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Research Article

Outcome of albendazole therapy in the management of hepatic hydatid disease

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ABSTRACT

Background: The treatment modalities for managing patients with hepatic hydatidosis include surgical treatment and non-surgical treatments. The non-surgical methods include albendazole therapy and percutaneous management. Use of albendazole as an adjuvant therapy to surgery has been found to significantly reduce the viability of daughter cyst and recurrence of hydatid disease. The aim of the study was to understand the effect of albendazole therapy on the viability of protoscoleces and recurrence rate of hydatid disease of liver.
Methods: The study was conducted at Sher-i-Kashmir Institute of Medical Sciences and Medical College, Srinagar, Kashmir India, from March 2010 to February 2012 with further follow up of 3-4 years and the total of 64 patients were studied. ; Patients were divided into two groups, Group A and Group B, each comprising of 32 patients. In group A, patients were given albendazole for 12 weeks preoperatively followed by further postoperative course for 12 weeks. In group B, patients were first taken for surgery followed by postoperative course of albendazole for 12 weeks. The two main outcome measures studied and compared during present study were the viability of the hydatid cysts and the recurrence rate in two groups.
Results: Out of those, patients who received preoperative albendazole, 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 received only postoperative albendazole therapy, recurrence rate was 18.75% while as there was no recurrence was in patients who received both preoperative and postoperative albendazole therapy.
Conclusions: Study concludes that albendazole is safe and effective adjuvant therapy in the treatment of hydatid liver disease.

Keywords: Albendazole, Hydatid cyst, Protoscoleces, Viability, Recurrence

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 level of hygiene and sanitation. The disease is more prominent in rural areas with poor and unhygienic living 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 commonly complain of mild to moderate right upper quadrant pain or heaviness in the right hypochondrium. Acute, severe abdominal pain does occur occasionally and usually indicates rupture, biliary complications or secondary bacterial infection.[5]

Ultrasonography is the best and safest diagnostic tool as it can be used to recognize cysts as small as 1 cm in diameter.[1] Computed tomography abdomen has a sensitivity of 100% in detecting liver cyst and helps in accurate anatomic localization of cysts.[1] Various 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.

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

Successful results of chemotherapy in hydatid disease using membendazole was first reported by Bekhti et al.[7] Albendazole is another benzimidazole carbamate with better absorption properties. It has been seen that its metabolite albendazole sulphoxide is active against protoscoleces of Echinococcus granulosis in in-vitro cultures and it is able to penetrate into hydatid cysts.[8] Comparative assessment of the therapeutic effect of two drugs has favored albendazole.

METHODS

The study was conducted at Sher-i-Kashmir Institute of Medical Sciences and Medical College, Srinagar, Kashmir India, over a period of two years from March 2010 to February 2012 with further follow up of 3-4 years. The study included 64 cases in the age group of 18 years to 60 years, comprising 36 males and 28 females. The aim of our research was to study the effect of albendazole therapy on the viability of protoscoleces at the time surgery and its effect on the recurrence rate of hydatid disease of liver. The confirmation in every case was done by demonstrating hydatid material-sand, hooklets, and protoscoleces or daughter cysts at the time of surgery.

Patients were included in the study after taking an informed written consent. Following patients were excluded from the study; a) Infected cysts, b) the cyst who had ruptured into the biliary tree, pleural cavity or peritoneal cavity c) Densely calcified cysts (type V cyst), d) Patients with associated extra-hepatic cysts, e) Patients with multiple cysts and f) 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 various types of hydatid cysts (type I & II v/s type III and IV) and were randomized into two groups in a recurring block of four. In group A (n=32) patients were given Albendazole for 12 weeks preoperatively followed by further course of Albendazole for 12 weeks postoperatively (pre and postoperative albendazole group) with a gap of one week after every 4 weeks. In group B (n=32) patients underwent surgery followed by 12 week course of albendazole in the postoperative period (postoperative albendazole group). After entry into the study, all the patients were subjected to detailed history taking, physical and systemic examination. Baseline investigations like haemogram, kidney function test, liver function test, coagulogram, and electrocardiography and x-ray chest were done in all the patients in the study. Ultrasonography was the main tool for diagnosis. All patients were subjected to ELISA for hydatidosis.

CT abdomen was performed in all the patients. Patients in group A were given albendazole at a dose of 10mg/kg/day in divided doses both before surgery and after surgery, while as patients in group B were given albendazole only post operatively using same dose . All patients put on chemotherapy were initially monitored weekly and thereafter monthly by liver function test, kidney function tests, white cell and platelet counts.

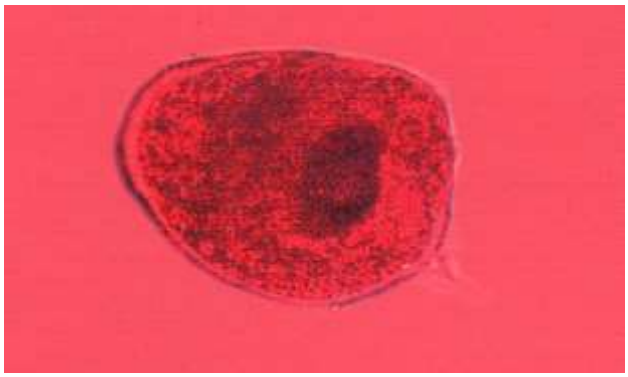

Figure 1: Cyst aspirate showing liver protoscolex – able to exclude 5% eosin (high power).

A right subcostal approach was used in all patients for surgical intervention. The steps of surgery included scolicidal irrigation, cyst evacuation followed by external tube drainage. Cytological and bacteriological examination of cyst contents was done in all cases. The cyst fluid was centrifuged and examined for the fragments of laminated membrane, hooklets and scoleces.

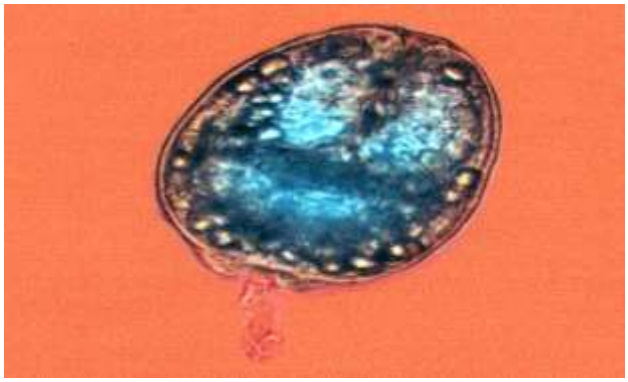

Figure 2: Cyst aspirate showing dead protoscolex – stained with 5% eosin (high power).

Viability assessment of the cysts was performed by observing the motility of the scoleces and their ability to exclude 5% eosin, under immediate microscopy. The

scoleces which were immotile and stained with eosin were considered dead (Figure 1), while as scoleces which were motile and did not stain with eosin were considered live (Figure 2).

All operative and postoperative complications were recorded. All patients were followed up initially monthly 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 preoperative stage of therapy.

During postoperative period ultrasonography examination was done during every visit to look for any 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.

RESULTS

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 I).

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).

		Males	Females	Overall
Number		36	28	64
Age (years)	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, 46.88% had type-I hydatid cysts followed by Type-II hydatid cysts in 25% of the cases, type-III in 14% of cases and type-IV hydatid cysts in 6.25% cases (Table 2).

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

Type	Total N (%)	Group A N (%)	Group B N (%)
Type I	30 (46.88)	16 (53.33)	14 (46.66)
Type II	16 (25.00)	8 (50.00)	8 (50.00)
Type III	14 (21.87)	6 (42.85)	8 (57.14)
Type IV	4 (6.25)	2 (50.00)	2 (50)

Comparison of cyst viability

Among patients who did not receive preoperative albendazole therapy (Group B), 93.75 % had viable protoscoleces at the time of surgery. While as only 6.25% patients in group-A (pre-operative albendazole group) had viable protoscoleces at the time of surgery (Table 3), which was statistically significant (p<0.01).

Table 3: Comparison of cyst viability in different study groups as determined by scoleces motility and ability to exclude 5% Eosin.

Study groups	Viable (no. %)	Non-viable (no.%)
Group A (N=32)	2 (6.25)	30 (93.75)
Group B (N=32)	30 (93.75)	2 (6.26)

$X^2 df_3 = 49.44$; $p<0.01$

Comparison of recurrence

In our series of 64 operated patients, 6 (18.75%) patients in group-B, developed post-operative recurrence, while as none of the patients from group- A, developed recurrence(Table 4),which again was statistically significant (P<0.05).

Table 4: Comparison of recurrence in different study group.

Study groups	Follow-Up (Years)	Recurrence	
		No.	%
Group A (N=32)	3 - 4	Nil	-
Group B (N=32)	3 - 4	6	18.75

P value- Group A v/s Group B = <0.05 (Significant).

DISCUSSION

Hydatidosis is the most common human larval cestodiasis. Liver is the most common site of involvement.[1] The mainstay of treatment of hepatic hydatid disease is surgery.[1] Different drugs have been used for management of hydatidosis including benzimidazole carbamate group.

Mebendazole was the first drug to be used for hydatid disease. Later on Albendazole was introduced as it has better absorption properties. Albendazole given preoperatively in dose of 10 mg/kg/day for 1 month kills most of the protoscoleces thereby causing sterilization of the hepatic hydatid cyst. However, high effectiveness of albendazole as liver cyst therapy has been reported after three months of uninterrupted treatment.[9,10] The usual dosage scheme for albendazole, suggested by Horton et al by WHO is, three 28 day courses of 10 mg/kg/day in divided doses separated by two weeks intervals.[11] These benzimidazole carbamate groups of drugs act by blocking glucose uptake in the parasite and depletion of its glycogen stores.

Praziquental 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 of whole cysts much less than on protoscoleces. Praziquental is probably the ideal agent for prophylaxis in the preoperative and postoperative setting to prevent implantation of protoscoleces and subsequent recurrence. It is unlikely to be as effective as albendazole in treating whole cyst.

Chemotherapy has been found to be more effective in small cysts less than 4cms in diameter, cyst with thin walls and in younger patients. Drug therapy is indicated in patients who are 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.

Percutaneous drainage of hydatid cysts, popularly known as PAIR (puncture, aspiration, installation of scolicidal agent and re-aspiration) technique has also been accepted as a mode of management in recent times.[11,12] A prospective study was undertaken to assess the utility of albendazole in the management of hydatid disease of liver. Albendazole therapy was a used in the dose of 10mg/kg in divided doses in all the 64 patients either post-operatively only or both preoperatively and post-operatively.

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 scoleces and their ability to exclude 5% eosin under immediate microscopy. Of those patients who received preoperative albendazole for three months only 6.25% had viable cysts at the time of surgery as compared to 93.75% of patients who did not receive any preoperative alblendazole therapy. This decrease in cyst viability was statistically significant ($p<0.01$) and indicates that three months preoperative course of albendazole kills most of protoscoleces within hydatid cysts.

Our observations are in agreement with some previous studies. Morris 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 protoscoleces. In contrast, each of the two remaining patients who received only one and three week's therapy had liver disease at the time of operation.[13]

Out of the patients who received preoperative albendazole in our study, only 2 patients had viable cysts and in both these patients, cysts contained multiple daughter cysts. Protoscoleces in the main cyst were dead, while as 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 scoleces inside the daughter cysts, due to poor penetration of the drug into the daughter cysts shielded within the mother cyst.[13]

Horton 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 to 6 months in the patients who did not receive any albendazole, while as perioperative (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. Mottaghlan et al observed recurrence of 11.3% over a period of 6 months to 3 years in a study comprising of 106 patients.[15] Little et al observed a recurrence of 22% in his study.[16] Morris observed no recurrence in patients treated with preoperative albendazole for one month with a median postoperative follow up of 28 months.[17]

In present study, patients who received both preoperative and postoperative albendazole, there was no recurrence in any of the 32 patients followed postoperatively for a period of 3-4 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 40mg/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 protoscloleces at the time of surgery. None of these patients had any recurrence of disease after a follow up of 15-67 months (average 41 months) [18].

All patients who were treated with albendazole 10mg/kg/day in two equally divided doses tolerated the drug without any severe untoward side effect. Nausea, vomiting and mild abdominal pain were observed in 4% of patients. Reversible alopecia was seen in 4% patients. One patient had abnormally low white cell count while receiving albandazole. It was not progressive despite continuing therapy. Asymptomatic deranged liver function test were observed in 16% of patients after albendazole therapy but returned to normal levels within a month of therapy. Mild anemia (Hb <9gm/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) and Horton.[12,19]

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 three months significantly decreases the chances of cyst viability at the time of surgery. Postoperative use of albendazole for three months also decreases the chances of cyst recurrence. Combined pre and post-operative albendazole use for a total of six 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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REFERENCES

1. Lewall DB. Hydatid disease. Biology, imaging and classification. Clin Radiol. 1988;53:863-74.
2. Jenkins DJ. Hydatidosis: A zoonosis of unrecognized increasing importance. J Med Microbial. 1993;31:3211-5.
3. 3. Sherlock S. Hydatid disease: Disease of liver and biliary system. Oxford: Blackwell Scientific Publications, 1981; 247-452.
4. Barmes Sa, Littlemoe KD. Liver abscess and hydatid cyst disease. Maingot's abdominal operations 10th ed. 1513-45.
5. Zargar SA, Khuroo MS, Khan BA, Dar MY. Intra-biliary rupture of hydatid cyst: Sonographic and cholangio-graphic appearances. Gastrointest Radiology. 1992;17:41-5.
6. Milicevic MN. Hydatid disease: Surgery of liver and biliary tract (L.H. Blumgart & Y. Fong) 3rd edition, W. B. Saunders Company Ltd; London 2000.
7. Morris DL, Gould SE. Serum and cyst concentrations of mebendazole and flubendazole in hydatid disease. Br Med J of Clinical Research, Edinburg. 1982;285:175.
8. Morris DL, Chinnery JB et al. Penetration of albendazole sulphoxide into hydatid cyst. Gut 1987;28:75-80.
9. Teggi A, Lastilla MG, DeRossa F. Therapy of human hydatid disease with mebendazole and albendazole. Antimicrob Ag Chemotherapy 1993;37:1679-84.
10. Malik AA, Bari SUL, Amin R, Jan M. Surgical management of complicated hydatid cysts of the liver. World J Gastrointest Surg 2010;2(2).
11. Khuroo MS, Dar MY, Yattoo GN, Zargar SA, Javaid G, Khan BA, et al. Percutaneous drainge versus albendazole therapy in hepatic hydatidosis: a prospective randomized study. Gastroenterology. 1993;104:1452-59.
12. Khuroo MS. Hydatid disease: Current status and recent advances. Annals of Saudi Medicine 2002;22:56-64.
13. Bari SUL, Arif SH, Malik AA, Khawja AR, Dass T A, Naikoo ZA. Role of Albendazole in the Management of Hydatid Cyst Liver The Saudi Journal of Gastroenterology. 2011;17(5):343-7.
14. Morris DL. Preoperative albendazole therapy for hydatid cyst. Br J Surgery. 1987;74:805-06.
15. Horton RJ. Chemotherapy of Echinococcus infection in man with albendazole. Trans of Roy Soc of Trop Med and Hyg. 1989;83:97-102.
16. Mottaghian H, Saidi F. Postoperative recurrence of hydatid disease. Br J Surgery. 1978;65:37-42.
17. Little JM, Hollands MT, Eckberg H. Recurrence of hydatid disease. World J of Surg. 1988;12:700-4.
18. Morris DL. Albendazole treatment of hydatid disease - followup at 5 years. Tropical Doctor 1989;19:179-180.
19. Evangelos C. Perioperative benzimidazole therapy in human hydatid liver disease. Int. Surg. 1995;80:131-3.

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