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Ultrasound-guided percutaneous treatment of liver hydatid cysts using 3% hydrogen peroxide as a scolicidal agent: The efficacy and clinical outcomes

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RESEARCH

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ABSTRACT

Background
Hydatid disease of the liver is endemic in cattle areas of the world. A variety of treatment options is available. The common treatment options are medical therapy, surgery and puncture-aspiration-injection-reaspiration (PAIR) therapy.

Aims
To evaluate the clinical outcomes and effectiveness of PAIR therapy in the treatment of liver hydatid disease using 3 per cent hydrogen peroxide (HP) as a scolicidal agent.

Methods
Between October 2012 and October 2015, seventy hydatid cysts in 52 patients were treated by PAIR procedure using three per cent HP as a scolicidal agent. Pre-procedural clinical, radiological and laboratory characteristics and post-procedural morbidity, mortality and length of hospital stay were recorded.

Results
We performed PAIR of 70 hydatid cysts in 52 patients with a success rate of 95 per cent without any mortality. The mean length of hospital stay was three days (ranges 1–8). In our series, minor complications occurred in six patients and major complications in five patients. The follow-up period ranged from 12–18 months, with a mean of 15.3 months. Three patients developed recurrence.

Conclusion
PAIR therapy is a minimally invasive procedure for Gharbi type I-III hepatic hydatid cysts. It is a relatively safe procedure with a significant reduction in the duration of hospital stay. We believed that HP by itself plays a role in influencing the results and the outcomes of PAIR.

Key Words
Hepatic hydatid cyst, hydrogen peroxide, PAIR, ultrasound

What this study adds:

1. What is known about this subject?
PAIR therapy is an effective minimally invasive procedure for Gharbi type I-III hepatic hydatid cysts.

2. What new information is offered in this study?
Hydrogen peroxide (HP) as a scolicidal agent plays a role in influencing the results and the outcomes of PAIR.

3. What are the implications for research, policy, or practice?
PAIR using 3 per cent HP as a scolicidal agent can be used as an alternative to surgery in treating types' I-III of hydatid liver disease.

Background

Hydatid disease caused by Echinococcus granulosus larvae is a common health problem especially in endemic areas such

as Mediterranean countries, the Middle East, South America and New Zealand.[1]

Echinococcus granulosus has both definitive and intermediate hosts.[1,2] The most common definitive and intermediate hosts are dogs, sheep and cows. Humans become infected as an intermediate host by ingestion of contaminated food or drinks or by direct contact with these animals.

Hydatid cysts are composed of both host and parasite tissue: the former consists of a dense, fibrous tissue called the pericyst, formed by a reaction of the liver to the presence of the parasite, while the latter, the endocyst is formed of two layers, an outer laminated layer and an inner germinal one.[3]

Hydatid cyst can develop in any organ of the body but commonly occurs in the liver (50–80 per cent). The right lobe of the liver is affected more frequently than the left. The second most common site is the lungs (5–30 per cent). Cysts have also been detected in the spleen, kidney, heart, bones, the central nervous system, and other organs, but with less frequency.[1,2,4]

Although hydatid cyst is usually a benign disease and incidentally detected on ultrasonography, the symptomatic and active cysts present a high risk of fatal complications making treatment mandatory.[5]

The traditional mainstay of treatment for liver hydatid cyst is surgery, which is, unfortunately, an invasive method with high rates of morbidity and mortality, lengthy hospitalisation, surgical scarring, high cost, and recurrence.[6] Recently non-surgical methods (medical and percutaneous approaches) have been progressively replaced in the last three decades to treat the disease as alternatives to surgery. Currently, albendazole and mebendazole are used in medical treatment.

Percutaneous treatment of hydatid cyst of the liver was first reported by Mueller et al. in 1985.[7] Since then, this method has seen increasing acceptance due to the low incidence of side effects and low mortality rates.[8] Percutaneous puncture, aspiration, injection of scolicidal agent and reaspiration (PAIR) is a minimally invasive procedure than surgery.[8] Hypertonic saline, cetrimide, chlorhexidine and ethyl alcohol are some of the compounds used as scolicidal agents in PAIR procedure.

In this study, we aimed to present our preliminary clinical outcomes and the efficacy of PAIR technique by using three per cent hydrogen peroxide solution as a scolicidal agent with pre/and post-procedural albendazole treatment. To our knowledge, ours is the first report describing the direct percutaneous injection of hydrogen peroxide into the hydatid cyst cavity.

Method

Study Population

This prospective interventional study was carried out in the department of radiology of our hospital from October 2012 to October 2015. PAIR technique was performed on 52 patients (27 female and 25 male) with 70 hepatic hydatid cysts and was followed-up for a maximum period of 18 months. The median patient age was 40.5 years (range 16–70 years). Forty-nine patients were recently diagnosed with hydatid liver cysts and had no previous medical treatment or surgical intervention. Three patients had a history of surgery for hydatid cyst prior to the intervention and had applied for percutaneous treatment due to relapse. Forty-three patients had single hydatid cyst while nine patients had multiple cysts (range 2–4).

All cysts were classified according to the Gharbi classification.[9] According to this classification, type I cyst refers to a pure fluid collection, type II refers to a cysts with fluid collection with a separated membranes (honeycomb sign), type III is a cyst that contained multiple septations and /or daughter cysts, type IV is a cyst with heterogeneous solid mass with high internal echoes, type V sonography reflecting calcified thick wall.

Inclusion criteria were patients having single/multiple hepatic hydatid cysts of Gharbi type I, type II, type III cysts with drainable matrices, with adequate liver parenchyma (>5mm) surrounding the cyst, cyst size >4cm, while those patients with Gharbi type III cysts with non–drainable contents, with severe septation with innumerable daughter cysts, type IV and V cysts, peripheral cysts having <5mm of surrounding hepatic tissue, cysts with communication to the biliary tree, history of anaphylaxis or atopy, uncooperative patients, patients who were pregnant or who had infected cysts at the time of initial aspiration were excluded from the study.

Informed written consent was obtained from all patients before the procedure. The study was approved by the ethical committee of the hospital. PAIR and other treatment modalities were explained and discussed with the patients.
After a detailed history and clinical examination, the diagnosis was confirmed by sonography and serological test

by enzyme-linked immunosorbent assay (ELISA). Computed tomography (CT) scan was only performed when calcification in the cysts and relation to the vessels and biliary tree needed to be established. Liver function tests were performed and blood counts and coagulation functions were determined. All patients undergoing percutaneous drainage were treated with prophylactic oral albendazole 10–15mg/kg twice a day, starting 1week before and continuing after PAIR procedure for a total of 8 weeks to minimise the risk of possible intraperitoneal seeding of scolices possibly spilt during the interventional procedure. In all cases, anti-allergic prophylaxis (diphenhydramine, 10–50mg/kg, and hydrocortisone sodium succinate, 100mg IV) was injected I.V for 15 min before the intervention. Emergency tray consisting of necessary medicines and equipment were kept ready in the procedure unit. The patients fasted overnight.

PAIR Technique

PAIR method can be summarized as follows: having ensured aseptic conditions in the intervention area, the procedure was performed under local anaesthesia using lidocaine two per cent at the point of puncture, but for irritable, uncooperative and patients with large cysts, the procedure done under heavy sedation (midazolam 0.1mg/kg intravenously (IV), propofol 2mg/kg IV) with close monitoring by an anesthesiology team to treat any potential complication. As a scolicidal agent, three per cent hydrogen peroxide (HP) solution, prepared under laboratory conditions were used in all patients. The puncture was made through normal liver parenchyma surrounding the cyst and whenever possible the right intercostals route was used to minimise the risk of hydatid fluid spillage into the peritoneum. Under aseptic conditions, 15 or 20cm long Teflon sheath needle was introduced into the cystic cavity by a transhepatic route under sonographic guidance (HD11 XE, Philips), with every effort being made to avoid direct puncture of the cyst. Most of the cyst contents were aspirated and once the cyst was almost empty, three per cent sterile HP solution in an amount equal to half of the aspired liquid was then injected and left in the cyst cavity for 15–20 min. After separation of the germinative membrane was seen, the fluid was then re-aspirated as much as possible and the cyst cavity was rinsed with normal saline.

Vital signs were monitored throughout the procedure. The aspirated cyst liquid was immediately subjected to cytologic, histopathologic, and parasitologic examinations after aspiration for detection of fragments of laminated membranes, hooklets, and scolices, to confirm the diagnosis and to assess the success of the drainage procedure**.** To exclude the presence of a biliary fistula, the bilirubin level in the aspirated fluid was determined by a semi-quantitative method (Combur-Test; Roche Diagnostics, Indianapolis, IN) within a few seconds before HP injection at each PAIR.

After that, the patients were closely observed for possible complications for 24 hours. The complications were defined according to the Society of Interventional Radiology (SIR) guidelines.[10]

Follow-up

The follow-up protocol included clinical assessment, laboratory tests and ultrasonography (US). Abdominal CT was only used in some cases. The patients were evaluated after the intervention using the US at the next day. Follow-up US then performed, at one month, three months, six months and one year and at the end of follow-up period with total follow-up periods varying from 12–18 months. Indirect hemagglutination (IHA) titers were measured during the same periods for all patients. Liver functions were tested.

Follow-up criteria were included initial and serial post-procedure cyst size; sonographic echo pattern, and wall structure of the cyst, the length of hospital stay; complications, including disease recurrence; and outcome.

The criteria that were used to define cure or success of PAIR procedure were clinical improvement and US finding of size reduction, separation of the endocyst (germinal layer) from the pericyst and rupture of secondary vesicles in multivesicular cysts, small residual cyst cavity with a high level of echogenic material, or complete obliteration with a heterogeneous echo pattern (pseudotumour formation). Recurrence was defined as a volumetric increase of a cyst and/or appearance of a cyst in the same or another organ after successful treatment. Complications of PAIR were defined as “major” (i.e., anaphylaxis, biliary fistula, cyst infection, liver/intra-abdominal abscess, or sepsis) or “minor” (generally non–life-threatening and/or nosocomial complications).

Results

During the study period, we performed PAIR for 70 hydatid cysts in 52 patients by using three per cent HP as a scolicidal agent. Clinical and parasitologic cure occurred in 95.8 per cent. No mortality or abdominal dissemination, no new cysts developed in other hepatic segments or in any extra-hepatic site during or after the procedure. The recurrence rate was 5.7 per cent (3/52 patients).

Forty-nine patients had one procedure of PAIR, three patients had two procedures. These latter three patients had multiloculated cysts, which represented the only cases of relapsing disease after the initial percutaneous treatment.

According to Gharbi classification, the majority of the cysts were Gharbi type I (n=50; 71.4 per cent). 11 cysts were type II (15.7 per cent). 9 patients were type III cysts (12.8 per cent) (Table 1). The average size of the cysts before treatment was 8.4 cm (ranges 5–12cm). The average pre-procedure cyst volume was 220cc (ranges 32–665cc) while the post-procedural volume was 115cc (ranges few cc–280cc). HP amount injected per procedure ranged between 10 and 200ml (mean 44ml). The duration of each one interventional procedure ranged between 30 and 60 minutes (mean 48 min). The duration of hospital stay was three days (ranges 1–8 days).

Minor complications were recorded in six patients (11.5 per cent) of the treated patients as follow: fever (one case), hypotension (one case), nausea and vomiting (two cases), abdominal pain lasting more than two hours (one case), and urticaria (one case) and these reactions were generally managed effectively with antipyretics, intravenous fluids, and antihistamines.

Major complications were recorded in five patients (9.6 per cent) of the treated patients (Table 2). Anaphylactic shock occurred in one patient (1.9 per cent) and this patient recovered promptly with appropriate medication and was kept under observation in the intensive care unit. Upon improvement in his general condition, the patient was discharged after five days and surgery was planned for a future date. Hepatic abscesses developed inside two treated cysts (two patients) within one month after PAIR; in both cases, the abscess cavities were treated with percutaneous drainage and antibiotics, and at the last US scan, reconstitution of liver parenchyma was observed without any focal lesion. In two patients, the procedure could not be completed due to complications developing during the intervention. One of those patients develops intracystic haemorrhage, which supervened just after insertion of an 18-gauge needle with moderate intra-peritoneal bleeding from iatrogenic liver injury forced us to give up the interventional procedure. This patient was kept under observation in the intensive care unit. The US examinations carried out the next day revealed haemorrhage inside the cyst and minimal free liquid in the pelvis. Blood transfusions and emergency surgery were not required. The patient's general condition improved and no further complications occurred, and the patient was discharged after 5 days. In the second patient, pultaceous bile material aspirated after the initial puncture, the bilirubin level was found to be high in the aspirated cyst fluid. The intervention was halted and the patient underwent endoscopic retrograde cholangiopancreatography (ERCP) on the suspicion of biliary fistula and this patient subsequently underwent elective surgery three months later.

Three patients developed recurrence during the follow-up period. They had multiloculated cysts, which during the period of follow-up had new, vital daughter cysts inside the post treatment heterogeneous masses. All of these patients were managed subsequently by another session of PAIR procedure. The daughter cysts disappeared at the end of the second month of treatment and a solid pattern was observed at the last US examination.

Follow-up

In follow-up US, at the first check-up during the first month, in all type I cysts treated with the PAIR method we observed further endocysts breaking off from pericysts floating in the cyst cavity while type II cysts had further detachment and folding of inner membranes was noted. A progressive reduction in the size observed after the first month as a result of degenerated endocyst. So that, the mean size of the cysts after two months US follow-up was 4.2cm indicating an about 50 per cent reduction in size compared to initial size. After six months, a significant gradual reduction was seen in the amount of cyst fluid with average 3cm cyst diameter which approximately indicates 65 per cent reduction in size and in some cases complete disappearance of the fluid component was noted. Heterogeneous pseudotumour appearance had occurred with a solid hyperechoic lesion appearance representing the degenerated and detached membranes. Thickening and irregularities were also observed in the cyst walls during the follow-up period and these findings considered as criteria for the cure in our study. The time taken to reach the final ultrasonographic pattern varied considerably. Generally speaking, type1, the smaller took a short time for ultrasonographic pattern changes to become evident (1-3 months), whereas the largest, complex cysts took longer (up to 18 months).

Discussion

For decades, surgery was the recommended treatment for hydatid cysts of the liver.[11] However, surgery is associated with significant morbidity and mortality. In the literature, mortality rates related to surgery have been reported to be 0–4 per cent depending on the various surgical procedures

applied.[12] On the other hand, recurrence, which is most important complication after surgery, has been reported to be 2–25 per cent.[12-14] Additionally, the surgical treatment of cyst which located near major biliary or vascular structures may cause serious complications. Smego et al.[15] reported a meta-analysis of surgical treatment for hydatid disease, minor and major complication rates were 33 per cent and 25.1 per cent respectively and the mortality rate was 0.7 per cent.

Recently, medical treatment and minimally invasive procedures such as laparoscopic surgery and percutaneous therapy have been progressively replaced surgery for the treatment of the liver hydatid disease. PAIR is a minimally invasive procedure than surgery. Firstly, it was introduced by Ben Amor et al in 1987.[16] US-guided PAIR is now commonly performed in conjunction with drug therapy consisting of albendazole or mebendazole provided before and after drainage and is very efficacious and results in a better outcome than surgery in Gharbi type I-III cysts.[17,18] The advantages of this technique have been reported in the literature over the last two decades and including greater clinical efficacy, low rates of complications, mortality and recurrence, low cost, shorter hospital stay, more patient's comfort, easily repeatable if needed and it can often be performed on an outpatient basis.[18-20]

In the literature, we noted that scolicidal agents were mainly used 20 per cent hypertonic saline and 95 per cent ethanol solution. But in the present study; even though WHO (1996)[21] recommends hypertonic saline as scolicidal, we used three per cent hydrogen peroxide (HP) as a scolicidal agent as it is easily available and has minimal side effects. HP is not toxic to the liver and biliary structures at the applied concentration, decreasing the possibility of chemical sclerosing cholangitis which is a well-known complication of chemical scolicidal agents.[22]

As far as side effects are concerned, minor complications such as fever, hypotension, nausea and vomiting, abdominal pain and urticaria were encountered in six patients (11.5 per cent) during the procedure and it was not much different from that reported in other series dealing with a percutaneous treatment but with scolicidal other than HP, but it proved to be lower than that reported in surgical series, ranging between 18 per cent and 84 per cent.[11,23,24] In our study, severe anaphylactic reactions occurred in one patient. The patient recovered promptly with appropriate medication in keeping with the findings of other authors.[19,23]

In our study, the biliary fistula was evident in one patient when bile-stained fluid was collected during the second aspiration. Our policy was adapted so that partially refilling the cyst with scolicidal after the first aspiration, we think this will hamper leaks into the biliary tree through small fissures in the pericyst, thereby explaining the lower rate of biliary fistula formation (1.4 per cent) when compared with that of about six per cent reported by Ustunsoz et al.[20] and Men et al.[24] studies. Zeybek et al.[25] reported that cystobiliary fistula rate was 18 per cent (six of 33 patients). However, this was not observed in any case studied by Livraghi et al.[26]

Recurrence one of the most serious reported problems after both surgical and percutaneous therapy in the patients with hydatid liver disease. However, the rate of recurrence in PAIR was much lower than with surgery. In our study, the rate of recurrence observed following percutaneous treatment was 5.7 per cent (three patients from 52) in an average observation period of 15.3 months and it was only seen in multiloculated cysts. In the series by Gargouri et al.[27], the ratio was reported to be four per cent (five of 120 cysts) during a follow- up period of 12–24 months. Many authors[20,28-30] did not observe these complications in their studies. This relatively high rate of relapse in our work may be explained by the inclusion of a large proportion of type 3 cyst (multi-loculated) in our study. As in other recent series[19,20,24], none of our patients had relapse of the disease in other liver segments or elsewhere in the body, namely the peritoneum and thorax perhaps as a consequence of spillage of hydatid fluid and this may be explained by a contributory role played by systemic prophylaxis with albendazole which has been shown to reduce relapse of hydatid disease after surgery and percutaneous treatment.

Some references even state that the cyst cavity disappears completely and is not differentiated from liver parenchyma.[29,30] In our study, we observed only five cyst cavity that disappeared totally; all were of small size (less than 6cm) and of type 1.

The factors of limitation in this study include the small number of cases, comparably shorter period of follow-up observations and lack of comparison with surgical methods. However, this study was intended to compare only percutaneous interventions. Compared with patients treated surgically, we found that PAIR therapy, had greater clinical efficacy (i.e., a higher incidence of cure); lower rates of major and minor complications, mortality, and disease recurrence; and a shorter duration of hospitalisation.

Conclusion

Our results indicate that PAIR using HP as the scolicidal agent is minimally invasive, relatively safe and less expensive treatment option which can be offered as an alternative to surgery for patients with Gharbi type I-III hepatic hydatid cysts. However, although very low in number, life-threatening complications make it necessary for this type of therapeutic modality to be reserved for centres where resuscitation measures and surgical facilities are at hand. We believed that HP by itself influenced the results and the outcomes of PAIR.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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ETHICS COMMITTEE APPROVAL

This study was approved by the Ethical Review Committee of Alkindy Teaching Hospital, Baghdad. Protocol No: 32/20l2

Table 1: Distribution of cysts according to Gharbi classification prior to intervention

Gharbi classification	Lesion features	No of treated cysts with PAIR
Type I	Pure cystic lesion	50
Type II	Cystic formation containing segregated membranes	11
Type III	Cyst containing multiple septa/daughter vesicles	9
Type IV	Semisolid heterogeneous lesion	-
Type V	Calcified wall hyperechogenic lesion	-
Infected	Abscess-like lesion	-
Total		70

Table 2 Outcomes after treatment with PAIR

Outcome	
Follow-up (months)	12-18
Hospital stay (days)	3 (ranges 1- 8)
Minor complications	6 patients (11.5%)
Major complications	5 patients (9.6%)
Anaphylaxis shock	1 Patient (1.9%)
Cyst haemorrhage	1 cyst (1.4%)
Biliary fistula	1 cyst (1.4%)
Abscess	2 cysts (2.8%)
Recurrence	3 patients (5.7%)