



Albendazole as an adjuvant to the standard surgical management of hydatid cyst liver

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ABSTRACT

Background: The treatment options for hydatid cyst liver include non-operative and operative methods. Operative methods include conservative and radical procedures. Non-operative methods include chemotherapy and percutaneous treatment of liver hydatidosis.

Material and methods: The study was conducted at Sher-i-Kashmir Institute of Medical Sciences, Soura, Srinagar, Kashmir, India, over a period of two years from March 2001 to February 2003 with further follow-up of 5–6 years. The study included 64 cases in the age group of 15 years to 64 years, comprising 36 males and 28 females. The aim of the study was to know the effect of preoperative and postoperative albendazole therapy on the viability of protoscolices and recurrence rate of hydatid disease of liver. Patients were divided into four group of 16 each. In group A, patients were directly subjected to surgery. In group B, patients were given albendazole for 8 weeks followed by surgery. In group C, patients were given albendazole for 8 weeks preoperatively followed by further postoperative course for 8 weeks. In group D, patients were first taken for surgery followed by postoperative course of albendazole for 8 weeks.

Results: Out of those patients who received preoperative albendazole only 9.37% had viable cysts at the time of surgery as compared to 96.87% of patients who did not receive any preoperative albendazole. In those patients who did not receive any albendazole therapy, recurrence rate was 18.75% whereas recurrence was 4.16% in patients who received albendazole therapy.

Conclusion: We conclude that albendazole is safe and effective adjuvant therapy in the treatment of hydatid liver disease.

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1. Introduction

Echinococcosis or hydatidosis or hydatid disease is the most frequent cause of liver cysts in the world.¹ The prevalence of hydatid cyst in humans appears to be directly related to a low level of sanitation. The disease is prominent in rural areas with poor housing conditions, where humans, dogs and cattle exist in close proximity.^{2,3}

The majority of patients with hydatid liver disease have indolent presentation and are otherwise healthy. 75% cases present with an asymptomatic abdominal mass.⁴ The symptomatic patients most common complain of mild to moderate right upper quadrant pain. Acute, severe abdominal pain does occur occasionally and usually indicates rupture, biliary complications and secondary bacterial infection.⁵

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Ultrasonography has the best diagnostic efficiency because it can be used to recognize cysts as small as 1 cm in diameter.¹ CT has a sensitivity of 100% in detecting liver cyst approach and helps in accurate anatomic localization of cysts.⁴ Number of serological tests have been used for diagnosis of hydatid disease. Among them ELISA is the most widely used.⁶

Treatment options for hydatid cyst of liver include non-operative and operative methods. Non-operative methods include chemotherapy and percutaneous treatment of liver hydatidosis. Operative methods include conservative and radical procedures (Figs. 1 and 2).

Chemotherapy has been used as an adjuvant to surgical treatment either preoperatively or postoperatively or both. A short course of chemotherapy after surgery reduces the risk of recurrence and preoperative therapy sterilizes the cysts and reduces their tension, making surgery easier.

Bekhti et al. (1977) were the first to report successful results of chemotherapy of hydatid disease using mebendazole.⁷ Albendazole is another benzimidazole carbamate with better absorption properties. It has been seen that its metabolite albendazole

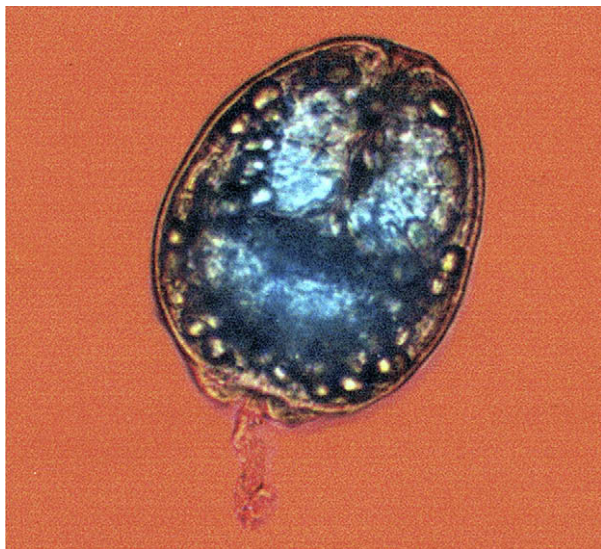


Fig. 1. Photomicrograph (high power) of cyst aspirate showing liver protoscolices – able to exclude 5% eosin.

sulfoxide is active against protoscolices of *Echinococcus granulosus* in in vitro cultures and it is able to penetrate into hydatid cysts.⁸ Comparative assessment of the therapeutic effect of two drugs has favoured albendazole.

2. Material and methods

This study was conducted jointly by the departments of General Surgery and Gastroenterology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Kashmir on all the patients admitted with diagnosis of hydatid liver from March 2001 to February 2003, with further follow-up for another 5–6 years. The aim of our study was to assess the effect of preoperative albendazole therapy on the viability of protoscolices at the time surgery and the effect of preoperative and/or postoperative use of albendazole on the recurrence rate of hydatid disease of liver. The confirmation in every case was done by demonstrating hydatid material—sand, hooklets, protoscolices or daughter cysts at the time of surgery.

Patients were included in the study after informed written consent. Patients were excluded if, a) the cyst was infected, b) the cyst had ruptured into the biliary tree, pleural cavity or peritoneal cavity c)

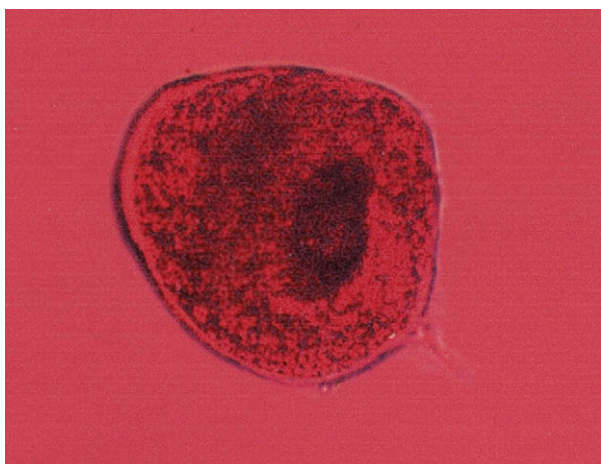


Fig. 2. Photomicrograph (high power) of cyst aspirate showing dead protoscolices – stained with 5% eosin.

the cyst was densely calcified (type V cyst), d) the cyst had associated extrahepatic cysts, e) the cysts were multiple and f) the patient was a married woman who was pregnant or intended to conceive during the study period.

After entry into the study, the 64 patients were stratified into the types of hydatid cyst (type I and II vs type III and IV) and were randomized into four groups in a recurring block of four as follows: In the group A ($n = 16$) patients were subjected to surgery (surgery group). In group B ($n = 16$) patients were given albendazole for 8 weeks and were subsequently operated upon (preoperative albendazole group). In group C ($n = 16$) patients were given albendazole for 8 weeks preoperatively followed by further course of albendazole for 8 weeks postoperatively (pre- and postoperative albendazole group). In group D ($n = 16$) patients underwent surgery followed by 8-week-course of albendazole in the post-operative period (postoperative albendazole group).

All patients after entry into the study underwent a detailed history, physical and systemic examination. All the patients were subjected to detailed investigations like haemogram, kidney function test, liver function test, coagulogram, electrocardiography and X-ray chest. Ultrasonography was the main tool for diagnosis. All patients were subjected to ELISA for hydatidosis. CT abdomen was performed in those cases where results of ultrasonography were equivocal. Patients were given albendazole at a dose of 10 mg/kg/day in divided doses. All patients were initially monitored weekly and thereafter monthly by liver function test, kidney function tests, white cell and platelet counts and urine analysis.

A right subcostal approach was used in all patients for surgical intervention. The steps of surgery included scolical irrigation, and cyst evacuation followed by external tube drainage.

Cyst contents were collected in all the cases for cytological and bacteriological examination. The cyst fluid was centrifuged and examined for the fragments of laminated membrane, hooklets and scolices. Viability assessment of the cysts was performed by observing the motility of the scolices and their ability to exclude 5% eosin, under immediate microscopy. Scolices which were motile and did not stain with eosin were considered live while the scolices which were immotile and stained with eosin were considered dead. The other factors which suggest that the cyst is viable include ovoid form, invaginated scolices and intact calcareous corpuscles and presence of vibrating movements. Fertility was defined as living protoscolices in relation to the total number of protoscolices.

All operative and postoperative complications were recorded. All patients were followed up initially every month for three months, and thereafter every three months for one year and subsequently every six months. Ultrasonography was done at every visit and cyst diameter, volume and cyst pattern was recorded. During ultrasonographic examination other abdominal organs were examined to exclude recurrent cyst formation. Radiograph of chest was done at 6 months intervals to look for any hydatid disease in the lung. Hydatid serology IgG and IgM by ELISA was done every six months.

In addition to descriptive statistics, the standard statistical methods were used for data analysis. These included the Student's *t*-test and the chi-square test. A *p* value of <0.05 was taken as the criterion of statistical significance.

3. Results and observation

The present study comprised of 64 cases of hydatid cyst liver. There were 36 (56.25%) males and 28 (43.75%) females with a male to female ratio of 1.3:1 (Table 1). The mean age of the patients was 36.77 ± 11.45 years. Majority of the patients were in the age group of 25–44 years 46 (71.87%) patients belonged to rural areas while the remaining 18 (28.13%) belonged to urban areas.

Table 1
Age and sex distribution of the study population ($n = 64$)

Number		Males, 36	Females, 28	Overall, 64
Age (yrs)	Mean	36.75	36.78	36.77
	+SD	11.34	11.79	11.45
	Range	15–64	16–62	15–64

Out of 64 cases included in our study, majority i.e. 46.88% had type I hydatid cysts. Type II hydatid cysts were found in 25% of the cases followed by type III in 14% of cases and type IV hydatid cysts in 6.25% cases (Table 2).

All the patients in group A i.e., surgery only group and 93.75% of patients in group D i.e. postoperative albendazole group had viable protoscolices at the time of surgery, whereas only 6.25% of patients in group B (preoperative albendazole group) and 12.50% of patients in group C (pre- and postoperative albendazole group) had viable protoscolices at the time of surgery (Table 3). All the patients in groups B and C with viable cyst had multiple daughter cysts in the main cyst.

Out of 32 patients who received preoperative albendazole (groups B and C), only 3 (9.37%) patients had viable protoscolices at the time of surgery, whereas in patients who did not receive any preoperative albendazole therapy, 31 (96.87%) had viable protoscolices at the time of surgery (Table 4). Patients who had received preoperative albendazole therapy had significantly lower percentage of viable cysts at the time of surgery ($p < 0.01$).

In our series of 64 operated patients, 3 (18.25%) patients in group A developed postoperative recurrence, whereas none of the patients from group C developed recurrence. One (6.25%) patient each from groups B and D developed postoperative recurrence in the mean follow-up period 5–6 years (Table 5).

Out of 48 patients who received albendazole therapy (pre- and/or postoperative therapy), only 2 (4.16%) patients had recurrence of the diseases whereas out of 16 who did not receive any albendazole therapy 3 (18.75%) patients, had recurrent disease (Table 6). Patients who had received albendazole therapy had significantly lower recurrence ($p < 0.01$).

4. Discussion

Hydatidosis is the commonest human larval cestodiasis. Liver is the most common site of involvement.¹ The mainstay of treatment of hepatic hydatid disease is surgery.¹ Medical therapy of hydatidosis has been tried with many drugs including benzimidazole carbamate group. Mebendazole was the first drug to be used for hydatid disease. Later on albendazole was introduced with better absorption properties. Albendazole given preoperatively in dose of 10 mg/kg/day for 1 month causes sterilization of the hepatic hydatid cyst, killing most of the protoscolices. However, high effectiveness of albendazole as liver cyst therapy has been reported after three months of uninterrupted treatment.⁹ The usual dosage scheme for albendazole, suggested by Horton (1989) and endorsed by WHO is, three 28 day courses of 10 mg/kg/day in divided doses separated by two weeks intervals.¹⁰ These benzimidazole carbamate groups of drugs act by blocking glucose uptake in the parasite and depletion of its glycogen stores.

Table 2
Types of hydatid cysts in different groups ($n = 64$)

Type	n (%)				
	Total	Group A	Group B	Group C	Group D
Type I	30 (46.88)	8 (26.66)	9 (30.00)	7 (23.33)	6 (20.00)
Type II	16 (25.00)	5 (31.25)	4 (25.00)	3 (18.75)	4 (25.00)
Type III	14 (21.87)	2 (14.28)	1 (7.14)	6 (24.85)	5 (35.71)
Type IV	4 (6.25)	1 (25.00)	2 (50.00)	–	1 (25.00)

Table 3
Comparison of cyst viability in different study groups as determined by scolices motility and ability to exclude 5% eosin

Study groups	Viable no. (%)	Non-viable no. (%)
Group A ($n = 16$)	16 (100)	0 (0)
Group B ($n = 16$)	1 (6.25)	15 (93.75)
Group C ($n = 16$)	2 (12.5)	14 (87.5)
Group D ($n = 16$)	15 (93.75)	1 (6.25)

$\chi^2df_3 = 49.44; p < 0.01$.

Praziquantel is another class of drugs used against hydatid cyst liver disease. It is the most active and rapid scolicidal agent. Its effect on the germinal layers is much less than on protoscolices. Praziquantel is probably the ideal agent for prophylaxis in the preoperative and postoperative setting to prevent implantation of protoscolices and subsequent recurrence. It is unlikely to be as effective as albendazole in treating whole cyst.

Chemotherapy is effective in small cysts less than 4 cm in diameter, cyst with thin walls and in younger patients. It is indicated in patients who are at high risk for surgery, in patients with multiple peritoneal cysts, cysts in multiple organs, bone cysts, cyst in brain, to prevent secondary echinococcosis after spillage during surgery and as a concomitant therapy with percutaneous drainage.

Recently, percutaneous drainage of hydatid cysts, popularly known as PAIR (puncture, aspiration, installation of scolicidal agent and respiration) technique has gained acceptance.^{10,11}

A prospective study was undertaken to assess the utility of albendazole as add-on therapy to the standard surgical management of hydatid disease of liver. Albendazole used in the dose of 10 mg/kg in divided doses as an adjuvant therapy to surgical treatment significantly improved the results in 48 patients out of 64.

Preoperative use of albendazole was associated with a significantly decreased rate of cyst viability at the time of surgery, as was assessed by the motility of the scolices and their ability to exclude 5% eosin under immediate microscopy. Of those patients who received preoperative albendazole for 2 months only 9.37% had viable cysts at the time of surgery as compared to 96.87% of patients who did not receive any preoperative albendazole therapy. This decrease in cyst viability was statistically significant ($p < 0.01$) and indicates that two months preoperative course of albendazole kills most of protoscolices within hydatid cysts.

Our observations are in agreement with some previous studies. Morris (1987) treated 16 patients with preoperative albendazole 10 mg/kg/day for a variable period of one week to one month. Out of the 14 patients who received albendazole for 1 month or more before operation, only one had viable protoscolices. In contrast, each of the two remaining patients who received only one and three weeks' therapy had liver disease at the time of operation.¹²

Out of the patients who received preoperative albendazole in our study, only 3 patients had viable cysts and in all these three patients, cysts contained multiple daughter cysts. Protoscolices in the main cyst were dead, whereas in daughter cysts, they were viable. It seems that preoperative albendazole while being successful in eradicating the hydatid parasites inside the mother cyst is not fully effective in treating the scolices inside the daughter

Table 4
Comparison of the cyst viability in the patients who received preoperative albendazole therapy vs those who did not receive any preoperative albendazole therapy

Group	Number	Viability	
		No	%
B and C	32	3	9.37
A and D	32	31	96.87

$\chi^2df_1 = 49.19; p < 0.01$.

Table 5
Comparison of recurrence in different study group

Study groups	Follow-up (yrs)	Recurrence	
		No.	%
A (n = 16)	3–4	3	18.25
B (n = 16)	3–4	1	6.25
C (n = 16)	3–4	0	0
D (n = 16)	3–4	1	6.25

p value: group A vs group B = NS; group A vs group C = NS; group A vs group D = NS; group A vs groups B and C = <0.05.

cysts, due to poor penetration of the drug into the daughter cysts shielded within the mother cyst. In group B there was only one patient while in group C, there were 2 patients with multiple daughter cysts within the main cyst, hence the low prevalence of viable cysts in group B, as compared to group C. Carlos Manterola et al.¹³ conducted a study to determine the plasmatc and intracyst concentration of albendazole sulfoxide and correlate them with the viability of the scolices in surgically treated patients who had received albendazole preoperatively. A total of 26 patients were studied and were given 10 mg/kg/day of albendazole for 4 days prior to the surgery. Plasma concentration and intracyst concentration of albendazole sulfoxide were measured by means of high performance liquid chromatography. The variables which were taken into concentration included diameter, type of cyst, number of cyst and development of cysto-biliary communications. They found no association between intracyst level of albendazole sulfoxide and the viability of scolices.

Horton (1989) treated 500 patients with 800 mg of albendazole daily in cycles of 28 days with a drug free interval of 14 days between the cycles for a mean duration of 2.5 cycles. Two hundred and fifty-three patients were evaluated for efficacy. After treatment 47 patients underwent surgery and viability was demonstrated in only 5 (10.6%) patients.¹⁴ Recurrence rate of 18.75% was noticed over a follow-up period of 5–6 months in the patients who did not receive any albendazole, whereas preoperative (pre- and/or postoperative) use of albendazole was found to significantly reduce the risk of recurrence to 4.16%. These observations are in general agreement with previously published data. Mottaghian and Saidi (1979) observed recurrence of 11.3% over a period of 6 months to 3 years in a study comprising 106 patients.¹⁵ Little et al. (1988) observed a recurrence of 22% in his study.¹⁶ Morris in 1989 observed no recurrence in patients treated with preoperative albendazole for one month with a median postoperative follow-up of 28 months.¹⁷

In our study, patients who received both preoperative and postoperative albendazole, there was no recurrence in any of the 16 patients followed postoperatively for a period of 5–6 years. This is in agreement with the observations made by Evangelos et al., who treated 67 patients of liver hydatidosis with preoperative mebendazole in the dose of 40 mg/kg/day (18 patients) or albendazole in the dose of 10 mg/kg/day in 49 patients for 5 days before surgery followed by one month course of same benzimidazole in patients with viable protoscolices at the time of surgery. None of these

Table 6
Comparison of recurrence in patients who received pre- and/or postoperative albendazole therapy (groups B, C and D) vs those who did not receive any albendazole therapy (group A)

Group	Number	Recurrence (% age)
A	16	3 (18.75)
BCD	48	2 (4.16)

$\chi^2_{df_1} = 25.04$; $p < 0.01$.

patients had any recurrence of disease after a follow-up of 15–67 months (average 41 months).¹⁸

All patients treated with albendazole 10 mg/kg/day in two equally divided doses tolerated the drug without any severe untoward symptom. Mild abdominal pain, nausea and vomiting were observed in 4% of patients. Reversible alopecia was seen in 4% patients. One patient had abnormally low white cell count while receiving albendazole. It was not progressive despite continuing therapy. Asymptomatic liver function test abnormalities were observed in 16% of patients after albendazole therapy but returned to normal levels within a month of therapy. Mild anemia (Hb < 9 g/dl) was observed in one patient and remained stable over the duration of albendazole therapy. These observations are in agreement with the study conducted by Morris (1988)¹² and Horton (1989).¹⁴

4. Conclusion

We conclude that albendazole is safe and effective adjuvant therapy in the management of hepatic hydatidosis in addition to the standard surgical treatment. Preoperative use of albendazole for two months significantly decreases the chances of cyst viability at the time of surgery. Postoperative use of albendazole for two months also decreases the chances of cyst recurrence. Combined pre- and postoperative albendazole use for a total of four months is highly effective in reducing the chances of the preoperative cyst viability as well as the postoperative cyst recurrence. Such combined pre- and postoperative use of albendazole may be superior to the use of the drug either preoperatively or postoperatively.

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