

The role of combination pre- and postoperative albendazole therapy in the surgical management of liver hydatidosis



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The role of combination pre- and postoperative albendazole therapy in the surgical management of liver hydatidosis

AIMS: ALB is the most commonly used drug for the treatment of echinococcosis. The aim of the present study was to evaluate the effect of ALB using the intraoperative and perioperative periods as dual therapy.

MATERIALS AND METHODS: Material of this retrospective study were the consecutive series of 98 patients operated for hepatic hydatidosis (HC) over a period of 7 years, at a single centre. Clinical examination, ultrasonography (US) and computed tomography (CT) were used for establishing diagnosis. Ninety-eight cases of hepatic hydatidosis were treated by albendazole intraoperatively and postoperatively together with surgery. Perioperative ALB treatment was given in a dose of 12-15 mg/ kg per day in four divided doses. The treatment started 2-28 days before the surgery when the diagnosis was established and continued for 2-24 months postoperatively in a cyclic monthly form. A total of 1.7 mg/mL ALB solution was used intraoperatively. Dual albendazole treatment (DALB) includes preoperative and postoperative oral ALB treatment and intraoperative irrigation of cystic cavity with ALB.

RESULTS: In the follow-up period one patient died and there was one recurrence of hepatic hydatidosis. Morbidity rates were 10.89%.

CONCLUSION: Results of this study suggest that ALB treatment with HC surgery is effective in the prevention of recurrences and/or secondary hydatidosis.

KEY WORDS: Albendazole, Recurrens Liver hydatid cyst, Surgical treatment

Introduction

E. granulosus lives as tapeworms in the intestine of dogs, its eggs are excreted in feces. Larvae liberated from the ingested eggs form hydatid cysts mostly in the liver and lungs of men and grazing animals¹.

Cystic echinococcosis or hydatid disease, also known as hydatidosis, remains a significant public health problem in endemic areas such as Mediterranean countries, the Middle East, Australia and South America. Although liver

is the most frequently infected organ, hydatid cysts can be developed in many other organs. Hydatid cysts are generally asymptomatic. However, they can be infected or ruptured or can exert pressure to adjacent organs after reaching remarkable sizes. The rupture can cause anaphylaxis or dissemination^{2,3}.

On the other hand, three modalities to treat HC are being used; chemotherapy, surgery, percutaneous drainage. Chemotherapy alone is not sufficient in the treatment of hydatidosis, but should be added to the preferred option to reduce the recurrence due to spillage of the cyst content during interventions. The main goal of the treatment should be the elimination of the parasite without recurrence with minimal morbidity and mortality. Benzimidazole derivatives have been the drugs of choice for the medical treatment of echinococcosis since Bekhti's first report in 1977. ALB is the most commonly used drug for the treatment of echinococcosis. Medical

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treatment is effective in the prevention of secondary hydatidosis and/or hepatic hydatidosis recurrence. Since 1995, dual albendazole treatment has been used for hepatic hydatosis. DALB includes pre- and postoperative oral ALB therapy and intraoperative irrigation of the cystic cavity with albendazole solution ¹⁻⁴. The aim of the present study was to evaluate the effect of ALB using the intraoperative and perioperative periods as dual therapy.

Materials and Methods

In this retrospective study ninety-eight patients with hepatic hydatidosis presenting between June 2007 and July 2014, treated by surgery and DALB (Table I). All patients were evaluated by one of the serology test, ultrasonography (US) and computed tomography (CT) preoperatively and postoperatively. The cysts were classified according to WHO classification (Table II). Intraoperative US was performed in all cases. The irrigation solution contained 1.7 mg/mL albendazole used as protoscolicidal agent as previously reported. Perioperative albendazole therapy was performed in all cases. A dosage of 12-15 mg/kg/day of ALB was started preoperatively when the diagnosis of hepatic hydatid disease was established and continued postoperatively. The ALB treatment was started 2-28 days before the

TABLE III - Surgical methods for the treatment of cysts in 98

	N. (%)
Drainage-omentoplasty	35 (35,71)
T-tube drainage	49(47,95)
Pericystectomy	4 (4,08)
Capittonage	4 (4,08)
Choledokoduodenostomi	2 (2,04)
T-tube drainage	2 (2,04)
Cystobiliary communication and sutur	2 (2,04)

TABLE IV - Complications of cysts in 98

	N. (%)
Incisional hernia	1 (0,99)
Wound infections	4 (3,96)
Biliary collection of the cystic cavity	3 (2,97)
Infection of the cystic cavity	1 (0,99)
Recurrence	1 (0,99)
Exsitus	1 (0,99)
Total	11 (10,89)

TABLE I - Charecterisitics of 98 cyst

		N. (%)
Sex	Male	52 (53,06)
	Female	46 (46,93)
age(years) mean $\pm$ SD		41,85($\pm$ 2,35)
cyst size (cm) mean $\pm$ SD		8,24 ($\pm$ 4,81)
Location	Right	52 (53,06)
	Left	42 (42,85)
	Bilobar	4 (4,08)
Hospital stay(day) mean $\pm$ SD		12,28 ($\pm$ 3,9)
No .cysts	1	57 (58,16)
	2	28 (28,57)
	3	8 (8,16)
	4	4 (4,08)
	5	1 (1,02)

TABLE II - Classification based WHO criteria

Grade	N. (%)
C-E1	15 (15,30)
C-E2	22 (22,44)
C-E 3A-3B	42 (34,69)
CE-4	16 (8,16)
CE-5	3 (3,06)



Fig. 1: Cyst hydatidic in right and left lobe of liver.

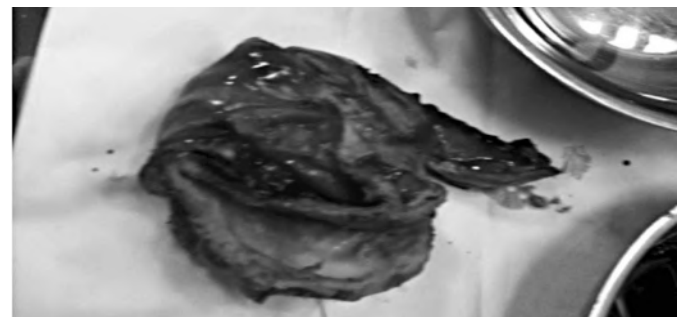


Fig. 2: Hepatic pericystectomy.



Fig. 3: Daughter vesicles and germinative membrane.

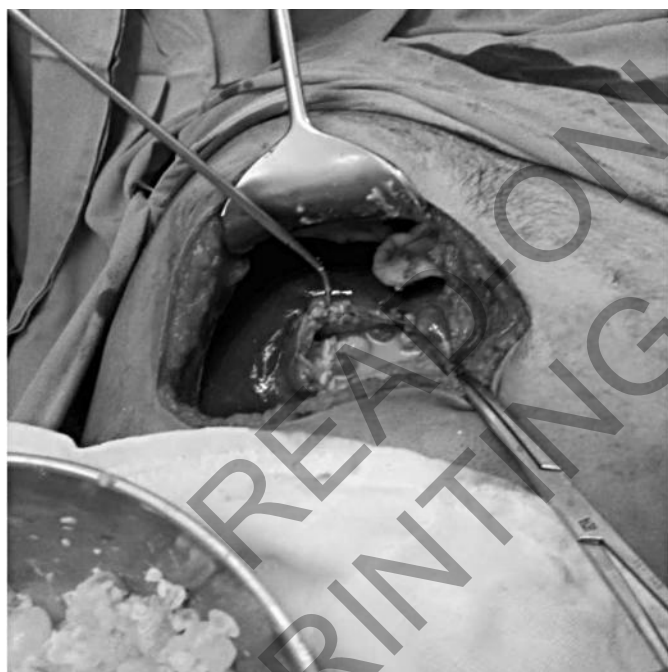


Fig. 4: Surgery image.

surgery, and it was continued for 2-24 months postoperatively. A total of 1.7 mg/ mL of ALB solution was used. DALB includes pre- and postoperative oral ALB therapy and intraoperative irrigation of the cystic cavity with ALB solution (Figs. 1, 2, 3, 4). The data was analyzed using Microsoft Office software. The results were presented as numbers and percent or mean and standard deviation.

Results

Fifty-two of the patients (53.06%) were female and forty-six (46.93%) were male; with a mean age of 41.85 ± 2.35 years. The follow-up period was 5-92 months.

The majority of the patients had solitary cyst ($n = 57$, 58.16%). Fifty-two patients (53.06%) had cysts in the right lobe and 42 (42.85%) in the left lobe. Four patients (4.08%) had cysts in both lobes. Fifteen patients had concomitant diseases unrelated to hydatid disease: hypertension ($n = 6$), cholelithiasis ($n = 2$), chronic respiratory disease ($n = 4$), diabetes mellitus ($n = 2$), coronary disease ($n = 1$), and chronic renal insufficiency ($n = 1$), hepatitis B infection ($n = 1$).

Ninety-two (93.8%) patients were treated by drainage, capitonage and omentoplasty with or without partial cystectomy. In six patients (6.12%) cystobiliary communication was diagnosed. Two of them were treated by intracystic ligation of communication. The two patients had a normal calibered choledochus containing daughter cysts, and were treated by T-tube drainage. The last two patients with a large-caliber choledochus full of daughter cysts were treated by choledochoduodenostomy. Cholecystectomy was also performed in cases of cholelithiasis.

Mean preoperative systemic albendazole therapy was 12.47 ± 13.14 days (1-120 days). Most of the patients treated by ALB less than 1 month. The patients treated by ALB postoperative 1-24 months (mean $\pm$ standard deviation 3.39 ± 2.11 months). Most of the patients treated by ALB 1-8 months.

A total of ten complications were encountered in ninety-eight (10.89%) patients. There were wound infection in four patients, incisional hernia in one patient, cavity infection in one patient and recurrence in one patient. All the patients with infectious complications received antibiotherapy. The patients with a cystic cavity infection or biliary collection were treated by percutaneous drainage. morbidity rates were 10.89%. All the complications are shown in Table III. The mean hospital stay was 12.28 ± 3.9 days.

Recurrence occurred only in one patient at postoperative month 55. This patient had a C-E2 cyst (11 cm in diameter) and was treated by cyst drainage and omentoplasty and received ALB for seven days preoperatively and three months postoperatively. One patient died after two months surgery. After radical excision of the cyst, a perihepatic abscess occurred and then several percutaneous drainages were performed. Despite aggressive treatment against infection, the patient died due to septic complications.

Conclusion

Echinococcosis is a zoonosis caused by *Echinococcus* spp. The oral intake of parasite eggs from a carnivore host

causes the infection in human body. The intermediate hosts are livestock like sheep, cattle, horses, and goats and small carnivores are the definitive hosts. After the eggs are ingested from an infected dog or its contaminant environment by human, the hydatid cyst filled with larvae is formed. Liver is the most common localization for hydatid cyst. Lung, spleen, kidney, bone, and brain are the less frequent sites for HC. Hepatic hydatidosis, an uncommon entity in Western countries, is still a serious public health issue in the Eastern Regions and European Mediterranean areas⁴⁻⁷.

There are three modalities to treat HC are being used; chemotherapy, surgery, percutaneous drainage.

Chemotherapy alone is not sufficient in the treatment of hydatidosis, but should be added to the preferred option to reduce the recurrence due to spillage of the cyst content during interventions. The main goal of the treatment should be the elimination of the parasite without recurrence with minimal morbidity and mortality. Although surgical procedures have been the golden standard option for HC, there is still an ongoing controversy about the optimal way of surgery. Mortality ranges 0% to 3.4% after surgical treatment of HC in literature. Mortality and morbidity are remarkably higher with radical procedures than conservative surgical options. Surgical approach is still a preferable option in patients with liver hydatidosis when it is performed by experienced surgeons⁸⁻¹².

The overall postoperative recurrence rate of HC is about 1% to 25%. Radical surgery, pericystectomy or liver resection, has lower risk of recurrence than conservative procedures (partial cystectomy, unroofing, capitonnage, omentoplasty). Surgical procedures can be performed by a conventional open or laparoscopic approach. We prefer conventional open techniques for surgical interventions. Radiological scanning, clinical and serologic evaluation are used to evaluate relapses. Although more radical procedures are usually preferred after recurrence, percutaneous drainage can be performed in patients with simple cysts and with increased risk for mortality and morbidity as an alternative approach to radical surgery¹³⁻¹⁷.

Recurrence and/or secondary hydatidosis are serious problems in hepatic hydatidosis surgery. They are usually due to either inadequate cystic content removal, spillage of cystic liquid or overlooked cysts. Although current surgical techniques reduce the recurrence and secondary hydatidosis rates, they remain high at 23%. Some authors report lower recurrence rates with radical procedures (e.g. pericystectomy; 0-4%) than with liver resection procedures (up to 25%)¹⁸⁻²¹.

There is controversy over the effect of perioperative ALB administration in preventing recurrence or secondary hydatidosis. Pelaez et al. have reported no recurrence after 2 months of perioperative ALB therapy. However, Montes et al. reported recurrence in a patient after 4 weeks of 16 mg/kg per day ALB use, contrasting with no recurrences in patients who did not receive

ALB. Recurrence was not seen during the follow-up period in the present study. Comparing recurrence rates in the published literature, it is considered that DALB may prevent recurrence in liver hydatid disease after surgery. Bekhti et al. were the first investigators to use mebendazole for the treatment of hydatid disease in 1977. After that, benzimidazole derivatives found widespread use worldwide. Recently ALB has been the most widely used agent in the medical treatment of hydatid disease. ALB inhibits some enzymes such as acid phosphatase, adenosine triphosphatase, pyruvate kinase, phosphoenolpyruvate kinase and alanine transferase and leads to a decrease in the glycogen content of the cyst wall. This causes cellular autolysis and degeneration in the microthrix and the microtubuli. There are novel studies about ALB being used for disinfecting of hydatid cysts preoperatively or perioperatively. Some authors state that a dose of 10-15 mg/kg per day of ALB is effective for hepatic hydatidosis in experimental and clinical studies. There is no agreement on duration of the ALB medication for cyst sterilization²²⁻²⁵.

In an experimental model, Morris et al. reported that 10 mg/kg per day ALB for 1 week after inoculation reduced peritoneal cyst formation. It has also been found that 93.75% of the cysts were sterile following preoperative ALB use for 1 month or longer with the same dose in a clinical study. Successful results with preoperative short-term (2-7 days), 3-week or 1-month medications have also been reported. In some studies, ALB was used for ≥ 2 months in the postoperative period after percutaneous drainage. Plasma albendazole sulfoxide (ALSF) levels ranged between 30 and 3200 ng/mL after administration of 10-mg/kg ALB daily doses. Saimot et al. also reported a serum concentration of 0.315 mg/mL and 0.911 mg/mL and 0.800 mg/mL ALSF in the cystic fluid and the cyst wall, respectively. In the present study the protoscolicidal solution used contained 1.7 mg/mL ALB, which is higher than the concentration used by Saimot et al. In experimental studies ALSF has been shown to have high scolicidal effect. In systemic administration, the side-effect of ALB is minimal, dose-dependent and reversible. In some cases, ALB administration may cause neutropenia, elevation of liver enzymes or alopecia. Morris et al. reported that 10 mg/kg per day ALB medication caused liver function abnormalities including cholestatic icterus as high as 18 mg/dL after 30 days of therapy. We have previously published results of experimental and clinical studies showing that intraoperative use of ALB produced no side-effect.

The pre-, post-, or perioperative use of ALB for the treatment of hydatid cysts has been studied, and an ALB dosage of 10-15 mg/kg/day was found to be effective in many of these studies. The effectiveness of ALB was reported as 71.5%, 88.7%, and 97% by Horton, Liu et al., and Chai et al., respectively. The duration of ALB treatment for cyst sterilization remains controversial.

Morris et al. reported that preoperative ALB treatment for one month or a longer period sterilized 93.75% of cysts in an experimental model. The same study reported that 10 mg/kg/day of ALB for one week after inoculation reduced the formation of peritoneal cysts. Other studies reported successful outcomes after preoperative short-term (three to seven days) or long-term (three weeks to one month) ALB treatment. ALB usage was recommended for two or more months after surgical treatment or percutaneous drainage^{18,25,26,31-34}.

The most common side effects of ALB are neutropenia due to bone marrow inhibition and elevation of liver enzymes. Morris et al. reported liver function abnormalities, including cholestatic icterus, in 18% of cases after ALB therapy for one month. Only one ALB-related death has been reported. In this study, neither neutropenia nor any other hematological abnormality was detected in our patients³⁵⁻³⁹.

In conclusion, our results suggest that DALB treatment is safe and effective in the prevention of secondary hydatidosis and/or hydatid disease recurrence. Surgery must be combined with perioperative ALB medication for the effective treatment of hydatid disease.

Riassunto

L'albendazolo è il farmaco più usato per il trattamento dell'echinococcosi. Lo scopo di questo studio retrospettivo è stato quello di valutare l'effetto dell'ALB nel trattamento duplice intraoperatorio e postoperatorio su una casistica di 98 pazienti operati consecutivamente per echinococcosi epatica nell'arco di 7 anni in un centro unico. Lo studio preoperatorio si è avvalso dell'esame clinico, dell'ecografia e della TC, ed i 98 pazienti sono stati trattati con albendazolo sia intraoperatoriamente che nel postoperatorio dell'intervento chirurgico di varia natura: 92 pazienti (93,8%) con drenaggio, capitonage e omentoplastica con o senza parziale cistectomia. In 6 pazienti (6,12%) è stata diagnosticata una comunicazione cistobiliare e sono stati trattati con legatura intracistica della comunicazione; due pazienti presentavano un normale calibro del coledoco contenente cisti figlie, e pertanto trattati con drenaggio secondo Kehr. Due pazienti con coledoco dilatato e pieno di cisti figlie sono stati trattati con coledocoduodenostomia.

Nel periodo postoperatorio l'ALB è stato somministrato nella dose di 12-15 mg/kg giornaliera suddivisa in quattro dosi. Il trattamento è stato iniziato da 2 a 28 giorni prima dell'intervento una volta stabilita la diagnosi e continuata da due a 28 mesi nel postoperatorio con ritmo ciclico mensile. Intraoperatoriamente è stata usata una soluzione con un totale di 1,7 mg/ml di ALB. Il trattamento duplice con albendazolo (DALB) è consistito con il dosaggio orale pre e postoperatorio e l'irrigazione intraoperatoria con ALB della cavità cistica. Nel postoperatorio un paziente è deceduto e ce n'è stato un

caso di recidiva. La morbilità generale è stata del 10,89%. Questi risultati indicano che il trattamento DALB insieme alla chirurgia dell'idatidosi epatica è efficace nella prevenzione delle recidive e dell'idatidosi secondaria.

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