Surgery and postoperative mebendazole in the treatment of hydatid disease

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ABSTRACT

Objective: Surgery was virtually the only curative method for hydatid disease until the early 1970s when studies have shown the safety and effectiveness of benzomidazole compounds for the treatment of hydatid cysts. Our aim is to establish the outcome of chemotherapy in the postoperative period on secondary hydatid cyst.

Methods: Between 1987 to 1996 inclusive, all patients who were diagnosed with hepatic hydatid disease and who underwent surgery and received a post operative course of chemotherapy at Princess Basma Teaching Hospital, Irbid, North Jordan, were retrospectively reviewed with special referral to side effects of chemotherapy and recurrence rate of hydatid disease.

Results: There were 78 patients (41 females, 37 males). All age groups were involved with an age range of 8-70 years. The main clinical presentation was upper abdominal discomfort, heaviness and mild pain. Ultrasonography and indirect hemagglutination test diagnosed more than 90% of cases. All patients were operated upon and received a postoperative prophylactic course of mebendazole. We reported a recurrence rate of less than 3%. Excessive loss of hair as a side effect to mebendazole therapy occurred in 2 young female patients.

Conclusion: The postoperative prophylactic course of mebendazole is reliable, safe and with minor side effects and the recurrence rate of the disease was reduced to the lowest possible levels.

Keywords: Hydatid disease, mebendazole, chemotherapy, surgery, recurrence, preoperative, postoperative.

Saudi Med J 2002; Vol. 23 (5): 568-571

Surgical treatment of hydatid disease was, and still is a curative method of treatment of hydatid cysts, but the main problem with surgical management is the high recurrence, most of them occur within the first 2 years after operation. Effective chemotherapy of hydatid disease has not proved to be curative of the disease until recently.[1] Since the natural history of the disease is not well documented and due to the many different factors related to both the host and the parasite, an evaluation of the results observed are difficult. Furthermore, it is hard to establish objective criteria to quantify therapeutic effectiveness. Anatomic cure, namely, disappearance of cysts should be the aim of treatment, but it can not be reached after medical treatment, perhaps because medical treatment leads to degenerative changes whose further evolution can hardly be predicted.[2,3] Concerning the relationship between the surgical and medical therapy of the patients with hydatid disease, surgery can be indicated for all cysts of more than 5 cm in diameter, complications and failure of chemotherapy, while medical therapy is indicated in patients who are unfit for or refuse surgery, for cysts less than 5 cm in diameter and for perioperative prophylactic use. We believe that medical and surgical therapy should be complementary to one another and the choice of therapy should be tailored for each patient.[4]

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Received 30th September 2001. Accepted for publication in final form 23rd January 2002.

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Methods. This study covers a 10 year period from 1987 through to 1996 inclusive, which included patients of hepatic hydatid disease who attended and were treated in Princess Basma Teaching Hospital, Irbid, North Jordan. The files were reviewed for age, sex, presenting symptom or symptoms. We reported the findings of ultrasonography (US) of the hepatic cyst or cysts and the titer of indirect hemagglutination test (IHA) that were performed for all patients. Chest x-ray, US of abdomen and pelvis and sometimes computerized tomography (CT) scanning were carried out to detect the presence of any extra hepatic loci. Complete blood count (CBC), serum glucose and electrolytes, urine analysis, renal and liver function tests were all noted at the time of surgery and were taken as a baseline for the postoperative medical treatment. Patients excluded from the study were those with chronic debilitated diseases (for example, impaired liver and kidney functions, congestive heart failure), pregnant women, uncooperative patients and those with extra hepatic sites. The operative procedures were uniformly applied to all patients by the operating surgeons of the unit and the approaches were recorded as laparotomy, right thoracotomy, or thoracoabdominal for easy accessibility and for thorough examination of the liver and complete removal of the cyst or cysts. The scolicidal agent used was cetramide 0.5% for the abdominal pads and 1% for the injection and pad packing inside the cyst. The cysts encountered were described in regard to their numbers, size, pressure and content of hydatid fluid, daughter cysts and bile staining. After evacuation of the cyst or cyst gauze pads soaked with 1% cetramide were left in the cavity for 10 minutes. Postoperative treatment with mebendazole 20mg/kg body weight/day in 3 divided doses was given to all patients for 3 months. Control during treatment was maintained by an early US (3-4 weeks) after surgery to detect the presence of any missed cyst and 4 weekly reports of CBC hepatic and renal function tests and its complications were recorded. Follow-up was maintained with US and IHA titer test every 6 months for a mean period of 4 years and the recurrence rate was reported.

Results. Seventy-eight patients entered into this study with an age range of 8-70 years and sex distribution was 41 (53%) females and 37 (47%) males. They presented mainly with upper abdominal discomfort, heaviness and mild pain in 56 (72%) cases, acute abdomen with ruptured hepatic hydatid cyst in 4 (5%) patients and incidental findings in 18 (23%) cases. Ultrasonography were diagnostic in all cases, plain abdominal x-ray showed partial calcifications in 12 (15%) patients. Computed tomography scan was performed in 43 (55%) cases that gave detailed anatomical display of the lesions and to exclude the presence of any extra hepatic site. Indirect hemagglutination test was positive in 71 (91%) cases, with no false positive results, but 7 (9%) cases with false negative results were reported. The surgical approaches were laparotomy in 68 (87%) cases, thoracotomy in 8 (10%) cases and thoracoabdominal in 2 (3%) cases. Laparotomy through a subcostal incision is the most common and it gives accessibility to all locations of hydatid cysts in the liver with less morbidity. The scolicidal agent used in all cases was cetramide 1% for intracystic injection and intracystic packing with soaked pads, 0.5% for peritoneal abdominal pads. The surgical procedure used was incision and evacuation of the cysts in all patients. The cysts were tense with clear hydatid fluid and daughter cysts in 56 (72%), tense with turbid fluid and daughter cysts in 16 (20%), soft cysts with toothpaste like material and destruction of germinal epithelium in 6 (8%). All patients had more than one cyst and the majority were more than 5 cm in diameter. Mebendazole was given to all patients for a period of 3 months after surgery without significant side effects except for noticeable excessive loss of hair that occurred in young females that was revived a few days after the end of the therapy. Recurrences were observed in 2 (3%) patients on a 6 monthly routine US and in 2 different sites; the first was located in the pelvis (Douglas' pouch), while the 2nd was found in the liver itself and it happened to be in one of those females who had hair loss and both were 5cm in diameters and their walls were thin and noticed 6 and 12 months respectively from the time of surgery. Indirect hemagglutination test showed a slow but constant decline in titer to a level below 1/200 over a period of 12-18 months except in those 2 recurrences.

Discussion. Hydatid disease is not rare in our country, it is common in endemic areas and it is now encountered in immigrants in non-endemic areas and in developed countries.[5] The main problem with surgical treatment of hydatid disease is a high recurrence rate 10%-30%[6-8] which is usually due to a spillage or incomplete removal of the cyst. In the early 1970s, many centers used albendazole or mebendazole alone for the treatment of human hydatid disease[9,10] and these drugs appeared to be effective in more than 50% of cases.[2] Many questions on the medical treatment are still unsolved, nevertheless, it is encouraging and they are safe drugs and can be ordered as drugs producing degenerative modifications in hydatid cysts.[4] The drugs available for the treatment of hydatid disease, its optimal use, advantages, limitations and side effects will be discussed. These drugs are benzoimidazole carbamates (mebendazole and albendazole) and they act by blocking glucose absorption producing degenerative changes in the endoplasmic reticulum and mitochondria of the

germinal layer leading to cellular autolysis.[11-13] Benzoimidazole carbamates sometimes have a parasiticidal and sometimes a parasitostatic action, as suggested by the relapses occurring after cessation of medical treatment, as if these drugs temporarily freeze the parasite.[14] In an experimental study, mebendazole was given for 4 days in a high dose of 40-65mg/kg/day before the experimental inoculation of scolices intraperitoneally in mice. This prophylactic therapy decreased the intraperitoneal formation of cysts significantly from 80% to 11%,[15] the circumstances of the experiment are similar to those in a postoperative situation where all cysts were evacuated and the spilled intraperitoneal hydatid fluid is now exposed to the action of drugs. The hydatid cyst shows degenerative morphological changes as a part of its natural history but the progress of these changes is much higher with medical treatment than that observed in the untreated cases.[4,16] Mebendazole is used as a broad spectrum anti-helminthic drug and it was the first used in the treatment of human hydatid disease.[17] It is proved that less than 10% of the dose taken of mebendazole is absorbed into circulation, the drug is rapidly metabolized and excreted in urine. In fully developed cysts, the adventitia is thick and it is held responsible for the relative low intra-cystic levels and ineffectiveness of systemically delivered drugs in an old and fully developed cyst.[18] It was thought that the absorption could be slightly increased in serum when mebendazole is taken with fatty meals, in large doses and for prolonged periods[19,20] but there was no significant improvement in the outcome.[17] The age of the patient and the age of the cyst can play a determining factor in the outcome of medical treatment, namely, cysts of less than 2 years have a thinner fibrous envelop and high metabolic rates with greater susceptibility to the action of mebendazole, also patients of less than 20 years old were more responsive to mebendazole.[21] The therapeutic response depends on the cyst size and its visceral location; a cyst more than 5 cm in diameter is less favorable for mebendazole and chemotherapy is not effective in hydatid disease of bone.[18,20] Side effects related to the use of mebendazole like nausea, abdominal pain, distention and headache were reported in the literature, are dose related, tolerable and self-limiting and disappear shortly after the cessation of treatment.[4,22] Serious toxicity attributable to high dose mebendazole treatment were reversible neutropenia,[23] prolonged fever,[24] glomerulonephritis,[25] abnormal liver function tests[26] and alopecia,[4] but again these are reversible after treatment had been stopped. In our experience, there were no serious toxic effects rather than the 2 cases of excessive hair loss, which disappeared after the end of treatment. The early contribution of the preoperative benzimidazoles therapy to the management of hydatid disease[27] is still under investigation in regard to the effectiveness and duration of the course of therapy, either long course of one month duration[22,27] or short course of a 5 day period.[28] The intra-cystic pressure (ICP) during surgery was used as a criterion to evaluate the viability of hydatid cyst, the reduced ICP in those patients receiving preoperative albendazole is regarded as decreased viability of the cysts and decreased incidence of postoperative recurrence should be expected.[29-31] A study is in progress in our unit to evaluate the value of preoperative and postoperative chemotherapy of hydatid disease. Chemotherapy in the postoperative period (after removal of the bulk of the disease) is effective in preventing secondary hydatidosis during a 2 year period of follow up.[32] We believe that surgical excision of the cyst with a proper surgical technique and the use of an effective scolicidal agent with a proper isolation of the cyst during surgery is indicated for multiple cysts and cysts more than 5 cm in diameter with multiple daughter cysts[33,34] and the use of mebendazole 20mg/kg body weight/day in 3 divided doses for a period of 3 months in the postoperative period can kill the scolices that was spilt and can also deal with a missed small cyst should this event happen.[22] In our study, the overall recurrences were less than 3% after 4 years period of follow up, so this is comparable to other reports in the literature.[22,27,30]

To conclude, surgical therapy of hydatid disease combined with a postoperative prophylactic course of mebendazole or albendazole, is considered an effective therapeutic approach to hepatic hydatid disease and, consequently decrease the risk of recurrence due to intra-operative peritoneal dissemination.

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