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## Iran J Parasitol

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Iranian Society of Parasitology  
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### Original Article

## Efficacy of Preoperative Albendazole on Protoscoleces Viability in Hydatid Cyst of the Liver

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Received 15 Jan 2022  
Accepted 22 Apr 2022

**Keywords:**  
Albendazole;  
Hydatid cyst;  
*Echinococcus granulosus*

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### **Abstract**

**Background:** Optimal duration for medical therapy of liver hydatid cysts before surgery is not certainly defined yet. In this study, we aimed to evaluate the effectiveness of 2 weeks preoperative albendazole in decreasing viable cysts.

**Methods:** Patients referring to Imam Reza Hospital, Mashhad, Iran with a diagnosis of hepatic hydatid cyst were randomly divided into intervention (44 patients) and control (46 patients) groups. The case group were treated with oral albendazole before surgery and the control group underwent surgery without albendazole therapy. Efficacy of albendazole on the reduction of prevalence and viability of the protoscoleces was finally evaluated.

**Results:** A number of 90 patients were included in the final analysis. Protoscoleces were reported alive in 10 (22.7%) and 17 (36.9%) of patients in the case and control group, respectively. The decrease of live protoscoleces in case group was not statistically significant ( $P=0.14$ ).

**Conclusion:** Decrease in the viability of protoscoleces in hepatic hydatid cysts after 2 weeks administration of oral albendazole at a dose of 10 mg/kg/day preoperatively, is not significant. Optimal duration of medical treatment before surgery seems to be 4 weeks or more.



## Introduction

Hydatid disease is still a common health problem in endemic areas, especially in the Mediterranean and Middle East countries (1-3). Prevalence of cystic echinococcosis in humans was 6.0% (95% CI: 4.0%, 7.0%) in Iran (4).

This zoonotic disease is caused by *Echinococcus granulosus*, a tapeworm that usually infects dogs (as definitive host), sheep, and goats (as intermediate host). Human is an incidental host of the parasite but, when infected, it can cause hydatid cysts in the body (5). The most common site of hydatid cyst is liver, followed by lungs but the cysts can be found in spleen, breast, heart, pancreas, and other organs too (6-10).

Management options for liver cysts include surgery, watch and wait, and medical therapy with an antiparasitic agent, which is usually albendazole. Decision for treatment depends mainly on the stage of the cysts (11, 12). When surgery is chosen (which usually is), there is a high chance for recurrence of the cysts unless effective preventive strategies are done. Recurrent disease is seen in almost 1 in 4 patients who are surgically treated and is associated with increased morbidity and mortality (13). Preventive strategies include use of protoscoleicides during surgery and use of systemic antiparasitic drugs (5). Unfortunately, there are not sufficient data regarding how to administer these medications to prevent the reoccurrence (5, 13, 14).

In the past decades, a number of studies have examined albendazole as an adjunctive treatment for prevention of recurrent disease. Shams et al. reported a successful elimination of viable hydatid cyst with 12 weeks preoperative albendazole in patients with liver hydatidosis (15). A significant reduction of viable cysts was seen in patients who received 8 weeks pre-operative albendazole compared with those without treatment (16). Preoperative albendazole for 4 weeks was also

studied and resulted in decreased viable cysts (17). Overall, there seems to be some evidence to indicate that pre-operative albendazole is effective but the remaining question is how long it should be given.

In the present study, a shorter course of pre-operative albendazole was administered to see if it could reduce the number of viable hepatic hydatid cyst. This could provide more information about the optimum timing for anti-infective therapy in these patients.

## Materials and Methods

This randomized clinical trial (National verification code: IRCT20090124001581N3) performed at Imam Reza hospital, Affiliated to Mashhad University of Medical Sciences, Mashhad, Iran.

Patients with a diagnosis of hepatic hydatid cyst were entered and randomly divided into intervention and control groups. Ultrasound was performed as the primary imaging method for diagnosis. Computed Tomography (CT) scan was ordered for patients whose diagnosis was uncertain at the ultrasound. Exclusion criteria were as follows: infectious hydatid cysts, hydatid cysts that entered the bile ducts, hydatid cysts ruptured inside the abdomen or pleural space, being pregnant or planning pregnancy during the study, and thickened calcified cysts.

After removing patients who met the exclusion criteria and those who did not want to participate, 44 patients in the case group were treated with oral albendazole at the dose of 10 mg/kg/day (18) for duration of 2 weeks before surgery and 46 patients in the control group underwent surgery without albendazole therapy. A complete and accurate history of all patients was obtained.

All patients underwent laparoscopic surgery and removal of cyst roof and drainage of intra-cyst contents with the injection of a

protoscolicidal agent. Hypertonic 15% saline was used for 10 min during operation as protoscolicidal agent. Through the surgery, the number, location, and size of the cysts in the liver were recorded. Prior to the injection of hypertonic 15% saline into the cyst, a fluid sample with cyst wall and membrane was immediately sent to the parasitology laboratory of the hospital. The laboratory expert was masked regarding intervention or control groups. The specimens were tested for protoscoleces viability using the scolex mobility assay as well as the 5% eosin permeation method under direct microscopy. Movable protoscoleces and those that did not stain the eosin permeability test were counted as live protoscoleces and those that were immobilized and stained in the permeability test were counted as dead protoscoleces.

Efficacy of albendazole on the reduction of prevalence and viability of the protoscoleces was finally evaluated. Data were analyzed by SPSS software version 22 (IBM Corp., Armonk, NY, USA) using Fisher's Exact test and  $P < 0.05$  was considered significant. Informed consent was obtained from all

patients and they were able to leave the study at any stage.

Prior to undertaking the investigation, ethical clearance was obtained from Ethics Committee of Mashhad University of Medical Sciences (Ethics code: IR.MUMS.FM.REC.1394.216).

## Results

Ninety patients (48 males, 53.3%) with hepatic hydatid cyst were included in the final analysis. The age of the patients ranged from 12 to 73 years with a mean age of  $47.5 \pm 12.4$  years. As shown in Table 1, there was no difference between the two groups in terms of gender ( $P=0.53$ ), but patients in the control group were significantly older than patients were in the case group ( $P=0.03$ ).

In the study of the location of the hydatid cysts, 65, 11 and 14 patients had cysts in the right, left, and both lobes, respectively. Location of the cyst was not significantly different between the two groups ( $P = 0.14$ ) (Table 1).

**Table 1:** Age, sex, cyst location, and Scolex viability distribution in the study population

<i>Variable</i>	<i>Case</i>	<i>Control</i>	<i>P-value</i>
Age, years (Mean $\pm$ SD)*	44.7 $\pm$ 13.58	50.24 $\pm$ 10.66	0.03
Sex, Male (N (%))**	22 (50)	26 (56.5)	0.53
Cyst location (N (%))***			0.14
Right lobe	28 (63.6)	37 (80.4)	
Left lobe	6 (13.6)	5 (10.9)	
Both lobes	10 (22.7)	4 (8.7)	
Scolex viability, live (N (%))**	10 (22.7)	17 (37.0)	0.14

\* Independent samples t-test, \*\* Fisher exact test, \*\*\* chi-square test

## Discussion

In the present study, the efficacy of albendazole as an adjuvant therapy along with the main surgical treatment for hepatic hydatid cysts was investigated. Although albendazole administration for a period of 2 weeks preoperatively decreased the protoscoleces

viability, this decrease was not statistically significant.

It is well known that medical treatment with albendazole in patients with liver hydatid cyst is useful as adjunctive therapy to surgery but the optimal duration of therapy is not well established. Preoperative albendazole consumption at a dose of 10 mg/kg/day for

12 weeks has been associated with 100% success in killing protoscoleces (15). Arif et al. examined 8 weeks preoperative albendazole at the same dose and reported a significant reduction in viable cysts. Nine percent viable cysts compared with 96.87% in control group (16). A shorter course (3 weeks) of therapy with similar dose of albendazole has been also resulted in a significant decrease in viable cysts (18). Another study tried even shorter course (4 days prior to the surgery) but this was not associated with reduced viable cysts (19). Bildik et al. investigated a dose of 20 mg/kg/day of albendazole preoperatively for 1, 2 and 3 months. At the time of surgery, 47.6%, 33.3%, and 0.9% of protoscoleces were alive respectively. The control group protoscoleces were 80% alive (20). Putting these results together, there is no doubt that the longer the duration of therapy, the higher success rate in killing protoscoleces. However, it may come to mind that as the treatment duration gets longer, risk of adverse effects goes up. In the study of Shams et al, 12 weeks albendazole therapy did not caused severe side effects or derangement in liver function tests (15). Only mild gastrointestinal symptoms and reversible alopecia were seen in less than 5% of patients. Manterola et al. also reported no adverse reactions to albendazole (19). Moreover, a higher dose of albendazole was generally well tolerated and serious side effects did not occur (20).

Viable protoscoleces in the time of surgery may lead the disease to spread into other cavities like the abdomen and pelvis. Hence, eradicating the protoscoleces prior to the surgery reduces the risk of recurrence in the future. This is accessible by treatment with albendazole prior to surgery (16, 18, 21). Since the rate of non-viable protoscoleces goes up with longer duration of therapy and since albendazole seems to be safe in these patients, that longer duration of therapy before surgery may be associated with better outcomes. Short course of treatment with albendazole (2 weeks or less) is not effective.

### **Study Limitations and Suggestions**

In this investigation, there were several sources for error. The main error was that the study did not match the patients in the case and control groups according to the World Health Organization ultrasound classification of cystic echinococcosis. Next, participants were not followed and consequently the rate of recurrence could not be calculated. Finally, patients were not asked to mention their symptoms when they were consuming albendazole, therefore minimal adverse effect were not recorded. We suggest further studies to address these drawbacks. In addition, combination therapy with albendazole and other drugs needs to be investigated.

### **Conclusion**

Decrease in the viability of protoscoleces in hepatic hydatid cysts after 2 weeks administration of oral albendazole at a dose of 10 mg/kg/day preoperatively, is not significant. Optimal duration of medical treatment before surgery seems to be 4 weeks or more.

### **Acknowledgements**

The results described in this paper are part of a thesis submitted by the first author for a postgraduate degree in general surgery. The study was supported by the Vice Chancellor for Research of Mashhad University of Medical Sciences (Grant No. 940097). Authors would like to thank and appreciate the efforts of the Parasitology Laboratory staff as well as the General Surgery residents of Imam Reza, who helped us to conduct this study

### **Conflict of interest**

All authors declare no conflict of interests related to the manuscript.

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