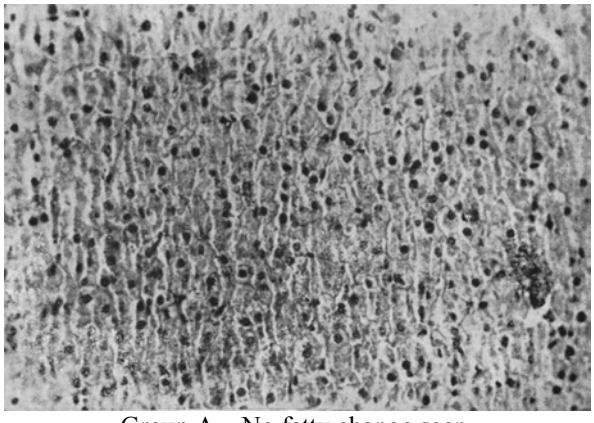
Group A – Mononuclear cell infiltration in portal area
(High power – Before treatment)



Group A – Normal recovery of liver cells
(High power – After treatment)



Group A – Fatty change in liver
(High power – Before treatment)



Group A – No fatty change seen.
Normal liver architecture
(High power – After treatment)

Presenting Complaints

Table 1: Shows the presenting manifestations of the patients with hepatic amoebiasis				
Sl. No.	Complaints	In patients treated with drug Group A	In patients treated with drug Group B	Total
1.	Abdominal pain	15	12	27
2.	Loose motions	6	6	12
3.	Constipation	8	9	17
4.	Nausea/Vomiting	2	2	4
5.	Diminished appetite	9	9	18
6.	Flatulence	8	8	16
7.	Dyspepsia	15	14	29
8.	Heart burn	1	1	2
9.	Feverishness	8	9	17
10.	Diminished libido	2	2	4
11.	Fatigue	13	12	25
12.	Cough	4	3	7
13.	Weight loss	7	3	10

Laboratory Investigations

Tables 2 and 3 show normal and abnormal values of laboratory investigations before and after treatment in patients treated with drug groups A and B.

It is evident from the above tablets that the percentage of improvement in laboratory tests is significantly higher in patients treated with drug group A.

It is seen from the above table, that the patients treated with drug group A revealed a higher percentage of improvement in symptoms than those receiving drug group B.

Table 2: Results in drug group A					
Investigations	Before therapy (15 cases)		After therapy (15 cases)		% of improvement
	Normal	Abnormal	Normal	Abnormal	
Hb (13-16 g%)	2 (13.3%)	13	6 (40%)	9	26.3%
TRBC (4.8-5.2 ml/cu mm)	3 (20%)	12	6 (40%)	9	20%
TLC (4-11,000 cu.mm)	15 (100%)	-	15	–	–
ESR (0-10 mm. 1st hr)	2 (13.3%)	13	7 (46.6%)	8	33.3%
LFT	12 (80%)	3	15 (100%)	-	20%
SGOT	14 (93.3%)	1	15 (100%)	-	6.6%
SGPT	14 (93.3%)	1	15 (100%)	-	6.6%
Prothrombin time	12 (80%)	3	15 (100%)	-	20%
Total protein A/G ratio	13 (86.7%)	2	15 (100%)	-	13.3%

Table 3: Results in drug group B					
Investigations	Before therapy (15 cases)		After therapy (15 cases)		% of improvement
	Normal	Abnormal	Normal	Abnormal	
Hb	5 (33.3%)	10	5 (33.3%)	10	Nil
TRBC	5 (33.3%)	10	5 (33.3%)	10	Nil
TLC	15	-	15	-	-
ESR	3 (20%)	12	4 (26.6%)	11	6.3%
LFT	13 (86.7%)	2	14 (93.3%)	1	6.6%
SGOT	15 (100%)	-	15 (100%)	-	-
SGPT	15 (100%)	-	15 (100%)	-	-
Prothrombin time	14 (93.3%)	1	15 (100%)	-	6.6%
Total protein A/G ratio	14 (93.3%)	1	15 (100%)	-	6.6%

Table 4: Shows degree of improvement in symptomatology after treatment with drug groups A and B								
Symptoms	Drug group A			% of improvement	Drug group B			% of improvement
	Cases in whom encountered	Relief	No relief		Cases in whom encountered	Relief	No relief	
Pain abdomen	15	14	1	93.3%	12	10	2	83.3%
Loose motions	6	6	-	100%	6	6	-	100%
Constipation	8	7	1	87.5%	9	8	1	88.8%
Nausea/Vomiting	2	2	-	100%	2	1	1	50%
Diminished appetite	9	9	-	100%	9	4	5	44.4%
Flatulence	8	8	-	100%	8	8	-	100%
Dyspepsia	15	14	1	93.3%	14	10	4	71.4%
Heart burn	1	1	-	100%	1	1	-	100%
Feverishness	8	8	-	100%	9	9	-	100%
Diminished libido	2	2	-	100%	2	1	1	50%
Fatigue	13	12	1	92.3%	12	10	2	83.3%
Cough	4	4	-	100%	3	3	-	100%
Loss of weight	7	6	1	85.7%	3	1	2	33.3%

All the nine cases in group A who complained of diminished appetite showed marked improvement in appetite after completion of therapy, while only 44.4 per cent of patients treated with drug group B admitted any improvement in appetite after therapy.

Table 5: Shows results of treatment with drug groups A and B				
Drug group	No. of patients	Extent of relief		
		Complete	Partial	Failure
Group A	15	11 (73.3%)	4 (26.7%)	0 (Nil)
Group B	15	6 (40.0%)	8 (53.3%)	1 (6.6%)

73.3 per cent of patients treated with drug group A were cured completely of their symptoms, while 26.7 per cent of patients showed partial improvement. There was no failure with drug group A.

Only 40 per cent of patients treated with drug group B showed complete cure, while 53.3 per cent of patients showed partial improvement. One patient did not show any response to therapy.

Average time of disappearance of symptoms

In patients treated with drug group A, the average time of disappearance of symptoms was 8 days, while it was 10 days in patients treated with drug group B.

SIDE EFFECTS

Side effects of the anti-amoebic drug were encountered in 8 cases: Three patients of group A and five patients of group B. Nausea and vomiting were the chief side effects encountered. Time of appearance of side effects was 2-3 days after initiation of therapy. Nausea persisted longer in patients treated with drug group B, while it was automatically relieved in those patients who were treated with drug group A.

HISTOPATHOLOGICAL STUDIES AND RESULTS

In each patient a needle biopsy of the liver was performed before, and after 15 days of therapy.

Ten of the 15 patients treated with drug group A showed normal architecture of the liver before therapy. The remaining 5 specimens showed varying degrees of liver cell damage in the form of focal necrosis, RE cell hyperplasia and mononuclear infiltration.

Three out of these five patients revealed normal architecture of the liver on repeat biopsy. In the other two cases, partial improvement was noticed on histopathological examination.

Six patients treated with drug group B showed histopathological evidence of liver cell damage. Repeat biopsy in these cases showed varying degrees of improvement in three cases and no improvement in the remaining three cases.

DISCUSSION

Extra-intestinal spread of amoebic infection is fairly common.

The commonest extra-intestinal lesions occur in the liver, producing initially a diffuse hepatic involvement, which eventually results in abscess formation. The hepatic involvement affects the entire metabolism.

Any drug which has a protective action on the liver and having effect on metabolism will be beneficial as an adjuvant in the management of amoebiasis.

Hepatic amoebiasis is commonly seen in young adults and middle-aged individuals. The patients of our study fell in the age group, 15 to 52 years.

The common complaints of our patients were vague, diffuse abdominal pain, dyspepsia, constipation, diminished appetite and early fatigue. The minor complaints included loose motions, nausea and vomiting, heart burn, feverishness, diminished libido, cough and loss of weight.

There is often, but not always, a history of previous attacks of dysentery. In our study, out of 30 patients, 22 gave a positive history of having loose motions in the past. Their duration varied from less than a month to 10 years.

Laboratory investigations in patients treated with drug group A (which on breaking of code was found to contain Liv.52 tablets and Nivembin) revealed a significant improvement in haemoglobin%, TRBC, ESR values and LFT. Moreover, histologically, three patients showed marked improvement in liver structure after initial damage.

Subjective and objective improvement was significantly faster in patients treated with drug group A.

73.3 per cent of patients treated with drug group A and 40 per cent of patients treated with drug group B showed complete cure while 26.7 per cent of group A and 53.3 per cent of group B showed partial improvement. There was no failure with drug group A.

The patients treated with drug group A showed improvement early (eight days) which proves the beneficial effect of the adjuvant drug. Moreover, all the patients treated in group A showed improvement in appetite.

Side effects of Nivembin encountered in patients treated in drug group A were minimal. This may be attributed again to the beneficial effect of the adjuvant drug Liv.52.

CONCLUSIONS

1. An earlier improvement in symptoms in patients treated with a standard anti-amoebic, Nivembin, plus Liv.52, than with the anti-amoebic and placebo.

2. 73.3 per cent of patients were cured completely, while 26.7 per cent showed partial improvement.

3. Restoration of altered laboratory tests to normal occurred more in patients treated with the anti-amoebic plus Liv.52.

4. All patients treated with the anti-amoebic plus Liv.52 showed improvement in appetite.

5. Side effects of the anti-amoebic drug were minimal in patients treated with the anti-amoebic plus Liv.52.

6. There was better restoration of liver architecture in patients treated with the anti-amoebic plus Liv.52 than in those treated with the anti-amoebic plus placebo.

Finally, it may be concluded that Liv.52 has a beneficial effect as an adjuvant in the treatment of hepatic amoebiasis, improving the therapeutic efficacy and lessening the side effects of the conventionally used anti-amoebic drugs.

ACKNOWLEDGEMENT

We express our thanks to Dr. H.L. Arora, *M.D. (Path. & Bact.),* Reader in Pathology, S.M.S. Medical College, Jaipur for his kind help in reading the liver biopsy slides.

We are thankful to M/s. The Himalaya Drug Company Private Ltd., for the free supply of Nivembin, Liv.52 and placebo tablets.