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Systematic Review

Percutaneous Needle Aspiration, Injection, and Reaspiration with or without Benzimidazole Coverage for Uncomplicated Hepatic Hydatid Cysts

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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 reaspiration (PAIR) method with or without benzimidazole coverage has appeared as an alternative to surgery over the past decade.

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

Methods: *The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Controlled Trials Register in The Cochrane Library, MEDLINE, EMBASE, DARE, and ACP Journal Club* and full-text searches were combined (all searched October 2004). Reference lists of pertinent studies and other identified literature were scanned. Researchers in the field were contacted.

Only randomized clinical trials using the PAIR method with or without benzimidazole coverage as the experimental treatment of uncomplicated hepatic hydatid cysts (i.e., 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 (i.e., performing all steps for puncture, pretending that PAIR is being performed, but actually not performing the procedure proper), surgery, or medical treatment were included.

Data were independently extracted and methodologic quality of each trial was assessed by the authors. The principal authors of the trials were contacted to retrieve missing data.

Results: We found no randomized clinical trials comparing PAIR versus no or sham intervention. We identified only two randomized clinical trials, one comparing PAIR versus surgical treatment (n = 50) and the other comparing PAIR (with or without albendazole) versus albendazole alone (n = 30). Both trials were graded as 'adequate' for allocation concealment; however, generation of allocation sequence and blinding methods were 'unclear' in both of them. Compared with surgery, PAIR plus albendazole obtain 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 with albendazole, PAIR with or without albendazole obtain significantly more often (*P* = 0.01) cyst reduction and symptomatic relief.

Conclusion: 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 cysts. Further well-designed randomized clinical trials are necessary to address the topic.

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Plain language summary

Insufficient evidence to support or refute the puncture, aspiration, injection, and reaspiration (PAIR) method with or without benzimidazole

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coverage for patients with uncomplicated hepatic hydatid cyst

Two randomized clinical trials on the PAIR method for patients with uncomplicated hepatic hydatid cysts were identified. One trial compared PAIR with surgical treatment. The other trial compared PAIR with or without albendazole with albendazole alone. Neither of the trials had high methodologic quality. The number of participants enrolled and the follow-up duration are insufficient for a definite conclusion to be drawn.

Background

Hydatid cyst disease, or cystic echinococcosis is a near-cosmopolitan zoonosis caused by larval forms of the cestode *Echinococcus granulosus*.[1] Humans are incidental intermediate hosts of the parasite, and the liver is the most common site of involvement.[2] The disease may remain silent for many years before coming into medical attention as an incidental imaging finding, or it may present with complications.[3,4] Management of uncomplicated hepatic hydatid cysts is currently surgical,[5] although 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.[6 – 12] 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.[13 – 15]

For many years, percutaneous aspiration of hydatid cyst was discouraged because of the potential risk of spillage and anaphylactic shock.[16, 17] However, unintended or deliberated cases of cyst puncture showed no significant complications.[18 – 20] The so-called PAIR method was then introduced accidentally by Mueller in 1985[21] and later on reported in case series with variable outcomes, most of the series authors claiming the technique was safe and effective.[22 – 29] PAIR is performed under ultrasound (US) guidance (or sometimes computerized tomography (CT) guidance) and includes drainage of the cysts with a fine needle or catheter, followed by instillation of protoscolicidal substances (e.g., hypertonic saline or absolute alcohol) and reaspiration. 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.[30, 31]

Despite its claimed safety and efficacy, PAIR is not yet accepted as the treatment of choice for uncomplicated hepatic hydatid cysts and many arguments remain about it.[32 – 34] We have been unable to identify metaanalyses or systematic reviews on the topic based on randomized 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?

Criteria for considering studies for this review

Types of studies

All randomized 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:

(1) Hepatic hydatid cysts 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.[35] (2) Intact, noninfected hepatic hydatid cysts with no clinical or biochemical suspicion of communication with the biliary system or other viscera.

Types of intervention

(1) Experimental intervention: PAIR of uncomplicated hepatic hydatid cysts performed US or CT guidance and followed by injection of scolicidal agents, and reaspiration; the PAIR method with or without benzimidazole coverage.

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

(2) 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 both arms of the trial.

Types of outcome measures

The outcome measures were:

(1) Mortality.

(2) Clinical beneficial effects that were estimated by assessing the following outcome measures:

(a) disappearance of uncomplicated hepatic hydatid cysts as assessed by transabdominal ultrasonography;

(b) decrease in size of uncomplicated hepatic hydatid cysts as assessed by transabdominal ultrasonography; and

(c) change in cyst echogenicity in favor of nonviability 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 rate of uncomplicated hepatic hydatid cysts.

(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 hospitalization or prolongation of existing hospitalization, result in persistent or significant disability, cause a congenital anomaly/birth defect, or any medical event, which may have jeopardized the patient or required intervention to prevent it (ICH-GCP 1997). All other adverse events were considered nonserious.

(8) Quality of life.

(9) Health economics.

Search methods for identification of studies

See: Hepato-Biliary Group methods used in reviews.

About the search strategy see Gluud 2004.[36]

- We searched The Cochrane Hepato-Biliary Group Controlled Trials Register (October 2004), The Cochrane Central Register of Controlled Trials (CENTRAL), and The Database of Abstracts of Reviews of Effects (DARE) in The Cochrane Library Issue 3, 2004 (see Table 1).

We conducted electronic searches utilizing MEDLINE from January 1966 to October 2004, EMBASE from January 1980 to October 2004, and The ACP Journal Club form January 1991 to October 2004 (see Table 1 for the search strategies and MeSH terms used). Both MeSH and non-MeSH terms were used.

- We searched published abstracts and proceedings from key scientific conferences of hydatidology (International Congresses of Hydatidology XVIII-XX) to identify any randomized 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 2004.

- We searched current clinical practice guidelines (WHO Informal Working Group on

Table 1. Search strategies.

Database	Search strategy	Time span of search
The Cochrane Hepato-Biliary Group Controlled Trials Register	#1 hydatid* #2 echinococc* #3 (#1 and #2)	June 2004
The Cochrane Renal Group Controlled Trials Register and The Cochrane Controlled Trials Register in the Cochrane Library	#1 hydatid* #2 echinococc* #3 ECHINOCOCCOSIS explode all trees (MeSH) #4 ECHINOCOCCUS explode all trees (MeSH) #5 (#1 or #2 or #3 or #4)	Issue 3, 2004
MEDLINE on Sliver Platter (ERL WebSPIRS 5.01)	#1 hydatid* #2 echinococc* #3 explode\echinococcosis-"/all SUBHEADINGS in ME #4 explode\echinococcus-" / all SUBHEADINGS in ME #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 (scolicid*) or (protoscolicid*)) #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 reaspiration* #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)	01/1966 to 10/2004
EMBASE on WebSPIRS (ERL WebSPIRS 5.01)	#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	01/1980 to 10/2004

Table 1. Search strategies *(continued)*.

Database	Search strategy	Time span of search
	#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 (scolicid*) or (protoscolicid*)) #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 reaspiration* #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)	Search for: (hydatid*) OR (echinococc*) Find docs that match: Any words Search type: Fuzzy	01/1991 to 10/2004
Database of Abstracts of Reviews of Effects (DARE) in the Cochrane Library	#1 hydatid* #2 echinococc* #3 ECHINOCOCCOSIS explode all trees (MeSH) #4 ECHINOCOCCUS explode all trees (MeSH) #5 (#1 or #2 or #3 or #4)	Issue 3, 2004

PAIR = puncture-aspriation-injection-reaspiration.

Echinococcosis (WHO-IWGE) manual) for relevant randomized clinical trials.

- We hand searched reference lists from review articles retrieved from *MEDLINE* or *EMBASE* and reference lists from randomized 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 randomized clinical trials on the topic.

Methods of the review

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.

Methodologic quality assessment

Methodologic quality was defined as the confidence that the design, conduct, and report restrict bias in the intervention comparison.[37 – 39] It was evaluated independently by the reviewers (SNM, AA, and RM). Disagreements were resolved by discussion. We wrote to the principle author of included trials for complementary information. The four major components of methodologic quality were registered and graded individually as follows:

Generation of the allocation sequence

- Adequate; by a table of random numbers, computer generated, or similar.
- Unclear; trials in which the authors did not report the generation of allocation sequence.
- Inadequate; by alternation, date of birth, or

similar. Such trials were excluded.

Allocation concealment

- Adequate; if the allocation of patients involved a central independent unit; serially numbered, opaque sealed envelopes; on-site locked computer, or other descriptions that contained convincing elements of concealment.
- Unclear; when the method used to conceal the allocation was neither described nor clearly explained.
- Inadequate; when allocation concealment was not performed or the following modalities were used: alternation; the use of case record numbers, dates of birth or day of the week, and any procedure that is entirely transparent before allocation, such as an open list of random numbers. Such trials were excluded.

Blinding

Double blinding in trials on surgery or other procedures is not always feasible. That is why we will report on who has been blinded. It could be the trial participants, healthcare providers, or outcome assessors. Judicial assessors of outcomes, data analysts, data safety monitoring committee members, and manuscript writers can also be blinded.

Follow-up

- Adequate; if the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.
- Unclear; if the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.
- Inadequate; if the number or reasons for dropouts and withdrawals were not described. Further, we registered 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: methodologic quality, type of randomized 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 randomized to each intervention arm, mean (or median) age, number of males, mean duration of disease at randomization, form of hepatic hydatid cyst (echo pattern, location), mean diameter/volume of cyst in each intervention arm, and 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), and protoscolicidal agents (hypertonic saline, alcohol).
2. Surgery: type of surgical procedure (radical, conservative, laparoscopic), type of residual cavity management, and 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), and route of administration.

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

Data analysis

We planned to do the following statistical analyses, using the statistical package provided by The Cochrane Collaboration, RevMan analysis version 4.2. to analyze the data by intention-to-treat 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 analyzed using weighted 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.[40] A random- and a fixed-effects 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.

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 2). 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-coordinator yielded no further randomized 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,[41] and the other trial compared PAIR (n = 25) versus surgical treatment (n = 25) in patients with uncomplicated hepatic hydatid cyst disease.[42] Descriptions of the trials are shown in the Table 3. We did not find any randomized clinical trials comparing PAIR with no or sham intervention.

Table 2. Characteristics of excluded studies.

Acunas 1992 [24]	Case series
Akhan 1996 [26]	Case series
Akhan 1999 [43]	Narrative review
Al-Karawi 1996 [44]	Case series
Aygun 2001 [45]	Case series
Bastid 1994 [25]	Case series
Bosanac 2001 [46]	Case series
Bret 1989 [23]	Case series
Brigic 2003 [47]	Case series
Crippa 1999 [48]	Case series
Dilsiz 1997 [49]	Case series
Duta 2002 [50]	Case series
Dwivedi 2002 [51]	Case series
Dziri 2004 [52]	Narrative review
Filice 1990 [53]	Case series
Filice 1990b [54]	Case series
Filice 1997 [55]	Case series
Gargouri 1990 [56]	Case series
Giorgio 1992 [57]	Case series
Giorgio 1991 [58]	Case series
Giorgio 1993 [59]	Case series
Giorgio 2001 [60]	Case series
Grigorov 2000 [61]	Case series
Haddad 2000 [62]	Case series
Hernandez 1996 [63]	Case series
Kabaalioglu 1998 [64]	Case series
Kabaalioglu 2000 [65]	Case series
Khuroo 1991 [66]	Case series
Kohlhaufl 1995 [67]	Narrative review
Men 1999 [27]	Case series
Mikic 1998 [68]	Case series
Mueller 1985 [21]	Case report
Odev 2000 [69]	Case series
Ormeci 2001 [29]	Case series
Pelaez 1999 [28]	Case series
Pelaez 2000 [70]	Case series
Polat 2002 [71]	Case series
Salama 1995 [72]	Case series
Salama 1998 [73]	Case series
Sayek 2001 [74]	Case series
Simonetti 1993 [75]	Case series
Sinha 2001 [76]	Case series
Smego 2003 [77]	Narrative review
Stoianov 1995 [33]	Case report
Stoianov 2002 [78]	Narrative review
Tan 1998 [79]	Nonrandomized trial
Ustunsoz 1999 [80]	Case report
Vishnevskii 1992 [81]	Case series
Wang 1994 [82]	Case series
Zarem 2003 [83]	Case series

Methodologic quality

Both trials were described as randomized. The four major components of methodologic quality were graded as follows:

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 randomization 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 or through sealed envelopes, 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'.

Results

PAIR plus oral albendazole versus surgery (cystectomy)

Table 4 shows the findings in the Khuroo et al trial (1997).[42] The trial compared PAIR versus

Table 3. Characteristics of included studies.

Study	**Khuroo 1993** [41]
Methods	Randomized clinical trial, with three parallel groups. Methodologic quality. Generation of the allocation sequence: unclear. No information. Allocation concealment: adequate. Sealed envelopes. Blinding: blinded outcome assessors, but methodologically unclear. Follow-up: adequate. Inclusion of all randomized participants at evaluation: No patients died before 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 (9.0, 7.4) range: 3 to 20 months. PAIR plus albendazole (6.3, 2.7) range: 3 to 11 months. 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 randomization: not reported. Number of males (proportion): 11/30 (36.6%). Mean age (SD): 39 (14) years. Form of HHYC: univesicular (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 was used as an aspiration tool. Aspiration route was transhepatic and the protoscolicidal agent was sterile hypertonic (20%) saline. No pre- or postdrainage 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 antiechinococcal 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.
Allocation concealment A	
Study	**Khuroo 1997**
Method	Randomized clinical trial, with two parallel groups. Methodologic quality. Generation of the allocation sequence: unclear. No information. Allocation concealment: adequate. Sealed envelopes. Blinding: blinded outcome assessors, but methodology unclear. Follow-up: adequate. Inclusion of all randomized participants at evaluation: No patients died before 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.

Table 3. Characteristics of included studies *(continued)*.

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 randomization: not reported. Number of males (proportion): 22/50 (44%). Mean age (SD): not reported. Form of HHYC: univesicular (32 cysts), and multivesicular (18 cysts). Duration of disease: not reported.
Interventions	PAIR plus albendazole A 5-French transhepatic catheter (Cook Europe, Bjeverskov, 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 postoperation prophylaxis was used. Cointervention: 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.
Allocation concealment A	

HHYC = hepatic hydatid cyst; US = ultrasound; SD = standard deviation.

surgery. The mean follow-up period 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 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 and oral albendazole alone, serial ultrasonography showed heterogeneous echo pattern of the cysts in 18, uniform echogenicity in 11, and disappearance in three patients. There were no deaths. 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%). There was no mortality.

Table 4. 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

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, randomized trials comparing PAIR with surgery or medical therapy in people with uncomplicated hepatic hydatid cysts. Both of the included trials had methodologic 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 US) may miss some persistent or recurrent infestations. Due to the few conducted trials, we could not perform metaanalyses.

In a recently published metaanalysis of uncontrolled studies, Smego[77] concluded that PAIR is safe and effective for treatment of uncomplicated hepatic hydatid cysts. Although the number of patients included in metaanalysis is appreciable, 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 arm were retrieved and how many were included. Second, there is no table showing excluded studies in either arm. Third, the authors have not performed a test of heterogeneity to look for methodologic differences between the studies. This is important because if the studies are heterogeneous, metaanalysis 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 from Smego's[77] metaanalysis. Therefore, conclusion should be considered with caution.

Another review has recently been published by Dziri et al[52] assessing all studies on different treatments of hydatid cysts.

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 a sensible conclusion, 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 randomized clinical trials. According to our systematic review and other authors, there are only a few randomized 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 randomized clinical trials with larger

numbers of patients and longer duration of follow-up are necessary to address the topic.

Conclusion

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 randomized clinical trials for treating patients with uncomplicated hepatic hydatid cysts.

Implications for research

Further well-designed randomized clinical trials are necessary to address the topic. We need randomized clinical trials comparing the PAIR method with or without benzimidazole coverage versus sham/no intervention, surgery, or medical treatment for patients with uncomplicated hepatic hydatid cysts. Because the disease is not so common, multicenter trials might be necessary. They also have the advantage of higher external validity. Future trials should have sufficient statistical power, high methodologic quality, adequate follow-up, intensive monitoring of adverse events, and should be reported according to the CONSORT guidelines (www.consortstatement. 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.

Potential conflict of interest

None known.

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