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Percutaneous Treatment of Hydatid Liver Cysts: An Update

Antonio Giorgio[1]*, Giorgio Calisti[1], Giorgio de Stefano[1], Nunzia Farella[1], Umberto Scognamiglio[1] and Valentina Giorgio[2]

[1]*IX Infectious Diseases and Interventional Ultrasound Unit, D. Cotugno Hospital, Naples, Italy;* [2]*Hepato-Metabolic Division, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy*

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Abstract: Liver hydatidosis is the most common clinical presentation of cystic echinococcosis. Although liver cystic hydatidosis is considered a benign disease and many patients do not develop symptoms for years, its complications can be severe and life threatening (usually as a consequence of rupture in the biliary tree, in the peritoneum, in the bronchi, and of anaphylactic shock), thus, treatment is recommended for all viable and active hydatid liver cysts. Among the therapeutical options available for this disease, such as open and laparoscopic surgery and chemotherapy, percutaneous treatments have gained considerable interest over the last two decades, due to their efficacy, safety and high patient acceptability.

Percutaneous treatments for liver cystic hydatidosis were once discouraged due to the risk of anaphylaxis following cyst puncture. Following the first uneventful attempts in the mid '80's, these treatments were increasingly used and techniques such as PAIR (Puncture, Aspiration, Injection, Re-aspiration) and its variants were developed and implemented in clinical practice. Although the evidence currently available is not sufficient to support or refuse the superiority of PAIR in terms of efficacy, numerous studies have demonstrated that it carries lower rates of morbidity, mortality, and disease recurrence and is associated with shorter hospital stays compared with surgery.

The present review provides a brief history of percutaneous treatments for liver cystic hydatidosis, summarizes the currently available evidence on the subject, gives a brief overview of potential future developments in this field focusing on radiofrequency ablation techniques and presents some new patents on the issue.

Keywords: D-PAI, Hepatic echinococcosis, liver hydatidosis, liver hydatid cysts, PAIR, percutaneous treatment, radiofrequency ablation.

INTRODUCTION

Echinococcosis is a zoonotic disease caused by infestation with the larval stage of tapeworms of the genus *Echinococcus*. Four species of Echinococcus are known to infect humans. Of these, *Echinococcus granulosus* and, to a lesser extent, *Echinococcus multilocularis* are the most common, causing cystic echinococcosis (CE), also called cystic hydatid disease, and alveolar echinococcosis respectively [1].

The geographic distribution and overall prevalence of the different *Echinococcus* species vary widely reflecting the different animal hosts involved in their life cycles. Unlike other species, *Echinococcus granulosus* is today well adapted to domestic animals, using dogs as definitive host and domestic ruminants, pigs and horses as intermediate hosts; for this reason, CE occurs worldwide, with higher prevalence rates in those regions where animal husbandry is more common [2]. In some countries of the European and African part of the Mediterranean area, of the Eastern Sub-Saharan Africa, the Middle East, the South and Central America, in Russia and China, CE is endemic and causes relevant public health problems and significant economic losses [3, 4].

Humans are incidental hosts in the life cycle of the parasite. Transmission of *Echinococcus granulosus* frequently occurs in settings where dogs have access to the viscera of slaughtered livestock. Infested dogs excrete eggs with their faeces and humans become infected through faecal-oral transmission [5]. Following ingestion, the eggs hatch in the small intestine, penetrate the mucosa and migrate through blood or lymphatic vessels to target organs. At this location, the early-stage larva, called oncosphere, matures into a vesicle that progressively grows and expands to become a hydatid cyst, which is usually unilocular and fluid-filled [6]. The liver is the most common site of involvement (> 65% of cases) followed by the lungs (around 25%); less frequently CE may affect the spleen, kidneys, bones, brain and the heart [5].

The infection is often acquired during childhood and does not cause symptoms until adulthood. The clinical presentation of CE depends upon the size of the cysts and their location. Liver involvement with CE frequently causes no symptoms until the cysts have reached a considerable diameter (>10 cm), for this reason many cases are detected inci-

*Address correspondence to this author at the Viale Colle Aminei 491, 80131, Naples, Italy; Tel: 0039 081 5908278; Fax: 0039 081 5908278; E-mail: assanui1@virgilio.it

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dentally on imaging studies and many others remain undiagnosed. When present, symptoms of CE of the liver are due to mass effect upon surrounding structures or complications such as cyst rupture into an adjacent site or superinfection [7, 8]. Mass effect may cause hepatomegaly with or without associated right upper quadrant discomfort, nausea, vomiting, jaundice and more rarely portal hypertension and venous obstruction. Hydatid liver cysts may rupture into the biliary tree, causing biliary colic, jaundice, cholangitis or pancreatitis, or less commonly into the peritoneum or the pleural space [7, 9]. Anaphylaxis has been reported in 10% of cases of intraperitoneal ruptures [6].

Although CE is considered a benign disease and many patients do not develop symptoms for years, its complications can be severe and life threatening, thus, treatment is recommended for all viable and active hydatid liver cysts [10]. Three options are currently available for the treatment of liver CE: surgery, percutaneous treatments and chemotherapy with benzimidazole compounds, the latter option being used either alone or in combination with the previous two. The choice of the most appropriate strategy should be based on patient characteristics (e.g. age, co-morbidities, personal preference), cysts characteristics (number, type, size, location, presence of complications) and the availability of local resources and expertise [11]. If the appropriate treatment is not available locally, then the patient should be referred to recognized regional or national referral centres [10]. Surgery was the only option until the mid '80 when benzimidazoles and percutaneous treatments were introduced for the treatment of CE; nowadays, surgery maintains its role of first choice treatment for complicated cysts, however, in uncomplicated cases, it should be carefully evaluated against other less invasive options [10, 12]. Indeed, even the more radical approaches have high recurrence rates, in addition to the considerable morbidity and mortality rates [13]. Over the past 3 decades, benzimidazole compounds have increasingly been used for the treatment of CE, however their efficacy is still debated; a recent meta-analysis of published studies estimated that 1 and 2 years after treatment initiation, 60% and 40% of cysts are still active or have reactivated [14]. Percutaneous techniques represent a safe and valid alternative to surgery and are gaining growing recognition due to their feasibility, minimal morbidity and low cost [15].

Aim of the present review is to update and expand a previous review focusing on percutaneous treatments for liver hydatidosis [16].

PERCUTANEOUS TECHNIQUES: STATE OF THE ART

Traditionally, puncture of hydatid cysts was strongly discouraged because of the risk of anaphylactic shock and disease seeding as a consequence of intra-abdominal protoscolices spillage [17]. In the early '80's, when introduction of ultrasonography and computed tomography in clinical practice allowed the first attempts of image-guided percutaneous drainage of hepatic cysts, patients with suspected or proven hydatid lesions were regularly excluded from these attempts [18]. However, in 1985, Mueller *et al.* first described the percutaneous aspiration and lavage with silver nitrate and hypertonic saline of a recurrent hepatic hydatid cyst, in a patient not suitable for surgery, and reported no complications [19]. Following this encouraging preliminary experience, Ben Amor *et al.,* in Tunisia, developed in sheep, and then successfully used in humans, a new interventional technique that they called PAIR (P for "puncture of the cyst with a fine needle under ultrasound guidance", A for "aspiration of the hydatid fluid", I for "injection of sodium chloride hypertonic solution into the cystic cavity", R for "reaspiration of the solution without drainage") [20, 21]. More than 20 years after its first description by the Tunisian colleagues, PAIR and its variants are still considered the percutaneous technique of choice and a growing body of literature over the last 2 decades have demonstrated their efficacy and safety [10, 12].

The main variations that have been proposed regard the choice of the scolicidal agent. The efficacy of different concentrations of hypertonic saline, ranging from 3 to 30%, has been tested *in vitro* and used *in vivo* with variable results [22-25]. Hypertonic saline creates a strong osmotic gradient across the outer membrane of the scolix that causes its lysis. *In vitro* studies clearly demonstrate that, as a general rule, the higher is the concentration and the longer the exposure times, the greater and faster is the scolicidal effect [26, 27]. In the light of these results, concentrations lower than 20% of hypertonic saline should not be used in clinical practice. Following the experience of percutaneous ethanol injection for the treatment of hepatocellular carcinoma and simple nonparasitic hepatic cysts, Filice *et al.* first reported the use of 95% sterile ethanol in liver hydatid cysts [28]. Although not clearly demonstrated in any comparative study, 95% ethanol is generally considered to have a more potent sclerosing effect compared to hypertonic saline and is the second most commonly used scolicidal agent [29]. An *in vitro* evaluation has shown that with ethanol concentrations lower than 95% are ineffective in killing the scolices and hence not recommended [27]. Various other scolicidal agents for intracystic injection have been proposed, including 0,04% chlorhexidine gluconate, 20% silver nitrate, 50% dextrose, 20% mannitol and aminomix-1 solutions, albendazole solutions, Satureja khuzestanica and Olea Europea leaf extracts and even warm water [30-33]. Although *in vitro* experiments suggest that some of these compounds present theoretical advantages compared to 20% hypertonic saline and 95% ethanol, further *in vivo* studies are needed to implement their use in clinical practice. An EP patent by Fourati describes a novel instrument for aspiration of hydatid cysts consisting in a cannula provided with a suction cup at its distal end and connected to a vacuum source at its proximal end, and at least one hollow aspirating needle with its distal end surrounded by the cannula [34].

In 1992, we introduced a modified technique called Double Percutaneous Aspiration and Injection (D-PAI), which consists in the following phases: 1) percutaneous aspiration of the cystic fluid; 2) injection of 95% ethanol (50-60% of the aspirated volume which then is not reaspirated); 3) repetition of the same procedure after 3-7 days [35]. The main difference with the traditional PAIR technique is that the scolicidal agent is injected twice a few days apart and not reaspirated. The rationale behind our method is that the longer the scolicidal agent is left in the cyst to exert its effect, the more likely it is that all scolices will be killed. In-

deed, we have found that viable scolices can be still retrieved in the aspirated fluid 3-7 days after the first ethanol injection, albeit this does not necessarily correlates with diseases recurrence [35]. In the following 18 years we have treated 208 hydatid liver cysts in 141 patients with the D-PAI method achieving a clinical and sonographic healing rate of 89.4% of cases after a mean follow-up time of 54 months [36].

The cumulative experience of the past decades indicates that the best results are achieved with active unilocular cysts (CE1 stage according to the WHO-IWGE standardized classification, type I cysts according to Gharbi's classifcatication) or transitional cysts with an inner floating detached membrane (CE3a stage according to the WHO-IWGE standardized classification, type II cysts according to Gharbi's classification) than with multivescicular cysts (CE2 and CE3b stages according to the WHO-IWGE standardized classification, type III cysts according to Gharbi's classification) [10, 37-39]. In our most recent series, 14 of the 15 patients that presented recurrence of the diseases after the procedure had multivescicular cysts when first treated [36]. Puncturing all the daughter cysts is indeed technically unfeasible in many cases and, as previously demonstrated in a simple but well designed *in vitro* study, 95% ethanol and 20% hypertonic saline are both ineffective in destroying the daughter cyst wall from the outside and killing the scolices contained in the cyst [40]. Moreover, multivescicular cysts commonly present biliary ductal communications that are difficult to detect even on cystography and can lead to caustic sclerosing cholangitis after ethanol injection [41].

Percutaneous procedures for liver hydatid cysts should always be performed under aseptic conditions, with an anaesthesiologist present and preferably in an operating theatre. Usually local anaesthesia suffices, but in some cases (anxious patients, very large cysts, difficult technical approaches) general anaesthesia without endotracheal intubation is advisable [42].

Although successful percutaneous drainage of hydatid cysts without concomitant systemic chemotherapy with benzimidazoles has been reported, pre- and post-interventional therapy with albendazole seems to reduce the risk of disease recurrence and intra-peritoneal seeding of the infection following cyst rupture and is therefore considered mandatory by the consensus of experts of the WHO-IWGE [10, 43, 44]. Albendazole 4 hours before and for 1 month after the procedure is the recommended prophylactic regimen [10].

Cyst fluid during the procedure should be sent to the laboratory immediately after aspiration for cytological and parasitological examination in order to confirm the diagnosis and assess viability of scolices [45, 46]. Viability can be assessed by observing scolices motility using light microscopy or staining them with 0.1% eosin (showing viable scolices) and methylene blue (showing dead scolices) [46]. An alternative method to assess scolices viability has recently been patented by a Moldovan research group [47]. According to proposed protocol, the aspirated fluid is coloured with a mixture containing distilled water 400 ml, aluminium alums 25 g, crystalline hematoxylin 0.5 g, glycerin 100 ml and potassium iodate (KIO_3) 0.03 g. On microscopic examination, 3 minutes after coloration, viable scolices do not stain whilst damaged or non viable scolices appear intensely violet stained.

As far as complications are concerned, one of the main concerns regarding percutaneous treatments for hydatid liver cysts has always been the risk of anaphylactic reactions following cyst puncture. This issue has been specifically addressed in a meta-analysis from Neumayr *et al.* [48]. In their review of 124 published studies including a total of 5943 percutaneous procedures performed on 5517 cysts, the Authors retrieved 101 reports of anaphylactic reactions, of which only 2 were fatal (0.03% of the procedures). These results suggest that although the possibility of anaphylaxis must certainly be considered when performing percutaneous procedures on hydatid cysts and resuscitation equipment should always be readily available, excessive fear is not justified in the light of the current evidence. Furthermore, although minor allergic reactions seems to be more frequent with PAIR than with surgical treatments, the overall probability of major complications (anaphylaxis, biliary fistula, cyst infection, liver/intra-abdominal abscess and sepsis), minor complications and death is higher with surgery [49].

The presence of a communication between the cyst and the biliary tree contraindicates intra-cystic injection of sclerosing agents, in particular ethanol, because of the risk of caustic sclerosing cholangitis. This complication has been reported in surgical series therefore scolicidals are not advocated at surgery [50, 51]. During percutaneous procedure it is possible to assess the presence of biliary communications before injecting the scolicidal agent, by analysing the aspirated fluid for bilirubin with a rapid test or by cystography [36, 41]. The management of cystic echinococcosis complications with particular reference to rupture into the biliary tree has been addressed in a recent meta-analysis by Dziri and colleagues [7].

Only two randomized clinical trials (RCTs), both conducted by Khuroo and colleagues, comparing PAIR to other treatments have been published to date [52, 53]. In the first trial published in 1993 PAIR, with or without albendazole, was compared to albendazole alone; 100% of cysts treated with percutaneous drainage and only 18.2% of cysts treated with albendazole alone reduced in size and changed in echopattern [52]. The second trial, published in 1997, showed a comparable efficacy of PAIR plus albendazole and surgery but with a significantly lower rate of procedure related complications and a shorter mean hospital stay for PAIR plus albendazole [53]. On the basis of these two RCT, a recent meta-analysis by the Cochrane Collaboration concluded that the evidence currently available was not sufficient to support or refuse the superiority of PAIR [54]. Nonetheless the authors of this meta-analysis have recognized that PAIR is a promising technique and that is worth to be further evaluated in future RCTs.

Smego and colleagues published a meta-analysis in 2003, including both comparative and noncomparative studies. In total, 769 patients treated with PAIR plus benzimidazole prophylaxis were compared with 952 era-matched historical controls that received surgical treatment. Although the quality of the evidence is certainly lower than in the Cochrane meta-analysis, by including a larger number of studies the authors showed that the rate of clinical and parasitologic cure was significantly higher, the mean duration of hospital stay was more than 5 times shorter and the rate of disease recurrence was lower with PAIR compared to surgery [49].

Fewer data are available regarding the efficacy and safety of these techniques in children, however results from 2 case series including 34 and 25 patients respectively seem to be comparable to those achieved in adults [55, 56]. Furthermore, the description of 6 pregnant women successfully and safely treated with PAIR without albendazole suggest that percutaneous treatment alone might be a reasonable option even in this particular subset of patients [57].

In conclusion, as stated by the WHO-Informal Working Group on Echinococcosis in the 2010 guidelines there is no "best treatment option" as no trial has compared all the 4 possible strategies for cystic echinococcosis including the "watch and wait" approach [10]. The role of benzimidazole therapy alone is limited to cases of multiorgan involvement or peritoneal cysts. As a general rule, when feasible surgery is considered the first choice in case of complicated cysts, cysts communicating with the biliary tree and cysts with multiple daughter cysts. On the other hand, PAIR is definitely the first choice for patients not eligible or refusing surgery and in case of relapse following cyst excision. Between these two extremes of the spectrum, there are many situations in which both approaches would be reasonable. In such cases, the choice should take in consideration many factors of which, local medical or surgical expertise availability is often one of the most important. We strongly believe that, in the light of the available evidence, when both techniques are equally applicable and available, percutaneous techniques, such as PAIR or D-PAI, should be preferred because are at least as effective as surgery and are less invasive, better tolerated and less expensive [36, 58, 59].

CURRENT & FUTURE DEVELOPMENTS

Radiofrequency Ablation (RFA) for Liver Hydatid Cysts

Over the last 15 years, RFA has been increasingly used for treating solid tumours, primarily hepatocellular carcinoma (HCC). On the basis of the excellent results shown in these years, some authors consider this technique as effective as surgical resection for the treatment of small ($\leq$ 2 cm) HCC [60, 61]. Also for hepatic cysts RFA has been reported to be effective; Du *et al.* treated 63 cysts of various sizes and achieved full ablation of all the lesions < 10 cm in diameter after 6 and 12 months of follow-up without complications [62]. In 2001 Brunetti and colleagues first described the use of RFA as a treatment for hydatid liver cysts in 2 patients [63]. Both patients had large Gharbi type IV (CE4 according to the WHO 2010 classification) liver cysts that had been treated with albendazole for at least 2 years with incomplete solidification. By using an umbrella-like needle electrode the authors could reach and break the surrounding daughter cysts and fully ablate the lesions with no complications. A few years later Bastid *et al.* successfully combined RFA and ethanol injection to treat a complex hydatid cyst in a young patient [64]. Following these experiences, we performed RFA with an expandable needle in 5 patients with 5 hydatid cysts stage CE4 still viable after PAIR [65]. Three to six months after the procedure no viable scolices were detectable in all cases and 4 of the 5 cysts showed a 60% decrease in volume.

Lamonaca and colleagues have recently published the results of an *ex vivo* experimental study that supports the efficacy of RFA for this indication [66]. The Authors have treated 28 hydatid cysts, 16 hepatic and 12 pulmonary, from slaughtered animals, 10 bovine and 2 ovine, with an expandable umbrella-like needle electrode. To monitor the temperature during the procedure a sentinel needle was placed into the cyst. At the end of the procedure all the cysts were sectioned and examined histologically and the results were compared to those of untreated 11 cysts, 7 hepatic and 4 pulmonary. All the treated cysts showed endocyst coagulative necrosis, and, unlike what is commonly observed during PAIR and peri-cystectomy, the endocyst did not detach from the pericystium. Based on these findings, the authors believe that it is reasonable to expect a low incidence of biliary fistula occurrence following RFA than with PAIR and peri-cystectomy.

In conclusion, preliminary reports and an *ex vivo* experimental study seem to suggest that RFA is a promising therapeutic option in case of surgery and PAIR failure and that the risk of biliary fistula might be reduced with this technique, however further *in vivo* controlled studies are needed to confirm this hypothesis.

CONFLICT OF INTEREST

The authors declare that they do not have any conflict of interest.

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