

## A placebo controlled study of albendazole in the treatment of pulmonary echinococcosis

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**ABSTRACT:** Infection with *Echinococcus granulosus* is endemic in Middle Eastern countries. Some patients are noted to undergo spontaneous resolution, but many require surgical removal with its associated risks. Although, there are studies showing favourable responses to medical treatment, there is no controlled study on the effect of albendazole.

In this study, 20 patients with 179 *E. granulosus* cysts affecting the lungs were entered into a triple blind parallel randomized clinical trial comparing the effects of albendazole versus placebo. Fifteen patients (150 cysts) completed 6 months of treatment; four patients (26 cysts) were in the placebo group and 11 patients (124 cysts) in the treatment group receiving 800 mg albendazole daily in three cycles of 6 weeks with 2 weeks between cycles.

Ten of 11 patients (91%) in the treatment group showed either cure (five patients) or improvement (five patients); in the placebo group, only one of four (25%) showed spontaneous improvement but no cure. In the treatment group, 88 of 124 cysts (71%) showed improvement compared to four of 26 (15.4%) in the placebo group ( $p=0.000$ ). Complication from therapy was insignificant; one case had recurrent disease, which responded to further therapy.

It is suggested that patients suffering from uncomplicated hydatid disease should be given a trial of albendazole before surgery is considered.

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Similar to other Middle Eastern countries, *Echinococcus granulosus* is endemic in Iran [1]. Hydatid disease is important both economically and from a health point of view. Each year, many patients undergo surgical removal of these cysts [2, 3].

To date, surgical resection of hydatid cysts has been the primary mode of treatment with its risks, postoperative complications and recurrences. On the other hand, some patients have widespread disease that makes surgical removal impossible and medical treatment remains the only option. Though there have been many studies on medical treatment [2, 4, 5], to date there has been no report to show that medical treatment can completely eradicate hydatid cysts in all patients. There are, however, reports showing that 10–30% of hydatid cysts undergo spontaneous resolution [2, 6, 7].

In order to answer the question of medical treatment was helpful in treating *E. granulosus* infection, a prospective study to evaluate the effect of albendazole on hydatid disease was performed.

### Material and methods

Between April 1994 and December 1995, 20 patients with hydatid cyst of the lung were entered into a triple blind parallel randomized clinical trial comparing the effects of albendazole versus placebo in the treatment of

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hydatid cysts. The characteristics of these patients are shown in table 1.

Patients were diagnosed as having hydatid cyst if they had radiological or ultrasonic findings in keeping with the disease along with indirect haemagglutinin test (IHA)  $>1/256$  or enzyme-linked immunosorbent assay (ELISA) titre  $\geq 1/200$  or previous histology confirming hydatid disease.

Patients who were inoperable, had multiple cysts, or refused surgery were entered into the study. Patients who were pregnant, lactating, or had liver or renal problems were excluded.

In a randomized balanced fashion, two of every three patients received albendazole and one received placebo. Dosage of albendazole was 800 mg or 10–15 mg·kg·day<sup>-1</sup> in two divided doses, and placebo was starch tablets twice a day of the same dosage. The patients, investigators and evaluators were blinded to treatment. Patients were subjected to three cycles of 6 weeks of treatment and 2 weeks rest period. At onset and at the end of 2, 4 and 6 months protocol, physical examination, full blood count and differential, ESR, liver function test, indirect haemagglutinin test or ELISA, and radiological evaluations were carried out. Radiographs were assessed by two trained radiologists (B. Davachi and R.H. Dabiri) who were blinded to treatment. At the end of 6 months, the treatment ceased and the patients were identified as having received albendazole or placebo.

Table 1. – Characteristics of the study patients

	Placebo		Albendazole		(p-value)	
	Completed treatment	All patients	Completed treatment	All patients	Completed treatment	All patients
Patients (cysts) n	4 (26)*	6 (42) <sup>+</sup>	11 (124)*	14 (137) <sup>+</sup>		
Sex M/F	3/1	3/3	5/6	8/6	0.57 <sup>‡</sup>	1.000 <sup>‡</sup>
Age of patients yrs	45±17	39±17	40±17	41±15	0.626	0.866
Cysts per patient n	8.8±7.6	10.8±13.7	16.3±13.97	12.2±13.4	0.33	0.84
Mean volume of cysts cm <sup>3</sup>	25.1±63.3	18.3±49.5	27.1±45.8	29.6±50.5	0.85	0.20
"Inactive" cysts/total cysts at onset of treatment <sup>#</sup>	10/26	19/42	20/124	31/137	0.0007	0.0043

Data are number or mean±SD. \*: completed treatment, patients with full 6 months of therapy; <sup>+</sup>: all patients, patients who completed 6 months of therapy and those who did not; <sup>‡</sup>: Fisher's exact test, two-tail; <sup>#</sup>: "inactive" (changes), ruptured, poorly defined, or collapsed.

Any patients who initially refused surgery or had multiple cysts or developed complication, then the treatment was terminated and surgery was recommended. Surgery was also recommended to these patients if they showed "worsening" or showed "no change" at the end of 6 months treatment with albendazole.

In each patient, the maximum diameter of each individual cyst and the number of cysts were recorded. The volume of each cyst was calculated by  $4/3 \pi r^3$ .

#### Assessment

The effects on individual cyst were evaluated as follows: 1) "Cure of the cyst" was defined as the complete disappearance of a cyst or marked changes such as the complete collapse or complete calcification, keeping in mind that death of the cyst is never certain unless the fluid is studied pathologically, is injected into mice peritonium that these patients undergo long term follow-up; 2) "Improvement of the cyst" was a volume reduction of  $\geq 25\%$  or a significant change on the chest radiograph: rupture (crescent, double arch, waterlily, cavitation), poorly defined, collapse, bulla or calcification. 3) "no change" was a change in volume  $< 25\%$  of original or no change in morphology; 4) "Worsening" was an increase in the size of the cyst by  $\geq 25\%$ , increased number of cysts or the appearance of a new cyst.

The effects on individual patient were evaluated as follows: 1) "Cured" was defined as patients who had  $> 50\%$  of their cysts cured or had  $> 75\%$  improvement in the cysts; 2) "Improvement" was attributed to patients who had  $> 25\%$  cure in their cysts or improvement in 50–75% of

their cysts; 3) "Unchanged" were patients who showed none of the above.

Statistical analysis was performed by using SPSS for windows, release 6.0 (SPSS Inc., Chicago, IL, USA) with the use of Student's t-test, Chi-square, two-tailed Fisher exact test, and correlation and regression analyses; values of  $p < 0.05$  were considered significant.

#### Results

In all 20 patients studied, 1–45 pulmonary hydatid cysts were identified with a total of 179 cysts. Fourteen patients (137 cysts) were in the treatment group and six patients (42 cysts) were in the placebo group. Of 20 patients (179 cysts) that entered the study only 15 patients (150 cysts) completed the 6 month treatment, 11 patients (124 cysts) in the treatment arm and four patients (26 cysts) in the placebo group. These patients were similar with regard to age, sex, number of cysts, and size of cysts (table 1).

The size reduction in the treated group and control groups is shown in table 2. Eighty-three of 124 (67%) cysts showed a reduction in size ( $> 25\%$ ) after treatment while in those receiving placebo, only three of 26 (11%) cysts had a spontaneous reduction in size ( $p = 0.000$ ). Of the 83 cysts, 16 were cured in the treatment group while none were cured in the placebo group ( $p = 0.075$ ).

When considering the total volume of cysts and using the t-test for paired samples, a significant reduction in the volume of the cysts in the treatment group ( $p = 0.000$ ) was noticed, although there was no significant change in the placebo group ( $p = 0.404$ ) (fig. 1).

Table 2. – Response of the cysts to albendazole versus placebo at different stages of the treatment regime

Drug	Cysts n	Number of cysts (%)					Disappeared
		Worse	No change	Decreased in size			
				$> 25\%$	$> 50\%$	$> 75\%$	
Albendazole							
2 months	137	18 (13)	70 (51)	49 (36)	21 (15)	9 (7)	4 (3)
4 months	130	6 (5)	49 (38)	75 (58)	45 (35)	24 (19)	14 (11)
6 months	124	9 (7)	32 (26)	83 (67)	60 (48)	36 (29)	16 (13)
Placebo							
2 months	42	11 (26)	27 (64)	4 (10)	2 (5)	0 (0)	0 (0)
4 months	41	14 (34)	24 (59)	3 (7)	1 (2)	1 (2)	0 (0)
6 months	26	10 (39)	13 (50)	3 (12)	1 (4)	1 (4)	0 (0)
p-value*				0.0000	0.0003	0.0675	0.0753

\*: Comparison between albendazole and placebo at end of 6 months treatment.

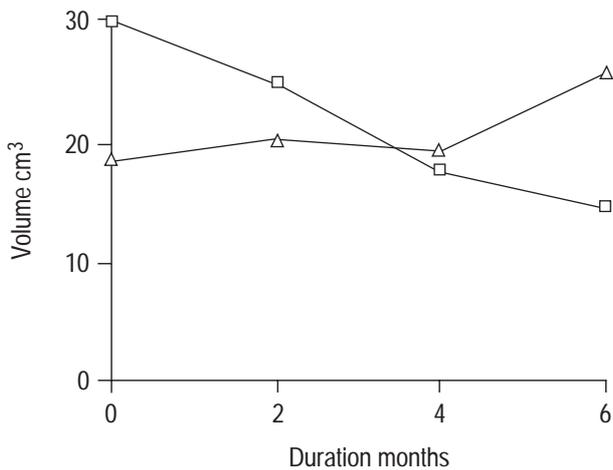


Fig. 1. — Mean change in volume of the cysts during treatment with albendazole (□) versus placebo (△).

At the beginning of the study, 20 of 124 (16%) cysts were either ruptured, poorly defined, or collapsed in the treatment group whereas 10 of 26 (46%) cysts in the placebo group showed these changes ( $p=0.007$ ). Of 124 cysts treated, 16 (13%) were cured (disappeared) and of the remaining 108 cysts, 83 (77%) showed a significant improvement in appearance (51/83 ruptured). No calcification was noted. In the placebo group, only two of 26 cysts showed a significant improvement ( $p=0.000$ ).

When considering either an improvement in size or appearance, 88 of 124 (71%) cysts in the treatment group showed an improvement, while in the placebo group four of 26 (16%) cysts demonstrated an improvement ( $p=0.000$ ).

Of 14 patients treated, 11 completed three courses of treatment. Of these, five showed an improvement and five were cured, using the definition described (fig. 2). One remained unchanged. Therefore, 10 of 11 (91%) patients showed a response, whereas in the control group of six patients, four completed the 6 months of placebo treatment and only one (25%) had a spontaneous improvement.

#### Complications

During treatment, there was increased cough, mild haemoptysis, and expectoration of the cyst membrane. However, none of these were significant when compared to placebo treatment. Two patients had an infection of the cysts as a result of rupture, which responded well to antibiotics. One patient had a recurrence of the disease within 4 yrs that again responded to treatment.

#### Discussion

For the treatment of hydatid cysts, most authors consider surgery the treatment of choice [3]; however, a recurrence rate of up to 10% requiring multiple operations has been reported [8–10], with a mortality of 0–20% [8, 11–14] and a complication rate of 25–40% [2]. Therefore, for many parasitic infections medical treatment should be the treatment of choice to prevent growth and recurrence of disease. Surgery should only be considered in special circumstances.

To find a suitable medical treatment for hydatid cysts there have been many studies since 1970 giving different results [15–25]. Although most studies show a favourable response to albendazole (table 3), there has been no controlled study showing the effect of medical treatment on hydatid disease.

It has been noted that spontaneous radiological changes and cures occur even in untreated patients. Therefore to better evaluate the effect of medical therapy, this controlled triple blind parallel randomized study was carried out. With the use of albendazole there was a significant cure rate and an improvement in the size and radiological appearance of cysts. One point that may have biased these

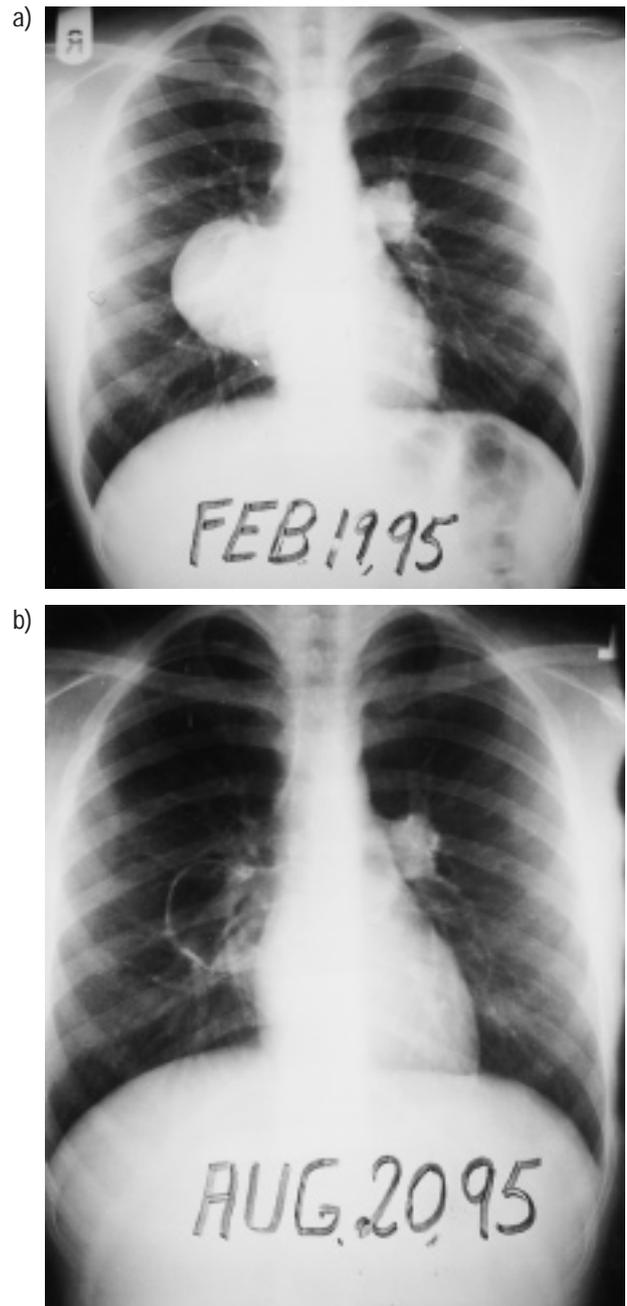


Fig. 2. — Chest radiographs of a 14-yr-old male child before treatment (a) and 6 months after treatment (b) with albendazole.

Table 3. – Treatment results with albendazole – a comparison of the present study with previous reports\*

First author [ref]	Country	Follow-up months	Daily dose	Treatment duration days	Patients n	Outcome number of patients					
						Full success	Partial success	Improved	No change	Worsen	Recurrence
Present study	Iran	15–48	400 mg b.i.d.	42–126	14	5	6	NG	3	NA	1
HORTON [15]	Multicentre	<24	10–15 mg·kg <sup>-1</sup>	30–365	253	72	NG	129	46	6	4
DAVIS [16]	Multicentre	<24	800 mg	60–90	30	5	4	14	7	NA	NA
NAHMIA [17]	Israel	36–90	400 mg b.i.d.	112	62	41	57	27	13	NA	2
TORODOV [18]	Bulgaria	20–30	10 mg·kg <sup>-1</sup>	120	23	10	10	NG	3	NA	NA
AGGARWAL [19]	China	–	15–20 mg·kg <sup>-1</sup>	360–540	58	14	NG	29	15	NA	NA
EL-MUFTI [20]	India	3–14	10 mg·kg <sup>-1</sup>	56	10	NA	NA	NA	10	NA	NA
CAREMANI [21]	Libya	9–13	400 mg b.i.d.	84–168	40	NA	21	NA	19	NA	2
DE ROSA [22]	Italy	6–42	10–12 mg·kg <sup>-1</sup>	90	50	9	NG	67	24	NA	3
HAO [24]	Italy	12–72	400 mg b.i.d.	90	47	30	10	NA	5	2	17

\*: Results based on patient response. NA: not applicable; NG: not given.

results in favour of treatment with albendazole is that at onset of the study there were significantly more "inactive" cysts (ruptured, poorly defined, or collapsed) in the placebo group versus the treatment group. Therefore, the albendazole group would show more changes during the 6 month treatment period since they had relatively more active cysts. In future studies when selecting the control group, this factor has to be kept in mind.

One of the important points in medical treatment is finding the proper duration of treatment. *In vitro* studies have shown that *E. granulosus* must be in contact with albendazole for at least 11 days to show a significant response [26]. In 1987, MORRIS [27] reported that treatment for <1 month was insufficient while in 1993 GIL-GRANDE *et al.* [28] showed that by increasing treatment from 1 month to 3 months the number of cysts that died increased 72–95%. In the present study, the duration of each cycle was increased from 4 to 6 weeks, and the number of cycles increased from one to three cycles giving a total drug period of 18 weeks.

As other observers have noted [16], the major radiological change was a rupture of the cysts. Its major complication being infection as reported by WASUNNA *et al.* [29]. Infection of the ruptured cyst can mimic a recurrence of cyst. This can be differentiated by the clinical presentation and its good response to antibiotics.

In conclusion, although many questions on the medical treatment of hydatid disease remain, this study has shown that albendazole can be considered as a drug producing either parasitocidal or parasitostatic effect on *Echinococcus granulosus* causing objective degenerative changes. It is recommended that patients with hydatid disease should have a trial of medical treatment; if they show regressive degenerative changes, they should be on long-term follow-up. Surgery should be recommended in cases with significant complication. This study has shown that it is possible to avoid surgery in most cases.

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