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Percutaneous needle aspiration, injection, and re-aspiration with or without benzimidazole coverage for uncomplicated hepatic hydatid cysts (Review)

Nasseri-Moghaddam S, Abrishami A, Taefi A, Malekzadeh R

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[Intervention Review]

Percutaneous needle aspiration, injection, and re-aspiration with or without benzimidazole coverage for uncomplicated hepatic hydatid cysts

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ABSTRACT

Background

Hepatic hydatid cyst is an important public health problem in parts of the world where dogs are used for cattle breeding. Management of uncomplicated hepatic hydatid cysts is currently surgical. However, the puncture, aspiration, injection, and re-aspiration (PAIR) method with or without benzimidazole coverage has appeared as an alternative over the past decade.

Objectives

To assess the benefits and harms of PAIR with or without benzimidazole coverage for patients with uncomplicated hepatic hydatid cyst in comparison with sham/no intervention, surgery, or medical treatment.

Search methods

The Cochrane Hepato-Biliary Group Controlled Trials Register, *The Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library*, *MEDLINE, EMBASE*, *DARE*, and *ACP Journal Club* and full text searches were combined (all searched October 2010). Reference lists of pertinent studies and other identified literature were scanned. Researchers in the field were contacted.

Selection criteria

Only randomised clinical trials using the PAIR method with or without benzimidazole coverage as the experimental treatment of uncomplicated hepatic hydatid cyst (ie, hepatic hydatid cysts, which are not infected and do not have any communication with the biliary tree or other viscera) versus no intervention, sham puncture (ie, performing all steps for puncture, pretending PAIR being performed, but actually not performing the procedure), surgery, or chemotherapy were included.

Data collection and analysis

Data were independently extracted, and the risk of bias in each trial was assessed by the authors. Principal authors of the trials were contacted to retrieve missing data.

Main results

We found no randomised clinical trials comparing PAIR versus no or sham intervention. We identified only two randomised clinical trials, one comparing PAIR versus surgical treatment (n = 50 participants) and the other comparing PAIR (with or without albendazole) versus albendazole alone (n = 30 participants). Both trials were graded as 'adequate' for allocation concealment; however, generation of allocation sequence and blinding methods were 'unclear' in both. Compared to surgery, PAIR plus albendazole obtained similar cyst disappearance and mean cyst diameter with fewer adverse events (32% versus 84%, P < 0.001) and fewer days in hospital (mean ± SD) (4.2 + 1.5 versus 12.7 + 6.5 days, P < 0.001). Compared to albendazole, PAIR with or without albendazole obtained significantly more (P < 0.01) cyst reduction and symptomatic relief.

Authors' conclusions

PAIR seems promising, but there is insufficient evidence to support or refute PAIR with or without benzimidazole coverage for treating patients with uncomplicated hepatic hydatid cyst. Further well-designed randomised clinical trials are necessary to address the topic.

PLAIN LANGUAGE SUMMARY

Percutaneous needle aspiration, injection, and re-aspiration with or without benzimidazole coverage for uncomplicated hepatic hydatid cysts

Two randomised clinical trials on the puncture, aspiration, injection, and re-aspiration method for patients with uncomplicated hepatic hydatid cyst were identified. One trial compared puncture, aspiration, injection, and re-aspiration with surgical treatment. The other trial compared puncture, aspiration, injection, and re-aspiration with or without albendazole with albendazole alone. Both trials had high risk of bias. The number of participants enrolled and the follow-up duration are insufficient for a definite conclusion to be drawn. In general, there is insufficient evidence to support or refute the puncture, aspiration, injection, and re-aspiration method with or without benzimidazole coverage for patients with uncomplicated hepatic hydatid cyst.

BACKGROUND

Hydatid cyst disease, or cystic echinococcosis is a near-cosmopolitan zoonosis caused by larval forms of the cestode *Echinococcus granulosus* (Pawlowski 1997). Humans are incidental intermediate hosts of the parasite, and the liver is the most common site of involvement (McManus 2003). The disease may remain silent for many years before coming into medical attention as an incidental imaging finding, or it may present with complications (Frider 1999; White 2001). Management of uncomplicated hepatic hydatid cysts is currently surgical (Thompson 2002), although percutaneous aspiration, injection, and re-aspiration (PAIR) has emerged as a potential first line treatment.

Various surgical methods are in use with variable outcomes, but the most common technique is total or partial cystectomy. Surgery is associated with considerable mortality, morbidity, and recurrence rate, is expensive, and needs expertise (Magistrelli 1991; Safioleas 1994; Medeiros 1997; Safioleas 2000; Wagholikar 2001; Liang 2002; Nari 2003). Medical treatment with benzimidazoles (albendazole or mebendazole) has been used for the treatment of patients not fit for surgery or as an adjunct to surgery. However, few controlled data are available regarding its claimed clinical efficacy (Keshmiri 2001; El-On 2003; Horton 2003).

For many years, percutaneous aspiration of hydatid cyst was discouraged because of the potential risk of spillage and anaphylactic shock (Schiller 1966; Saidi 1976). However, unintended or deliberated cases of cyst puncture showed no significant complications (Fornage 1983; McCorkell 1984; Livraghi 1985). The so-called PAIR method was then introduced accidentally by Mueller in 1985 (Mueller 1985) and later on reported in case series with variable outcomes, most of the series authors claiming the technique was safe and effective (Ben Amor 1986; Bret 1989; Acunas 1992; Bastid 1994; Akhan 1996; Men 1999; Pelaez 2000; Ormeci 2001). PAIR is performed under ultrasound (US) guidance (or sometimes computed tomography (CT) guidance) and includes drainage of the cysts with a fine needle or catheter, followed by instillation of protoscolicidal substances (eg, hypertonic saline or absolute alcohol) and re-aspiration. Prophylaxis with benzimidazoles may be used before and after the procedure. If the cyst communicates with the biliary tree, injection of scolicidal agents carries an almost universal risk of sclerosing cholangitis. Therefore, PAIR is contraindicated in a cyst communicating with the biliary tree (WHO-IWGE 1996; WHO 2001).

Despite its claimed safety and efficacy, PAIR is not yet accepted as the treatment of choice for uncomplicated hepatic hydatid cysts (Morris 2000; Stoianov 2002; Yaghan 2004). We have been unable to identify meta-analyses or systematic reviews on the topic based on randomised clinical trials. This systematic review was carried out to assess the available evidence on safety and efficacy of PAIR with or without benzimidazole coverage for treating patients with uncomplicated hepatic hydatid cysts.

OBJECTIVES

To assess the benefits and harms of PAIR with or without benzimidazole coverage versus no intervention, sham PAIR technique, surgery, or medical treatment for patients with uncomplicated hepatic hydatid cysts.

The study questions are:
1. Is the PAIR method with or without benzimidazole coverage more effective than no intervention, sham PAIR, surgery, or medical treatment for patients with uncomplicated hepatic hydatid cysts?
2. Is the PAIR method with or without benzimidazole coverage associated with less complications than no intervention, sham PAIR, surgery, or medical treatment for patients with uncomplicated hepatic hydatid cysts?
3. Is the PAIR method with or without benzimidazole coverage cost effective compared with no intervention, sham PAIR, surgery, or medical treatment for patients with uncomplicated hepatic hydatid cysts?

METHODS

Criteria for considering studies for this review

Types of studies

All randomised clinical trials using the PAIR method with or without benzimidazole coverage as the primary treatment of uncomplicated hepatic hydatid cysts versus no intervention, sham PAIR, surgery, or medical treatment were considered for inclusion, irrespective of blinding, language, or publication stage. Observational studies including case-only studies (studies presenting series or single cases of patients without a control group) were identified; however, they were not included in the review concerning beneficial effects, only concerning harms.

Types of participants

All patients with uncomplicated hepatic hydatid cysts defined as:
- hepatic hydatid cyst confirmed either by examination of the aspirated fluid (evident hepatic hydatid cysts) or imaging and/or serologic techniques (highly probable or probable hepatic hydatid cysts) as described by Niscigorska et al (Niscigorska 2001), and
- intact, non-infected hepatic hydatid cysts with no clinical or biochemical suspicion of communication with the biliary system or other viscera.

Types of interventions

Experimental intervention: percutaneous puncture, aspiration or drainage (PAIR) of uncomplicated hepatic hydatid cysts performed under ultrasound (US) or computer tomography (CT) guidance and followed by injection of scolicidal agents, and re-aspiration: the PAIR method with or without benzimidazole coverage.

Alternative percutaneous techniques, including PPDC (percutaneous puncture with drainage and curettage, PAI-D (double percutaneous aspiration and injection of scolicidal agents without re-aspiration), and PEVAC (percutaneous evacuation of cyst) are not in the scope of this review.

Control intervention(s): none, sham PAIR with or without benzimidazole coverage, surgical treatment including laparoscopic surgery, or medical treatment with benzimidazole compounds.

Co-interventions were allowed as long as they were used similarly in all groups of the trial.

Types of outcome measures

1. Mortality.
2. Clinical beneficial effects that were estimated by assessing the following outcome measures:

a) nondisappearance of uncomplicated hepatic hydatid cysts as assessed by transabdominal ultrasonography;
b) no decrease in size of uncomplicated hepatic hydatid cysts as assessed by transabdominal ultrasonography;
c) no change in cyst echogenicity in favour of non-viability of the cestode as assessed by transabdominal ultrasonography.
3. Complications:
a) Short-term complications.
a-1) Infections.
a-2) Bleeding.
a-3) Cyst perforation.
a-4) Anaphylaxis.
a-5) Skin rash.
b) Long-term complications.
b-1) Biliary sclerosis.
b-2) Seeding of the cysts.
4. Recurrence of uncomplicated hepatic hydatid cyst.
5. Communication with the biliary system.
6. The need for switching to surgery while treating uncomplicated hepatic hydatid cysts with PAIR.
7. Frequency and severity of adverse events.
Serious adverse events are events which lead to death, are life-threatening, require inpatient hospitalisation or prolongation of existing hospitalisation, result in persistent or significant disability, are a congenital anomaly/birth defect, or any medical event, which may have jeopardised the patient or required intervention to prevent it (ICH-GCP 1997). All other adverse events were considered non-serious.
8. Quality of life.
9. Health economics.

Search methods for identification of studies

Electronic searches

We searched *The Cochrane Hepato-Biliary Group Controlled Trials Register* (Gluud 2010), *The Cochrane Renal Group Controlled Trials Register*, *The Cochrane Central Register of Controlled Trials (CENTRAL)* and *The Database of Abstracts of Reviews of Effects (DARE)* in *The Cochrane Library*, *MEDLINE*, *EMBASE*, and *The ACP Journal Club.* Search strategies with the time span of the searches are given in Appendix 1.

Searching other resources

We also searched published abstracts and proceedings from key scientific conferences of hydatidology (International Congresses of Hydatidology XVIII-XX) to identify any randomised clinical trials not published in journal format. This included the Internet versions of *Acta Tropica, Radiology, Hepatology*, and *Journal of Hepatology* from January 1990 to October 2010.

We searched current clinical practice guidelines (WHO Informal Working Group on Echinococcosis (WHO-IWGE) manual) for relevant randomised clinical trials.

We hand searched reference lists from review articles retrieved from *MEDLINE* or *EMBASE* and reference lists from randomised clinical trials to identify additional trials.

We wrote to the principal author of included trials (Dr. Khuroo) and the Informal Working Group on Echinococcosis - PAIR coordinator (Dr. Filice) about additional published or unpublished randomised clinical trials on the topic.

Data collection and analysis

We performed the review and meta-analyses following the recommendations of The Cochrane Collaboration (Higgins 2009) and The Cochrane Hepato-Biliary Group (Gluud 2010). The analyses were performed using Review Manager 5 (RevMan 2008).

Application of inclusion criteria

- We assessed titles of research articles retrieved from the electronic database and hand searches to determine which abstracts should be reviewed for possible inclusion as per the reviewers defined eligibility criteria described under 'Types of studies', 'Types of participants', 'Types of interventions', and 'Types of outcome measures'.
- All abstracts were assessed using the eligibility criteria proposed by the reviewers for selecting papers.
- We listed excluded trials with the reasons for exclusion.
- We resolved discrepancies between individual authors (SNM, AA, and RM) through consensus.

Methodological quality assessment

Methodological quality, hence risk of bias, was defined as the confidence that the design, conduct, and report restrict bias in the intervention comparison (Schulz 1995; Moher 1995; Kjaergard 2001; Wood 2008). It was evaluated independently by three authors (SNM, AA, and RM). Disagreements were resolved by discussion. We wrote to the principle authors of included trials for complementary information. The following domains used to judge the included trials for risk of bias were:

Sequence allocation generation

- Low risk of bias. Sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice are adequate if performed by an independent adjudicator.
- Uncertain risk of bias. The trial was described as randomised, but the method of sequence generation was not specified.
- High risk of bias. The sequence generation method was not, or might not be, random. Quasi-randomised studies, those using dates, names, or admittance numbers in order to allocate patients are inadequate studies for our review and were to be excluded for the assessment of benefits but not for harms.

Allocation concealment

- Low risk of bias. Allocation was controlled by a central and independent randomisation unit, opaque, sealed, and serially numbered envelopes or similar, so that intervention allocations could not have been foreseen in advance of, or, during enrolment.
- Uncertain risk of bias. The trial was described as randomised, but the method used to conceal the allocation was not described, so that intervention allocations might have been foreseen in advance of, or during enrolment.
- High risk of bias, if the allocation sequence was known to the investigators who assigned participants, or if the study was quasi-randomised. Quasi-randomised studies were excluded for the assessment of benefits but not for harms.

Blinding of participants, personnel, and outcome assessors

- Low risk of bias. Blinding was performed adequately, or the outcome measurement is not likely to be influenced by lack of blinding.
- Uncertain risk of bias. There was insufficient information to assess whether the type of blinding used is likely to induce bias on the estimate of effect.
- High risk of bias. There was no blinding or incomplete blinding, and the outcome or the outcome measurement is likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias. The underlying reasons for missingness were unlikely to make treatment effects depart from plausible values, or proper methods had been employed to handle missing data.
- Uncertain risk of bias. There was insufficient information to assess whether the missing data mechanism in combination with the method used to handle missing data was likely to induce bias on the estimate of effect.
- High risk of bias. The crude estimate of effects (eg, complete case estimate) was clearly biased due to the underlying reasons for missingness, and the methods used to handle missing data were unsatisfactory.

Selective outcome reporting

- Low risk of bias. The trial protocol is available and all of the trial's pre-specified outcomes that are of interest in the review have been reported or similar.
- Uncertain risk of bias. There was insufficient information to assess whether the magnitude and direction of the observed effect is related to selective outcome reporting.
- High risk of bias. Not all of the trial's pre-specified primary outcomes have been reported or similar.

Baseline imbalance

- Low risk of bias. There was no baseline imbalance in important characteristics.
- Uncertain risk of bias. The baseline characteristics were not reported.
- High risk of bias. There was a baseline imbalance due to chance, or due to imbalanced exclusion after randomisation.

Trials assessed as having 'low risk of bias' in all individual domains above were considered 'trials with low risk of bias'. Trials assessed as having 'uncertain risk of bias' or 'high risk of bias' in one or more of the specified above individual domains were considered trials with 'high risk of bias'.

Furthermore, we registered the length of follow-up and also whether the trial had reported the use of intention-to-treat analysis.

Data extraction
All three authors extracted data independently from the included trials.

- Methods: methodological quality, type of randomised clinical trials (parallel or crossover), number of intervention arms, first author, country/institution of study, date, and status of publication.
- Participants: numbers of patients and cysts randomised to each intervention arm, mean (or median) age, number of males, mean duration of disease at randomisation, form of hepatic hydatid cyst (echo pattern, location), mean diameter/volume of cyst in each intervention arm, inclusion and exclusion criteria.
- Interventions.

1. PAIR: prophylactic regimen (dosage, duration), type of imaging guidance (US or CT), aspiration route (transhepatic, intercostal), aspiration tool (fine needle or catheter), protoscolicidal agents (hypertonic saline, alcohol).
2. Surgery: type of surgical procedure (radical, conservative, laparoscopic), type of residual cavity management, protoscolicidal agents.
3. Medical treatment: type of medication (albendazole, mebendazole, etc), dose of medication, duration of therapy, name of the pharmaceutical manufacturer, type of therapeutic schedule (cyclic or continuous treatment), route of administratio.

- Outcomes: all outcomes were extracted from each included trial.

Data analysis
We planned to do the following statistical analyses: intention-to-treat analyses using the last reported observed response (carry forward) and including all patients irrespective of compliance or follow-up. Binary outcomes would have been expressed as risk difference and 95% confidence intervals (CI). Continuous data would have been analysed using mean difference. The number-needed-to-treat would have been calculated as 1/(1-relative risk)*control group event rate. Rare events (morbidity plus mortality) would have been estimated by Peto odds ratio (Deeks 1998). A random-effects model and a fixed-effect model would have been used. In case of significant heterogeneity, potential causes for the heterogeneity would have been explored by sensitivity analyses. Due to the few trials identified, it was not possible to perform a meta-analysis.

RESULTS

Description of studies

After excluding the duplicate and clearly irrelevant publications, a total of 52 references were identified and assessed for inclusion in the review. Of these, 50 references (45 case-only studies and five review articles) were excluded (see table 'Characteristics of excluded studies'). Only two trials met the inclusion criteria. We did not identify any duplicate publications for the included trials. No additional trials were identified from bibliographic lists. Personal communication with the principal author of the included trials and the WHO-IWGE PAIR-co-ordinator yielded no further randomised clinical trials.

The included trials were carried out by the same lead author in India. Both trials were in English. One trial compared PAIR with or without oral albendazole (n = 20) versus oral albendazole alone (n =10) in patients with uncomplicated hepatic hydatid cyst disease (Khuroo 1993), and the other trial compared PAIR (n = 25) versus surgical treatment (n = 25) in patients with uncomplicated hepatic hydatid cyst disease (Khuroo 1997). Descriptions of the trials are shown in the table 'Characteristics of included studies'. We did not find any randomised clinical trials comparing PAIR with no or sham intervention.

Risk of bias in included studies

Both trials were described as randomised. We judged the risk of bias domains as follows (Figure 1; Figure 2).

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

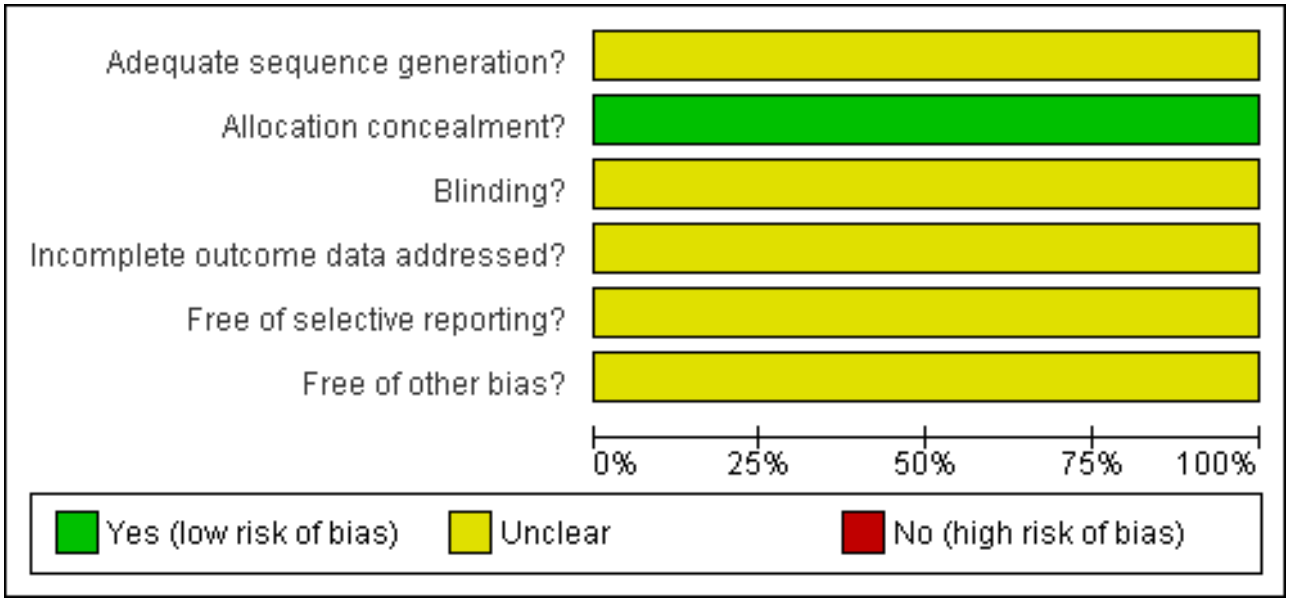
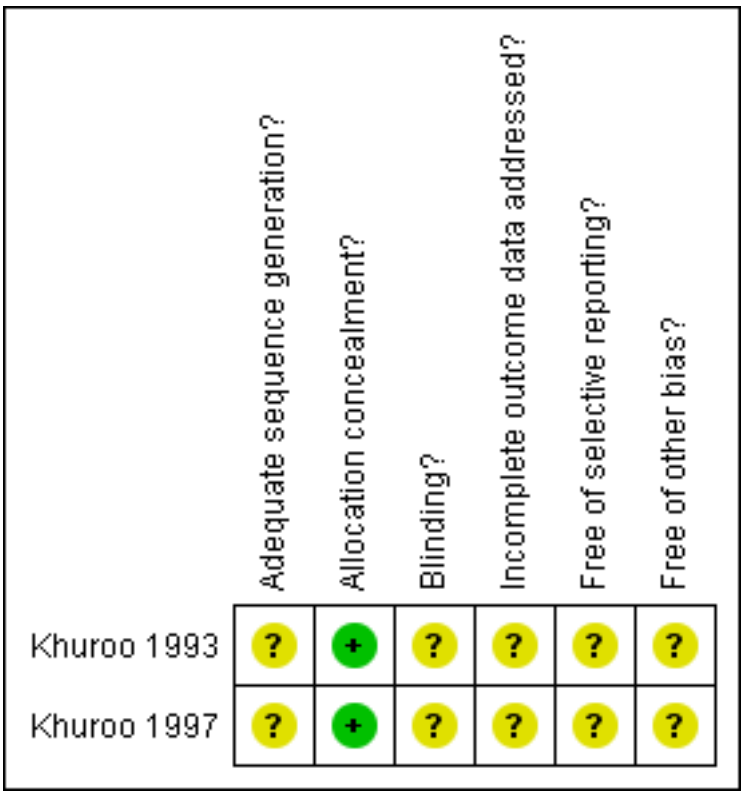


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Generation of the allocation sequence

None of the trials reported how the allocation sequence was generated. When the author was contacted, he did not describe how the randomisation was done. Therefore, both trials were ranked as 'unclear'.

Allocation concealment

None of the trials reported the allocation concealment method. Therefore, the principal author was contacted. According to the author's reply allocation was centralized in one of the trials and through sealed envelopes in the other, hence it was graded as 'adequate' in both trials.

Blinding

The outcome assessors were reported to be blinded in both trials. However, the method of blinding was not clearly explained. When the author was contacted he could not describe how the blinding was exactly done. Therefore, blinding was reported as unclear.

Handling of dropouts and withdrawals

The principal author was contacted regarding handling of dropouts and withdrawals. According to his reply there were no dropouts or withdrawals at the end of the trial or follow-up period in either of the trials. Therefore, both trials were graded as 'adequate'.

Incomplete outcome data

According to the authors' reply, the follow-up data have been complete and there were no incomplete outcome data to handle.

Selective outcome reporting

The authors have reported on all possible outcomes and no selective reporting is apparent in their trials.

Other bias risks

None found except for those mentioned above.

Effects of interventions

PAIR plus oral albendazole versus surgery (cystectomy)

Table 1 shows the findings in the Khuroo 1997 trial. The trial compared PAIR versus surgery. Mean follow-up of patients was 17 months. There was no mortality in either group. The final cyst diameter did not differ significantly between the two groups (P = 0.20). The echinococcal-antibody titers fell progressively after an initial rise in both groups. Procedure-related complications significantly occurred more frequently in the surgery group (32% versus 84%; P < 0.001). However, 17 of the 21 surgery-related complications were fever.

The mean (+ SD) hospital stay was 4.2 + 1.5 days in the PAIR group versus 12.7 + 6.5 days in the surgery group (P < 0.001).

PAIR with or without oral albendazole versus oral albendazole alone

In the comparison made between PAIR with or without oral albendazole versus oral albendazole alone (Khuroo 1993), there was no mortality (Table 2). Serial ultrasonography showed heterogeneous echo pattern of the cysts in 18, uniform echogenicity in 11, and disappearance in three patients. Symptoms were relieved in all PAIR-treated patients (100%; n = 20) versus two (20%; n = 10) of the albendazole-treated patients (P < 0.001). All the cysts treated with percutaneous drainage (n = 22) and only two (18.2%) of those treated with oral albendazole alone showed reduction in size and changes in echo pattern compatible with loss of viability (P < 0.01). Maximum size reduction was observed in cysts treated with a combination of percutaneous drainage and albendazole (P < 0.05). Complications observed with PAIR were cyst infection in two patients (10%), fever in three (15%), cyst biliary rupture in one (5%), and urticaria in two (10%). Three patients (15%) who received albendazole developed reversible elevation of liver enzymes.

Neither of the studies evaluated cost-effectiveness of their interventions.

DISCUSSION

Our systematic review of the available literature shows that there is a paucity of well designed, randomised trials comparing PAIR with surgery or with medical therapy in people with uncomplicated hepatic hydatid cysts. Both of the included trials had methodological flaws. They had adequate allocation concealment and follow-up. However, generation of allocation sequence and blinding method were unclear in both. The number of patients enrolled in these trials are scanty for a definite conclusion to be drawn. Moreover, in both trials, the follow-up duration of less than 18 months is too short to assess outcome measures like recurrence rate and long-term complications. In addition, the current methods of assessing response to treatment (that is, volume loss and change in echo pattern on transabdominal ultrasound) may miss some persistent or recurrent infestations. We could not perform meta-analyses due to the insufficient number of trials for each comparison.

In a recently published meta-analysis of uncontrolled studies, Smego et al (Smego 2003) concluded that PAIR is safe and effective for treatment of uncomplicated hepatic hydatid cyst. Although the number of patients included in their meta-analysis is appreciable, their work has some shortcomings. First, they have explained that from 45 entries retrieved for PAIR, 21 were included, while it is not clear how many entries for the surgical group were retrieved and how many were included. Second, there is no table showing excluded studies in either group. Third, the authors have not performed a test of heterogeneity to look for methodological differences between the studies. This is important because if the studies are heterogeneous, their meta-analysis will not provide meaningful information unless relatively homogeneous subgroups are defined and assessed separately. Fourth, the authors have described the PAIR method in detail, while they have gone through the surgical methods only in brief. Fifth, it is not clear what type of patients have gone to surgery. Have more complicated patients with a predictable poorer outcome from the very beginning been sent to surgery (which is the usual case) or were the two patient populations (PAIR and surgery groups) comparable? Sixth, several different surgical methods have been used in the surgical studies included. This has important messages; first, probably different patient populations were being dealt with, and second, these different methods affect the outcomes significantly, so they cannot be compared effectively. These are important pieces of information that are missing in the meta-analysis of Smego 2003. Therefore, their conclusion should be considered with caution.

Another review was published by Dziri et al, assessing all studies on different treatments of hydatid cysts (Dziri 2004). The authors described their work as a systematic review and have explained a relatively detailed methodology, but there are some problems with

this work. First, the authors have tried to cover several questions. Each of these questions needs its own definitions and is probably the subject of a separate systematic review. Therefore, they are not addressing a focused clinical question but several broad questions. Second, outcome measures are not clearly defined by the authors and they are not addressed adequately. Third, we have been unable to identify a published, peer-reviewed protocol for their review. Therefore, we cannot assess if the review has been conducted in a systematic manner. Although the authors have come to what seems to be sensible conclusions, their study should be regarded as an excellent narrative review, but not a systematic one.

One of the major issues in patients treated with PAIR and other percutaneous techniques is the definition of a successful outcome. Usually, therapeutic response is measured by volume loss of the cyst or change of echo. These outcome measures may not correlate sufficiently with the risk of long-term recurrence. Also serological tests may not adequately reflect the clinical course of patients.

The uncontrolled trials and the reviews of them show promise for PAIR with or without benzimidazole coverage in treatment of hepatic hydatid cysts. This can serve as a basis for future randomised clinical trials. According to our systematic review and other authors, there are only a few randomised clinical trials in the literature addressing the issue. The quality of the trials can at best be judged as moderate; therefore, one can conclude that PAIR with or without benzimidazole coverage, although promising in selected cases of uncomplicated hepatic hydatid cysts, cannot be yet recommended as a first line treatment. Future well-designed and high-quality randomised clinical trials with larger numbers of patients and longer duration of follow-up are necessary to address the topic.

AUTHORS' CONCLUSIONS

Implications for practice

According to our systematic review, PAIR with or without benzimidazole coverage may be comparable or superior to surgery or medical treatment with benzimidazoles alone for uncomplicated hepatic hydatid cysts, but the data are not sufficient to draw definite conclusions. Therefore, we cannot recommend the use of PAIR with or without benzimidazole coverage outside randomised clinical trials for treating patients with uncomplicated hepatic hydatid cyst.

Implications for research

Further well-designed randomised clinical trials are necessary to address the topic. We need randomised clinical trials comparing the PAIR method with or without benzimidazole coverage versus sham or no intervention, surgery, or medical treatment for patients with uncomplicated hepatic hydatid cyst. Because the disease is not so common, multicentre trials might be necessary. They also have the advantage of higher external validity. Future trials should have sufficient statistical power, low risk of bias, adequate follow-up, intensive monitoring of adverse events, and should be reported according to the CONSORT guidelines (www.consort-statement.org). If the effects of PAIR are as promising as indicated in the present review, then the size of trials does not need to be very large, and data should be monitored closely by an independent data monitoring and safety committee.

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Contact Editor: Christian Gluud, Denmark.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Khuroo 1993

Methods	Randomised clinical trial, with three parallel groups. Inclusion of all randomised participants at evaluation: No patients died after treatment. No patients were crossed-over to another group during follow-up. There were no losses to followup. Follow-up period (mean months, SD) PAIR (9.0, 7.4) range: 3 to 20 months. PAIR plus albendazole (6.3, 2.7) range: 3 to 11 months.

Khuroo 1993 *(Continued)*

	Albendazole alone (7.8, 3.6) range: 3 to 12 months.
Participants	Inclusion criteria: All patients with probable HHYC (patients with signs and symptoms of a hepatic hydatid cyst, which had anechoic or hypoechoic appearance, and back-wall echo enhancement at US examination). Exclusion criteria (one or more of the following): Presence of infected or calcified cysts and cysts with hyperechoic pattern or communications with biliary tree or other viscera. Married women, if they were pregnant or intended to conceive during the follow-up period. Characteristics of included patients: Number of patients included: 30. Number of cysts included: 33. Number of cysts in each arm: PAIR: 10, PAIR plus albendazole: 12, albendazole alone:11. Number of patients excluded before randomisation: not reported. Number of males (proportion): 11/30 (36.6%). Mean age (SD): 39 (14) years. Form of HHYC: uni vesicular (24 cysts), and multivesicular (9 cysts). Duration of disease: not reported.
Interventions	PAIR A 5-French transhepatic catheter (Cook Europe, Bjeverskov, Denmark, or William Cook) or a 22-gauge cholangiography needle were used as an aspiration tool. Aspiration route was transhepatic and the protoscolicidal agent was sterile hypertonic (20%) saline. No pre- or -post drainage prophylaxis was used. PAIR plus albendazole As PAIR group but they had received albendazole (Zentel SK & F, India) in a dose of 10 mg/kg/d for 10 days at the time of puncture. Albendazole alone Albendazole (Zentel SK & F, India) in a dose of 10 mg/kg/d for eight weeks. Co intervention: not reported.
Outcomes	Primary measures of efficacy: cyst disappearance or changes in the cyst size and appearance over time at US examinations, the length of hospital stay, and procedure-related complications. The secondary outcome of efficacy was the serum anti-echinococcal titers over time. Outcomes regarding health economics and quality of life were not reported.
Notes	We received additional information from the author, Dr. Khuroo, on 01.11.2003.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No description.
Allocation concealment?	Low risk	Sealed envelopes.
Blinding? All outcomes	Unclear risk	Blinded outcome assessors, but methodologically unclear.
Incomplete outcome data addressed? All outcomes	Unclear risk	Unclear.

Khuroo 1993 *(Continued)*

Free of selective reporting?	Unclear risk	Unclear.
Free of other bias?	Unclear risk	Unclear.

Khuroo 1997

Methods	Randomised clinical trial, with two parallel groups. Inclusion of all randomised participants at evaluation: No patients died after treatment. No patients were crossed over to another group during follow-up. There were no losses to follow-up. Follow-up period (mean months, SD). PAIR plus albendazole (17.5, 7.0) range: 9 to 24 months. Surgery (17.4, 6.5) range: 9 to 24 months.
Participants	Inclusion criteria: All patients with probable HHYC (patients with signs and symptoms of a hepatic hydatid cyst, which had anechoic, or hypoechoic appearance and back-wall echo enhancement at US examination). Exclusion criteria (one or more of the following): Presence of infected or calcified cysts and cysts with hyperechoic pattern or communications with biliary tree or other viscera. Married women, if they were pregnant or intended to conceive during the follow-up period. Characteristics of included patients: Number of patients included: 50. Number of cysts included: 50. Number of cysts in each arm: PAIR plus albendazole: 25 and in surgery: 25. Number of patients excluded before randomisation: not reported. Number of males (proportion): 22/50 (44%). Mean age (SD): not reported. Form of HHYC: uni vesicular (32 cysts), and multivesicular (18 cysts). Duration of disease: not reported.
Interventions	PAIR plus albendazole A 5-French transhepatic catheter (Cook Europe, Bjaeverskov, Denmark) or a 22-gauge cholangiography needle was used as an aspiration tool. Aspiration route was transhepatic and the protoscolicidal agent was sterile hypertonic (20%) saline. All patients received oral albendazole (10 mg/kg/d) for eight weeks and puncture was performed on the 10th day of drug therapy. Surgery The surgical procedure was simple cystectomy plus capitonnage and tube drainage. Povidone-iodine was used as protoscolicidal agent. No pre- or -post operation prophylaxis was used. Co intervention: not reported.
Outcomes	Primary measures of efficacy: cyst disappearance or changes in the cyst size and appearance over time at US examinations, the length of hospital stay, and procedure-related complications. The secondary outcome of efficacy was the serum anti-echinococcal titers over time. Outcomes regarding health economics and quality of life were not reported. Patients in both groups were followed for a mean duration of 17 months.
Notes	We received additional information from the author, Dr. Khuroo, on 01.11.2003.

Khuroo 1997 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No description.
Allocation concealment?	Low risk	Sealed envelopes.
Blinding? All outcomes	Unclear risk	Blinded outcome assessors, but methodology unclear.
Incomplete outcome data addressed? All outcomes	Unclear risk	Unclear.
Free of selective reporting?	Unclear risk	Unclear.
Free of other bias?	Unclear risk	Unclear.

HHYC = hepatic hydatid cyst.
U = ultrasound.
SD = standard deviation.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Acunas 1992	Patient series.
Akhan 1996	Patient series.
Akhan 1999	Narrative review.
Al-Karawi 1996	Patient series.
Aygun 2001	Patient series.
Bastid 1994	Patient series.
Bosanac 2001	Patient series.
Bret 1989	Patient series.
Brigic 2003	Patient series.
Crippa 1999	Patient series.
Dilsiz 1997	Patient series.
Duta 2002	Patient series.
Dwivedi 2002	Patient series.

Study	Reason for exclusion
Dziri 2004	Narrative review.
Filice 1990	Patient series.
Filice 1990b	Patient series.
Filice 1997	Patient series.
Gargouri 1990	Patient series.
Giorgio 1992	Patient series.
Giorgio 1991	Patient series.
Giorgio 1993	Patient series.
Giorgio 2001	Patient series.
Grigorov 2000	Patient series.
Haddad 2000	Patient series.
Hernandez 1996	Patient series.
Kabaalioglu 1998	Patient series.
Kabaalioglu 2000	Patient series.
Khuroo 1991	Patient series.
Kohlhaufl 1995	Narrative review.
Men 1999	Patient series.
Mikic 1998	Patient series.
Mueller 1985	Patient report.
Odev 2000	Patient series.
Ormeci 2001	Patient series.
Pelaez 1999	Patient series.
Pelaez 2000	Patient series.
Polat 2002	Patient series.
Salama 1995	Patient series.
Salama 1998	Patient series.
Sayek 2001	Patient series.
Simonetti 1993	Patient series.

Study	Reason for exclusion
Sinha 2001	Patient series.
Smego 2003	Narrative review.
Stoianov 1995	Patient report.
Stoianov 2002	Narrative review.
Tan 1998	Non-randomised trial.
Ustunsoz 1999	Patient report.
Vishnevskii 1992	Patient series.
Wang 1994	Patient series.
Zarem 2003	Patient series.

PAIR = puncture-aspiration-injection-reaspiration.

ADDITIONAL TABLES

Table 1. Summary of comparison of PAIR and surgery

	PAIR plus albendazole	Surgery	P value
Mean hospital stay (SD) (days)	4.2 (1.5)	12.7 (6.5)	< 0.001
Mean cyst diameter after treatment (SD) (cm)	1.4 (3.5)	0.9 (1.8)	0.20
Cyst disappearance (n)	22 (88%)	18 (72%)	0.29
Echinococcal antibody negativity (< 1/160) (n)	19 (76%)	17 (68%)	0.74
Procedure related complications (n)	8 (32%)	21 (84%)	< 0.001
Recurrence rate of uncomplicated hepatic hydatid cyst	0	0	No data provided.
Communication with the biliary system	No data provided.	No data provided.	No data provided.
The need for switching to surgery when using PAIR	No data provided.	No data provided.	No data provided.
Quality of life	No data provided.	No data provided.	No data provided.
Health economics	No data provided.	No data provided.	No data provided.

PAIR = puncture-aspiration-injection-reaspiration.

Table 2. Summary of PAIR with or without oral albendazole versus oral albendazole alone

	PAIR with or without oral albendazole	Oral albendazole alone	P value
Mortality	0	0	
Symptom relief (%)	100	20	< 0.001
Reduction in size (%)	100	18.2	< 0.01
Communication with the biliary system	No data provided.	No data provided.	No data provided.
The need for switching to surgery when using PAIR	No data provided.	No data provided.	No data provided.
Quality of life	No data provided.	No data provided.	No data provided.
Health economics	No data provided.	No data provided	No data provided.

PAIR = puncture-aspiration-injection-reaspiration.

APPENDICES

Appendix 1. Search strategies

Database	Time Span of Search	Search Strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	October 2010.	hydatid* AND echinococc*
The Cochrane Renal Group Controlled Trials Register in The Cochrane Library	Issue 7, 2010.	#1 hydatid* #2 echinococc* #3 ECHINOCOCCOSIS explode all trees (MeSH) #4 ECHINOCOCCUS explode all trees (MeSH) #5 (#1 or #2 or #3 or #4)
The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	Issue 3, 2010.	#1 hydatid* #2 echinococc* #3 ECHINOCOCCOSIS explode all trees (MeSH) #4 ECHINOCOCCUS explode all trees (MeSH) #5 (#1 or #2 or #3 or #4)
Database of Abstracts of Reviews of Effects (DARE) in the Cochrane Library	Issue 3, 2010.	#1 hydatid* #2 echinococc* #3 ECHINOCOCCOSIS explode all trees (MeSH) #4 ECHINOCOCCUS explode all trees (MeSH) #5 (#1 or #2 or #3 or #4)
MEDLINE on Sliver Platter (ERL WebSPIRS 5.01)	1966 to October 2010.	#1 hydatid* #2 echinococc* #3 explode "echinococcosis-" / all SUBHEADINGS in ME #4 explode "echinococcus-" / all SUBHEADINGS in ME

(Continued)

		#5 (#1 or #2 or #3 or #4) #6 "PAIR" #7 percutaneous* #8 explode "Administration-Cutaneous" / all SUBHEADINGS in ME #9 puncture* #10 aspiration* #11 explode "Drainage-" / all SUBHEADINGS in ME #12 explode "Suction-" / all SUBHEADINGS in ME #13 explode "Ultrasonography-Interventional" / all SUBHEADINGS in ME #14 explode "Radiography-Interventional" / all SUBHEADINGS in ME #15 (injection*) and ((silver nitrate*) or (hypertonic*) or (ethanol*) or (alcohol*) or (sco?l??cid*) or (protosco?l??cid*)) #16 explode "Anti-Infective-Agents-Local" / all SUBHEADINGS in ME #17 explode "injection-intralesional" / all SUBHEADINGS in ME #18(explode "Injections-" / all SUBHEADINGS in ME)) and ((explode "Anticestodal-Agents" / all SUBHEADINGS in ME) or (explode "Sclerosing-Solutions" / all SUBHEADINGS in ME) or (explode "Alcohols-" / all SUBHEADINGS in ME) or (explode "Saline-Solution-Hypertonic" / all SUBHEADINGS in ME)) #19 re?aspiration* #20 (#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19) #21 (#5 and #20)
EMBASE on WebSPIRS (ERL WebSPIRS 5.01)	January 1980 to October 2010.	#1 hydatid* #2 echinococc* #3 explode "hydatid-cyst" / all SUBHEADINGS in SU #4 explode "echinococcosis-" / all SUBHEADINGS in SU #5 explode "echinococcus-" / all SUBHEADINGS in SU #6 (#1 or #2 or #3 or #4 or #5) #7 "PAIR" #8 percutaneous* #9 explode "percutaneous-drainage" / all SUBHEADINGS in SU #10 explode "percutaneous-transhepatic-drainage" / all SUBHEADINGS in SU #11 puncture* #12 explode "puncture-" / all SUBHEADINGS in SU #13 explode "aspiration-puncture-and-suction" / all SUBHEADINGS in SU #14 aspiration* #15 explode "aspiration-" / all SUBHEADINGS in SU #16 explode "interventional-radiology" / all SUBHEADINGS in SU #17 explode "sclerotherapy" / all SUBHEADINGS in SU #18 explode "injection-intralesional" / all SUBHEADINGS in SU #19 (injection*) and ((hypertonic*) or (ethanol*) or (alcohol*) or (silver nitrate*) or (sco?l??cid*) or (protosco?l??cid*)) #20 (explode "injection-" / all SUBHEADINGS in SU) and ((explode "antiparasitic-agents" / all SUBHEADINGS in SU) or (explode "alcohol-" / all SUBHEADINGS in SU) or (explode "hypertonic-solution" / all SUBHEADINGS in SU) or (explode "sodium-chloride" / all SUBHEADINGS in SU)) #20 re?aspiration* #22 (#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21) #23 (#5 and #22)
ACP Journal Club (www.acpjc.org)	January 1991 to October 2010.	Search for: (hydatid*) OR (echinococc*) Find docs that match: Any words Search type: Fuzzy

WHAT'S NEW

Date	Event	Description
17 October 2010	New search has been performed	Searches for new trials were lastly performed on 17 October 2010.
17 October 2010	New citation required but conclusions have not changed	The updated searches did not identify any new trials that could fulfil the inclusion criteria of the review.

HISTORY

Protocol first published: Issue 2, 2002
Review first published: Issue 2, 2006

Date	Event	Description
24 October 2004	Amended	Following a primary review of literature, the authors found out that the PAIR method was usually performed with concomitant benzimidazole coverage; ie, albendazole, mebendazole, or any other drugs of the benzimidazole group. Therefore, in order to better reflect the substance of the review, the protocol title 'Percutaneous needle aspiration with or without oral albendazole for uncomplicated hepatic hydatid cysts' was changed into 'Percutaneous needle aspiration, injection, and reaspiration with or without benzimidazole coverage for uncomplicated hepatic hydatid cysts' (03/07/2003).

CONTRIBUTIONS OF AUTHORS

Siavosh Nasseri Moghaddam (SNM): the principal and contact author. Development and editing of the protocol, development and editing of the search strategy, reviewing, selecting, and abstracting the retrieved papers. Summarising and analysing data, drafting the review.

Amir Abrishami (AA): co-author, development and editing of the search strategy, reviewing, selecting and abstracting the retrieved papers. Summarising and analysing data, drafting the review.

Reza Malekzadeh (RM): co-author, selecting and abstracting the retrieved papers. Summarising data, helping in editing of the review.

Amir Taefi(AT): co-author, searching, preparation of the final manuscript.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

- None, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The bias risk domains were updated following the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2009). Some of the outcome measures were presented as negative in view of possibility of performing meta-analyses if randomised clinical trials fulfilling the inclusion criteria of the review are identified at a subsequent update.

INDEX TERMS

Medical Subject Headings (MeSH)

Albendazole [*therapeutic use]; Anticestodal Agents [*therapeutic use]; Benzimidazoles [*therapeutic use]; Biopsy, Fine-Needle [adverse effects] [*methods]; Combined Modality Therapy [methods]; Echinococcosis, Hepatic [*therapy]; Radiography, Interventional; Randomized Controlled Trials as Topic; Suction [adverse effects] [methods]; Ultrasonography, Interventional

MeSH check words

Humans