

Change in viability signs of human unilocular hydatid cysts post- albendazole administration (*In vivo* study)

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ABSTRACT

Objective: The purpose of this study was to investigate the antihydatidosis efficacy of pre-and post-operative albendazole administration (in vivo study).

Methods: The study was conducted during 2013 to 2017, in Department of surgery, Al-Jomhory hospital in Mosul City/ Ninawa governorate, on eighty nine patients those diagnosed to have hydatid disease. Patients ages were ranged from 10 to 93 years old. The diagnosis was based on liver function test, renal function test, chest x -ray, abdominal Sonography, CT scan, MRI, and MRCP if there is evidence of jaundice. The patients were administered albendazole 10 mg/kg/day orally for three months preoperatively, two doses a day. All the patients then subjected to surgery, followed by a further post operatively courses of albendazole for three months. Criterion of the hydatid cyst viability were included: change in cyst diameter, calcification of the cyst, viability of the protoscolices. Follow up of each patient was continue for two years to detect recurrence of the disease after post-operative albendazole treatment by repeated examination.

Results: Among the 89 diagnosed patients with hydatid cyst those were included in the present study; hydatid cyst was most prevalence in 60-69 aged group patients (25.8%), were as 10-19 age group had the less prevalence percentage (1.1%). On the other hands, infection percentage in males (62.9%) was higher than that in females (37.1%). Generally, number of whole diagnosed and treated cysts were 122. As expected liver were the most targeted organ among the other sites, with 85 (70%) of the whole diagnosed cysts. Lungs were becoming the second grade with 22 pulmonary cyst (18%). Sixty seven patients were found to be infected with single cyst, while 22 patients had multiple cysts, there were significant different between single cyst and multiple cysts infections at $P \le 0.01$. Fifty four (44%) of the hydatid cysts were detected and diagnosed accidentally, while 41 (34%) of the cysts were diagnosed after pain, and 27 (22%) cysts were diagnosed due to complications like jaundice, pneumonitis, etc. The diameter of the primarily diagnosed cysts were ranged from 1-22cm. There were significant different between cyst size before and after treatment at $P \le 0.01$, ie. mean reduction ranged in cysts size post albendazole treatment were 5.4%-45.8% (mean=24.6%) of the whole cyst diameter, with progressive changes in cysts patterns. It is seemed that reduction percentage in cyst diameter inversely proportional to the hydatid cyst size at correlation of 0.102 using paired sample T-Test, so that reduction percentage in cysts of 1-3 cm diameter were 45.8%, while reduction percentage in cysts of 18.1-22 cm diameter were 5.4%. All surgically removed cyst were checked up microscopically for viability using vital stain. No cysts with living protoscolices were found, furthermore noticeable thickening of the cysts wall were observed, In addition to 9 completely calcified cysts (7.3%). After 2 years of surgery then sonographic follow-up, no new growing cysts were found in the 89 studied cases.

Conclusions: pre-operative plus post-operative albendazole administration often represent an ideal method to terminate the recurrence of unilocular hydatid disease infections in Ninawa governorate .

Keywords: *Echinococcus granulosus*, unilocular hydatid disease, pre-operative albendazole administration, post-operative albendazole administration.

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INTRODUCTION

Hydatidosis is a globally distributed zoonotic disease. The causal agent are *Echinococcus spp*, belong to phylum: Platylminthes, class: Cestoda, order: Cyclophyllidae.^[1] The vast majority of echinococcosis infestation in human and animals are caused by *Echinococcus granulosuss* species.^[2] The disease is endemic in Mediterranean regions, South America, Eastern and Southern Europe, the Middle East, Southern Australi, New Ziland and extensive areas of Asia, Including Iraq.^[3,4,5] *Echinococcus granulosuss* cause unilocular hydatid cyst, the larval stage of the tapeworm. Hydatidosis is a medically important disease that may cause serious health problems, human and other herbeverous mammals act as intermediate hosts those harbour the hydatid cyst, dogs and other canidian animals act as difinitive hosts those harbour the adult worm (small intestinal cestode). Man can get infection when he ingest the infectious egg with contaminated foods and fluides.^[6] Primerly hydatid cyst undergo a silent growth period, in which the infection is a symptomatic, and seconderly the symptom may depends on the site and size of the cyst. The slowly growing hydatid cysts can attain a volume of several liters and contain many thousands of protoscolices..^[7] Barnes and Lillemoe showed that 50-75% of hydatid cysts were almost found in the liver, while 25% of the hydatid cyts were found in the lungs, and 5-10% were distributed along the arterial system.^[8] In most cases hydatidosis infection are diagnosed accidentally. Both ultrasound and C.T. scan are sensitive in detecting the hydatid cysts. Plain radiographs are useful in certain circumstances. Cerebral hydatidosis can be imaged by MRI, this technique has a multiplanar capabilities and more detailed anatomical resolution.^[9]

Current treatment of hydatidosis is mainly surgery, and to lesser extend percutaneous aspiration and medicinal treatment using benzimidazole compounds.^[10] Benzimidazole have a broad spectrum activities (vermicidal, ovicidal, and larvicidal activities). Most human intestinal and systemic cestodes are susceptible to one or more of benzimidazole compounds.^[11,12] The most frequently used benzimidazoles in human medicine are albendazole and mebendazole.^[13] Evaluation of hydatid cyst viability post treatment may gain further insight into the activities of drugs used against hydatidosis infection . *In vivo* research found in Iraq that evaluate the status of patients with hydatid disease who administrate albendazole pre-surgery and after surgery is scarce. Related studies about the subject were done around the world by some researchers like: Wilson, *et al.* (1992); Horton, (1997); Keshmiri , *et al.* (2001) and Polat, *et al.* 2005.^[14,15,16,17]

Thus, the purpose of this paper is to review in details our 5-year experience with chemotherapy for unilocular hydatid disease in Nineveh governorate, depending on change in viability signs of the cyst post treatment (protoscolisis viability %, change in cyst pattern and diameter , and calcification of treated cyst) and to evaluate efficacy of post-operative administration of albendazole in eradication of hydatidosis infection, (*in vivo* study).

PATIENTS AND METHODS

A case series study was conducted in the Department of surgery, Al-Jomhory hospital in Mosul city on patients admitted with diagnosis of hydatid disease infection. From 2013 to 2017 with further follow up for 2 years/case. Eighty nine cases in the age groups of 10-19 to 90-99 years old were studied. The diagnosis was based on first clinical manifestation and investigation that was include performing: complete blood picture examination, liver function test, renal function test, chest x -ray, Sonography, abdominal CT scan, MRI, and MRCP if there is evidence of jaundice. The diameter of each diagnosed cyst were recorded. Patients scheduled for surgery were ordered to albendazole administration for three months preoperatively, an oral dose of 10 mg/kg/day was taken with meals according to a protocol in which 28-days courses of therapy were alternated with 14-day drug-free intervals, followed by a further post operatively courses for three months.^[15,17]

Surgical Technique:

All of the confirmed cases with hydatidosis were subjected to surgery. The surgical procedure performed in all patients was including: Aspiration 10 ml of hydatid fluid using the suitable syringe; injecting hypertonic saline solution 20% inside the cyst to kill the viable part of the hydatid cyst, then waiting for 10 minutes; putting two stay sutures and open the cyst; removing the cyst fluid then removing daughter cysts.^[18,19] Dealing with the residual cavity either by simple closure or by leaving drain inside the cavity or by omentoplasty or marsupialization and finally resection of the whole organ in some cases like splenic hydatid cyst.

Testing viability signs of the uprooted cysts:

The efficacy of chemotherapy for unilocular hydatid cyst was assessed by estimation changes in cysts diameter and pattern after chemotherapy; measuring viability of each uprooted cyst and recording cyst calcification cases. Diameter of the cysts were measured using vernier caliper mm. then compared with the diameter of the same cyst that were determined before albendazole administration. The color of primarily collected hydatid fluid were observed also. In addition, microscopic examination of the fluid immediately after surgery to check viability of protoscolices found in the cyst depending on: flame cell activity of the protoscolices and their reaction with vital stain (0.1% aqueous eosin).^[20]



Follow up of each patient were continued for 2 years by repeated examination (Sonography and CT scan) to detect the recurrence of hydatid cysts and to observe the efficacy of pre- and post-operative Albendazole treatment for such patients.

Statistical Analysis: one sample T Test and paired sample T Test was used for the analysis of data to compare differences between any two treatments.^[21] Statistical package for society (SPSS) program, Version 11.5 was sought to analyze the data by computer. All results were significant with $p \le 0.01$.

RESULTS AND DISCUSSION

Infection with unilocular hydatid disease is one of the most common parasitic disease of worldwide distribution including Iraq.^[3] In the present work, investigation about the antihydatidosis efficacy of pre- and post-operative albendazole administration (*in vivo* study) was applied. Eighty nine hydatidosis patients have been included with the age groups 10 to 99 years, (56 male and 33 female). (Table1) showed that hydatidosis infections were most commonly found in the age group of 60-69 years old with 23 cases (25.8%); otherwise there is low prevalence in patients of the age groups 10-19 and 90-99 years old at 1.1% and 3.4% respectively.

Table (1): Distribution of hydatid disease in patients according to the age groups:

Age (year)	Number of patients	Prevalence%
10-19	1	1.1
20-29	11	12.4
30-39	12	13.5
40-49	14	15.7
50-59	10	11.2
60-69	23	25.8
70-76	11	12.4
80-89	4	4.5
90-99	3	3.4
Total	89	100%

Present research revealed that unilocular hydatidosis were more prevalence in males (62.9%) than in females (37.1%) (see Table-2).

Table (2): Distribution of hydatid cysts in patients according to gender:

Age group	Gender		
	Female	Male	
10-19y	0	1	
20-29у	5	6	
30-39у	5	7	
40-49y	5	9	
50-59y	6	4	
60-69у	4	19	
70-76у	5	6	
80-89y	2	2	
90-99y	1	2	
Total	33 (37.1%)	56 (62.9 %)	

Furthermore, 122 hydatid cyst were diagnosed, the most common site of the hydatidosis infection was the liver: 85 cyst (70%), lungs were attain the second grade with 22 cysts (18%) while the least targeted sites were the thyroid gland and lesser sac :one cyst (0.8%) for each as showed in (figure1). This result was came agree with those of Oudii, *et al.* (2013); Barnes and Lillemoe (1997); Al-Doghan, *et al.* (2017). [5,8,10]



Number of the hydatid cysts (%) in the body organs



Figure (1): Number of hydatid cysts and percentage (%) found in the 89 patients according to the body organs.

The study showed also that there were significant different at $P \le 0.01$ between single cyst infections (67 patients) and multiple cyst infections (22 patients) (Table-3), . In the present study, higher number of patients have single cyst and male have higher chance to be infected with the parasites, and that conformed with the observations of.^[5]

Table (3): The numbers of hydatid cysts according to the type of infection (either single cyst or multiple cysts) concerning the age groups:

Age group (years)	No, of cases	Single cyst infection±SE	Multiple cysts infection±SE
10-19	1	1	0
20-29	11	8	3
30-39	12	12	0
40-49	14	11	3
50-59	10	10	4
60-69	23	10	12
70-76	11	10	0
80-89	4	2	0
90-99	3	1	0
Total	89	67 [*] ±1.313	22*± 1.516

*Referred to presence of significant differences between the values at $P \le 0.01$, according to t-test, two sample analysis.

As seen in (Table 4); the whole diagnosed and treated hydatid cysts were 122; 54 (44%) of the hydatid cysts were diagnosed accidentally, while 41 (34%) of the cysts were detected after pressure pain, and 27 (22%) cysts were diagnosed down to complications like jaundice, pneumonitis.....etc. 53% of hepatic cysts were detected by accident, while 32% of the hepatic cysts were diagnosed after pressure pain and only 15% of the hepatic cyst were diagnosed after complications.

On the other hands, 55% of pulmonary hydatid cysts were detected after complications, 36% of the pulmonary cysts were diagnosed after pressure pain, and only 9% of the pulmonary cases were detected accidently. According to the previous studies, hepatic hydatid cysts can compress bile ducts, causing obstruction that can manifest as obstructive jaundice, abdominal pain, anorexia, and pruritus.^[22] In lungs, pulmonary hydatid cysts can irritate the lung membranes leading to chronic cough, dyspnea, pleuritic chest pain, and hemoptysis.^[23,24]



	Total number of cysts/organ	Hydatid cyst discovered by:		
The infected organ		Accident	Pressure pain	Complications like jaundice, pneumonitis, etc.
Liver	85	45 (53%)	27 (32%)	13 (15%)
Lungs	22	2 (9%)	8 (36%)	12 (55%)
Spleen	5	2 (40%)	2 (40%)	1 (20%)
Mesentry	3	2 (67%)	1 (33%)	0 (0%)
Ovary	3	1 (33%)	2 (67%)	0 (0%)
Greater ommentum	2	2 (100%)	0 (0%)	0 (0%)
Lesser sac	1	0 (0%)	0 (0%)	1 (100%)
Thyroid gland	1	0 (0%)	1 (100%)`	0 (0%)
Total	122	54 (44%)	41 (34%)	27 (22%)

Table (4): Distribution of uprooted hydatid cysts according to clinical manifestation of the patients:

Generally, manifestations those due to hydatidosis infections are depending on : the size and location of the cyst; the amount of pressure on the surrounding tissues which exerted by the cyst, producing abdominal discomfort and pain;^[23,25,26] and whether or not the cyst is ruptured or leakage which can cause immunologic symptoms from the initiation of an immunoglobulin (Ig)E response, leading to allergic reactions which are most frequently characterized by hives, flushing, and mucous membrane swelling.^[25] Hydatid cyst rupture can cause life-threatening anaphylactic shock and lead to liberation of the viable contents of hydaid cyst, which in turn result in secondary hydatidosis.^[27] Ruptured cysts can release viable cystic contents and protoscolices into the peritoneum, resulting in secondary hyatidosis.^[24]

In the present study patients with giant cysts were more frequently symptomatic than were the patients with smaller cysts, that is consisted with that observed by Usluer, *et al.*(2010).^[28] This result may referred to the fact that each hydatid cyst primarily undergo period of silent growth, which may takes up several years before hydatidosis debut because of the slow growth and development of cysts and the response of the host's immune system.^[29,30]

Benzimidazole derivatives (flubendazole, albendazole, and mebendazole) are commonly used for the treatment of hydatid disease in high-risk patients, to prevent secondary hydatidosis, or both.^[31,32,33,34] However, the results of enteric medical therapy are still controversial and of limited effectiveness.^[35]

Albendazole was chosen in the present study because it is not toxic to the liver and biliary structures at the applied concentration when compared with other scolicidal agents;^[36,37] as well as there are some reports those verify that small cysts can be cured with albendazole.^[37,38]

Generally, the goal of surgical treatment is to prevent the complication, recurrence and recurrence rate, and to minimize morbidity and mortality.^[5,13,19] In the status work, hypertonic saline solutions (20%) were used as scolicidal agent during surgery. Derici, *et al.* (2006) were reported that hypertonic saline is not appropriate because it may damage the peritoneal surfaces and may cause hypernatremia.^[39] It is worthy to say that in the present investigation, no complications in all followed cases were observed with the usage of hypertonic saline solutions of 20% concentration after surgery. This result was came agree with that of Oudaii, *et al.* (2013) those sited also that the use of scolicidal agents during surgery is necessary for preventing intra-abdominal recurrence of hydatid disease.^[5] Furthermore, in the present research, albendazole were given pre- operatively to such patients, so that post-operative albendazole therapy is effective for preventing recurrence of the disease, noting that 35 unlike other scolicidal agents, albendazole is not toxic to the liver and biliary structures at the given dose, which potentially decreases the possibility of chemical sclerosing cholangitis.^[37,40,41] [37] reported that direct application of albendazole and mebendazole solutions to the biliary system of rabbits did not cause any side effects.

In the present investigation, no complications were reveal for biliary system considering liver functions, and no recurrence state of hydatidosis have been noticed through 2 years/patient follow up in the patients under study.^[37] The efficacy and safety of albendazole treatment have been demonstrated in various studies.^[15,42,43] Our results came agree with that of [44] those referred to the eradication of hydatidosis post albendazole treatment.^[44] However, other studies showed that the recurrence rates of hydatidosis after albendazole treatment were 6.7%, 7.1%, 7.7%, 11, and 14% cited by previous researchers.^[4,5,39,45,46]

During the Sonographic follow-up, It is seemed that the cyst cavity was obliterated in addition to noticeable shrinkage of the cysts wall and cysts pattern in some cysts post albendazole treatment (see Figure-2). All the 122 surgically removed cysts were checked up microscopically for viability using vital stain. No cysts with living protoscolices were found, furthermore complete calcification were observed in 9 cyst (7.3%) i.e. 8 of the 22 pulmonary uprooted cysts (36%) and 1 of the 85 hepatic cysts (1.1%). Cysts calcification may due to the immune system responds of the host



which eventually resulted in forming of calcified fibrous capsule around the cyst (see figure-2), which is the layer that is most often visualized on imaging studies.^[23]

On the other hands, diameter of each uprooted cyst were measured with vernier and compared with diameter of the same cyst pre- albendazole treatment. It is worthy to say that the hydatid cysts those proved to have secondary bacterial infection were ruled out of the present investigation.





Figure(2): Sonografic picture for patient with hepatic hydatid cyst; A- The form of active hydatid cyst prealbendazole treatment; B- Form of the same hydatid cyst post-albendazole treatment, note: the calcification, change in pattern and shrinkage of the treated cyst.

Diameters of the 122 diagnosed hydatid cyst were ranged from 1-22 cm before albendazole treatment. Generally, reduction in the diameter of the treated cysts were ranged from 1.4-3cm (Table-5), using paired sample T-Test was showed significant different between cyst diameter (cm) before and after treatment at P \leq 0.01. It is seemed that reduction percentage in cysts diameter inversely proportional to the hydatid cyst size with correlation of -0.102, since that mean reduction percentage in cysts group of 1-3 cm in diameter was(45.8%), while reduction percentage in cysts group of 18.1-22 cm in diameter were (5.4%).

Range (& mean)of cysts diameter (cm) before albendazole administration	No.of cysts according to diameters grouping	location and number of cysts within the 89 patients bodies according to diameter	Diameter of cyst cm. post treatment	Reduction mean cm. (& reduction %) in cysts diameter after albendazole administration/cysts group
1- 3 (2.4) cm	6	4 liver; 1 lungs; 1 momentum	1.3	2.1cm (45.8%)
3.1-6 (5.4)cm	35	23liver; 8 lungs; 2 ovary; 1 lesser sac; 1 thyroid gland	3.3	2.1cm (38.9%)
6.1-9 (8.3)cm	40	29 liver; 5 lungs; 4 spleen;2 momentum	5.8	2.5cm (30.1%)
9.1-12 (10.8)cm	24	17 liver; 5 lungs; 1 spleen; 1 ovary	8.2	2.6cm (24.1%)
12.1-15 (13)cm	6	5 liver; 1 lung	10.5	2.5cm (19.2%)
15.1-18 (16.3)cm	5	5 liver	13.3	3cm (18.4%)
18.1-22 (20.2)cm	6	6 liver	19.1	1.4cm (5.4%)
Mean=10.91±2.34	Total=122		Mean=8.79*±2.32	2.3*cm±0.19(24.6%)

 Table (5): Reduction% in diameters of the hydatid cysts after pre-surgery albendazole treatment:

*Reffered to presence of significant differences between the values at P≤0.01, according to paired sample T Test.

After two years of surgery and sonographic follow-up, no new growing cysts were found in the 89 studied cases. Reduction in cysts diameter, Shrinkage and change in cyst pattern, calcification of some cysts, in addition, no living



protoscolices were found after albendazole pre-surgery treatment, all these evidence indicating to the hydatid cyst abolishing, and have been accepted as healing signs, as stated in the literatures.^[37,41,47,48,49] These findings implied that the protocol of pre- and post-surgery albendazole treatment were safe and effective in preventing recurrence of hydatidosis infection. The effect of benzimidazole treatment is due to their metabolites which reach the definite serum concentration and passes to the hydatid fluid.^[50,51] Post-operative albendazole therapy is effective for preventing recurrence of the disease.

CONCLUSION

Generally, pre-operative administration of albendazole for patient with hydatidosis were proved to reduce hydatid cyst diameter, changed cyst pattern, terminate viability of the treated cysts, and when followed by post-operative albendazole treatment, no recurrence of hydatosis was recorded.

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