

The Comparison of 2 New Promising Weapons for the Treatment of Hydatid Cyst Disease: PAIR and Laparoscopic Therapy

Xinhua Chen, PhD, MD,* Chao Cen, MD,* Haiyang Xie, MD,*
Lin Zhou, PhD,* Hao Wen, PhD, MD,† and Shusen Zheng, PhD, MD*

Background: To compare the effectiveness and safety for hydatid disease treatment, the 2 new minimally invasive therapies: laparoscopic and PAIR (puncture, aspiration, injection, and reaspiration) were compared by systematic meta-analysis.

Methods: A comprehensive analysis of published cases from 1990 to 2014 was performed using PubMed database. A total of 231 publications on laparoscopic treatment of hydatid cysts and 298 publications on the PAIR treatment were identified. Thirty-eight studies involved 1230 laparoscope-treated subjects and 41 involved 2686 PAIR-treated subjects in this review. The effectiveness and safety of emphasis is placed on the recurrence, insufficient response, death, cure, and postoperative complications. Operation time and hospital stay are also discussed as new evaluation index. The stages of cyst are summarized to determine which stage is suitable for PAIR.

Results: Clinical and parasitological cure occurred in 98.7% of patients undergoing laparoscopic intervention and in 97.5% of patients receiving PAIR plus chemotherapy ($P < 0.014$). Recurrence occurred in 1.0% and 1.6%, respectively ($P < 0.087$). Insufficient response occurred in 0.16% and 0.9%, respectively ($P < 0.009$); 2 patients died in each group ($P < 0.594$). Allergic reaction/urticarial/anaphylactic shock occurs in 0.14% and 4.24% of patients receiving laparoscopic intervention and PAIR plus chemotherapy, respectively ($P < 0.001$). Infection/abscess (5.37% and 2.57%; $P < 0.001$) and surgical-related complications (7.32% and 3.43%; $P < 0.001$) were seen more frequently in laparoscopic intervention subjects than PAIR plus chemotherapy subjects.

Conclusions: Laparoscopic therapy and PAIR intervention are shown to be safe and effective alternative for open surgery with suitable indication such as cyst type and location. They have different postoperative complication features. The biliary fistula/bile leakage was more frequent in laparoscopic intervention ($P < 0.001$) and fever occurred more in PAIR plus chemotherapy patients.

Key Words: hydatid disease, minimally invasive therapy, PAIR (puncture, aspiration, injection, and reaspiration), laparoscopic surgery

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Human cystic echinococcosis (CE), or hydatid cyst disease, is a parasitic disease caused by tapeworms of the genus *Echinococcus*. Hydatid cyst disease has been a public problem for long. The latest health statistics derived from WHO shows human incidence rates for CE can reach > 50 per 100,000 person-years in endemic regions. It is globally distributed and found in every continent except Antarctica, which is mainly endemic in pastoral and semipastoral areas in Asia, Middle East, Europe, and Latin American countries.¹ Hydatid cyst disease could develop in nearly all organs of the body and the most common infection site is the liver (70%), followed by lung (20%), kidney, bone, and brain.^{2,3}

It is often known as neglected disease for the asymptomatic incubation period of the disease can last many years until hydatid cysts grow to an extent that triggers clinical signs. However, if untreated, it may lead to low quality of life or even lethal disability. In general, management options for CE include surgery, percutaneous management, drug therapy, and “watch and wait.”⁴ Surgery has been the traditional approach for treatment of CE and yields good clinical results. As the open procedures are followed by significant morbidity, especially in terms of wound infection, the laparoscopic approach has become increasingly popular in the recent years. Laparoscopic surgery seems to be effective and safe with low morbidity and recurrence rates.⁵ Traditionally, percutaneous management of hydatid cysts was long considered to be contraindicated to avoid the risk of leakage of cyst contents, which can lead to anaphylaxis and seeding of intra-peritoneal structures.⁶ With the advent of drug therapy effective for CE, PAIR (puncture, aspiration, injection, and reaspiration) plus preoperative and postoperative chemotherapy is now advocated in health care centers worldwide.^{7–10} Laparoscopic surgery and PAIR therapy are new powerful weapons for the treatment of hydatid cyst disease.

To see which one might be more promising in the future, we seek to compare the effectiveness and safety of the 2 therapies. Emphasis is placed on the recurrence, insufficient response, death, cure, and postoperative complications. Operation time and hospital stay are also discussed as new evaluation index. In addition, the stages of cyst are summarized to determine which stage is suitable for PAIR.

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Reprints: Hao Wen, PhD, MD, The Department of Laparoscopic Surgery, the First Affiliated Hospital, Xinjiang Medical University, 137 South Liyushan Road, Urumqi 830054, Xinjiang, China (e-mail: dr.wenhao@163.com).

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METHODS

A comprehensive analysis of published cases from 1990 to September 2014 was performed using the PubMed database. Publications were in the English language. Search phrases were “hepatic hydatidosis or hepatic echinococcosis or Hydatid disease of liver or Hepatic hydatid disease or Echinococcosis or hydatid disease or hydatidosis,” “laparoscopic or minimal invasive,” “PAIR or percutaneous treatment.” A total of 231 publications consisting of reviews and series on the laparoscopic treatment of hydatid cysts were identified and 298 publications on the PAIR treatment of hydatid cysts were identified. All titles and abstracts were screened. Reviews and duplicates were removed. Thirty-eight comparative or noncomparative studies involved 1230 laparoscope-treated subjects and 41 comparative or noncomparative studies involved 2686 PAIR-treated subjects that reported details of clinical diagnoses, operative procedure, postoperative outcomes, and complications were included in this review. The diagnosis of hepatic CE was performed by means of ultrasonographic and/or computed tomography, cytologic or parasitologic, or serologic levels. The stage of cyst was categorized in accordance with the Gharbi classification.¹¹

PAIR was initially named as the procedure of puncture, aspiration, injection, and reaspiration. Patients received modified “PAIR” like PAI (percutaneous aspiration and injection),¹² D-PAI (double puncture-aspiration-injection)¹³ were included in this review, whereas the other percutaneous treatment catheterization was excluded. All patients undergoing PAIR therapy were treated with either albendazole or mebendazole preoperation and postoperation.

Laparoscopic therapy also has many variants when applied. The operative approach consists of totally, hand-assisted, and gasless laparoscopic. The extent of resection consists of cystectomy, pericystectomy, and liver resection.

Postoperative outcome were defined as follows: recurrence, appearance of a cyst in the same organ after successful treatment, insufficient response, increase/no change in cyst size or morphology, or an incomplete response to treatment. Postoperative complications were mainly categorized as infection/abscess, allergic reaction/urticarial/anaphylactic shock, hematoma, scolical-induced complications, surgical-related complications, and other complications.

Data were extracted and summarized. The statistical analysis was made with SPSS, version 18.0. Relevant statistic methods include Fisher test, χ^2 test. $P < 0.05$ was considered to be statistic significant.

RESULTS

Clinical and outcome details for the 1230 patients undergoing laparoscopic therapy are reviewed in this study. The mean number of patients per study was 32 (range, 1 to 105) and the mean age was 40 years. The mean operation time of all the 1230 laparoscopic interventions was 83 minutes. The most time-saving health care center cost only 40 minutes, whereas the longest mean operation time was 260 minutes. The mean hospital stay of all the 1230 laparoscopic interventions was 4.9 days (range, 0 to 9.9 d). The mean follow-up time was 29.7 months (range, 3 to 54 mo). Recurrence occurs in 12 of 1230 (1.0%).

Table 1 shows details of 2686 patients receiving PAIR plus chemotherapy. The mean hospital stay was 2.2 days (range, 0 to 6 d) and the mean follow-up time was 41 months (range, 3 to 120 mo). Recurrence occurs in 42

TABLE 1. Distribution of the Treated Cysts According to Gharbi Classification Treated With PAIR Plus Chemotherapy

Gharbi Classification	Lesion Feature	No. Cysts (%)
Type I	Pure fluid	870 (60.3)
Type II	Fluid collection, spilt-wall floating membrane	304 (21.1)
Type III	Fluid collection with septa, daughter cysts, and honeycomb image	159 (11.0)
Type IV	Heterogeneous echographic pattern	88 (6.1)
Type V	Reflecting thick walls	22 (1.5)
Total		1443 (100)*

*1770 cysts in 1327 patients with hepatic echinococcosis undergoing PAIR plus chemotherapy for the cysts type in the remaining 1776 patients are unknown.

PAIR indicates puncture, aspiration, injection, and reaspiration.

(1.6%) and insufficient response were seen in 24 (0.9%). A total of 1443 cysts were reported the stage of cyst in accordance with Gharbi classification (more than half of the literature use Gharbi classification, so stage of cysts shown in accordance with WHO classification was transformed to Gharbi classification). The majority receiving PAIR plus was type I (60.3%), followed by type II (21.1%), type III (11.0%), type IV (6.1%), and type V (1.5%).

As shown in Table 2, clinical and parasitological cure occurred in 98.7% of patients undergoing laparoscopic intervention and in 97.5% of patients receiving PAIR plus chemotherapy ($P < 0.014$). Recurrence occurred in 1.0% and 1.6%, respectively ($P < 0.087$). Insufficient response occurred in 0.16% and 0.9%, respectively ($P < 0.009$); 2 patients died in each group ($P < 0.594$). Table 3 illustrated the complications. Allergic reaction/urticarial/anaphylactic shock occurs in 0.14% and 4.24% of patients receiving laparoscopic intervention and PAIR plus chemotherapy, respectively ($P < 0.001$). Infection/abscess (5.37% and 2.57%; $P < 0.001$) and surgical-related complications (7.32% and 3.43%; $P < 0.001$) were seen more frequently in laparoscopic intervention subjects than PAIR plus chemotherapy subjects. It is worth mentioning that biliary fistula/bile leakage was more frequent in laparoscopic intervention ($P < 0.001$) and fever occurred more in PAIR plus chemotherapy patients.

TABLE 2. Clinical Outcomes in Patients Undergoing Laparoscopic Intervention or PAIR Plus Chemotherapy for Hepatic Echinococcosis

Clinical Outcomes	No. Patients (%)		P
	Laparoscopic Intervention (n = 1230)	PAIR Plus Chemotherapy (n = 2686)	
Recurrence	12 (1.0)	42 (1.6)	< 0.087
Insufficient response	2 (0.16)	24 (0.9)	< 0.009
Died	2 (0.16)	2 (0.07)	< 0.594
Cure	1214 (98.7)	2618 (97.5)	< 0.014

PAIR indicates puncture, aspiration, injection, and reaspiration.

TABLE 3. Comparison of Complications in Patients With Hepatic Echinococcosis Treated With Laparoscopic Intervention or PAIR Plus Chemotherapy

Complications	No. Patients Treated With Laparoscopic Intervention (n = 1230)	No. Patients Treated With PAIR Plus Chemotherapy (n = 2686)	P
Infection/abscess	66 (5.37)	69 (2.57)	< 0.001
Residual cavity infection/abscess	25 (2.03)	47 (1.75)	< 0.541
Hepatic	1 (0.08)	5 (0.19)	< 0.672
Port-side infection	26 (2.11)	4 (0.15)	< 0.001
Subphrenic abscess	2 (0.16)	—	NS
Pleural effusion/empyema	1 (0.08)	13 (0.48)	< 0.078
Allergic reaction/urticarial/anaphylactic shock	13 (0.14)	114 (4.24)	< 0.001
Hematoma	5 (0.41)	8 (0.30)	< 0.561
Perihepatic hematoma	1 (0.08)	8 (0.30)	< 0.289
Subcutaneous hematoma	4 (0.33)	—	NS
Scolicidal-induced complications	4 (0.33)	20 (0.74)	< 0.119
Ileus	3 (0.24)	—	NS
Methemoglobinemia	1 (0.08)	—	NS
Scolicidal-induced cholangitis	—	20 (0.74)	NS
Surgical-related complications	90 (7.32)	92 (3.43)	< 0.001
Biliary fistula/bile leakage	77 (6.26)	68 (2.53)	< 0.001
Spillage of cystic contents	10 (0.81)	24 (0.89)	< 0.801
Incisional hernia	2 (0.16)	—	NS
Perforated small bowel	1 (0.08)	—	NS
Other complications	10 (0.81)	170 (6.33)	< 0.001
Fever	7 (0.57)	128 (4.77)	< 0.001
Pneumonia	2 (0.16)	—	NS
Atelectasis	1 (0.08)	—	NS
Peritoneal/intraperitoneal leakage	—	2 (0.07)	NS
Hypernatremia	—	2 (0.07)	NS
Transitory leukocyte elevation	—	16 (0.60)	NS
Pneumothorax	—	2 (0.07)	NS
Hypotension	—	10 (0.37)	NS
Nausea and vomiting	—	10 (0.37)	NS

PAIR indicates puncture, aspiration, injection, and reaspiration.

DISCUSSION

Hydatid cyst disease has a worldwide geographical distribution and remains to be a public health issue in several countries and regions.^{14,15} The greatest prevalence of CE in human and animal hosts is found in countries of the temperate zones, including several parts of Eurasia (the Mediterranean regions, Southern and Central parts of Russia, Central Asia, China), Australia, some parts of America (especially South America), and North and East Africa.^{3,16} Twenty-seven and 13 publications were from Turkey (Mediterranean regions) and India (Central Asia)

respectively, which consist of more than half the total 79 publications. They were followed by Italy (6 publications) and France (5 publications). A total of 2822 of 3916 (72.1%) patients were from 3 countries of great prevalence: Turkey, India, and Italy. It does not mean that Turkey, India, and Italy are the top 3 countries with high incidence, but we are inferred that hydatid cyst disease has become a big health and economic burden for these countries.

The goals of hepatic hydatid cyst treatment are a complete elimination of the parasite, prevention of recurrence, and minimizing mortality and morbidity risk. With the potential to remove the endocyst and lead to a complete cure, surgery is always considered as the definitive and optimal treatment.¹⁷ Open surgery has been long adopted as a traditional option. But now laparoscopic therapy is preferred because of its lower morbidity and mortality rates and the advantage of a shorter hospital stay.^{18,19} The mortality rate of laparoscopic therapy in this review is 0.16%, which is far lower than open surgical operative mortality rate (0.5% to 4%).²⁰ The mean hospital stay of patients receiving laparoscopic therapy was 4.9 days, whereas open surgery costs a mean 15 days of hospital stay.²¹ In addition, with the improvement of laparoscopic skills and adjuvant application of albendazole/mebendazole, the recurrence rate has reduced to 1%, which is lower than reported recurrence rates ranging from 2% to 25%² in earlier times. It shows another superiority to open surgery (6.3%).²¹

Another minimally invasive technique is the percutaneous treatment. It was once strongly discouraged for fear of anaphylactic shock and disease seeding as consequence of intra-abdominal protoscolices spillage.⁶ Mueller et al⁷ first reported a successful case of a recurrent hepatic hydatid cyst with percutaneous aspiration and lavage with silver nitrate and hypertonic saline in 1985. Following this preliminary attempt, Ben Amor and colleagues improved the technique and put forward a new creative therapy named PAIR.^{22,23} Since then, plenty of variants came out to improve the treatment effect. Among these variants, scolical agent was most often discussed. Hypertonic saline with concentration ranging from 3% to 30% has been reported by different literature.^{24–27} Hypertonic saline could create a strong osmotic gradient across the outer membrane of the scolix that causes its lysis. As the concentration and time increase, the scolical effect will be enhanced. Another widely used scolical agent was 95% sterile ethanol,²⁸ which was considered to have a more potent sclerosing effect.²⁹ Other scolical agents including 0.04% chlorhexidine gluconate, 20% silver nitrate, 50% dextrose, and 20% mannitol^{30,31} have been introduced to application with potential advantage over hypertonic saline.

PAIR was considered a more time-saving therapy compared with laparoscopic intervention. The mean hospital stay was 2.2 days, which showed a significant reduction than 4.9 days of laparoscopic intervention. Quite a few literatures reported that patients could discharge from hospital just at the same day of receiving PAIR and continue the chemotherapy at home.^{5,32–36} But the clinical outcome of PAIR was a bit inferior to laparoscopic therapy. The overall cure rate was lower than laparoscopic therapy and the insufficient response rate was higher than laparoscopic therapy. It was generally concluded that recurrence was usually due to either inadequate cyst removal or to previously undetected cysts. The laparoscopic therapy allows surgeons to operate in a visual field of view.

PAIR intervention has to be operated with the aid of radiographic techniques (ultrasound/computed tomography), which make it difficult to identify inadequate cyst or undetected cysts. Moreover, the longer follow-up time (41 vs. 29.7 mo) often means more probability to record recurrence. Besides, the treatment effect also depends on many other factors, such as the proficiency of operators, basic status of patients, and effect of chemotherapy.

Laparoscopic therapy and PAIR intervention have different postoperative complication features. After laparoscopic operation, patients have more risks to have infection/abscess (port-side infection), surgical-related complications (biliary fistula/bile leakage), whereas patients receiving PAIR intervention have the tendency to suffer from allergic reaction/urticarial/anaphylactic shock or fever. The major disadvantage of laparoscopy is the lack of precautionary measures to prevent spillage under the high intra-abdominal pressures caused by pneumoperitoneum.³⁷ The most difficult part of the laparoscopic procedure is the initial cyst puncture and aspiration of the cyst fluid.³⁸ To avoid biliary fistula/bile leakage, several methods have been invented.^{39–41} Bickel et al⁴⁰ proposed a new device with a transparent cannula and vacuum for complete fluid evacuation, which seems promising in the future. Larger operative incision often means more risks to get infected. Moreover, biliary leakage, whether transient or persistent, can be the source of secondary cavity infections.⁴² It can be implied that more attention should be paid to avoid infection after laparoscopic therapy. In accordance with previous studies,^{9,10,43–45} anaphylaxis occurred much more in patients with PAIR intervention. Perceived risk of anaphylaxis linked to PAIR intervention was always quoted by physicians preferring surgery than PAIR and hinders the widespread application.

PAIR is not suitable for all types of cysts. PAIR is indicated for type I and II cysts of > 5 cm and type III cysts treated by PAIR tend to relapse.⁴ Of the 1443 reported cysts, > 80% cysts receiving PAIR therapy were types I and II and it yields good clinical results.

Although laparoscopic therapy showed higher cure rate and lower insufficient response rate, it does not mean the superiority for the diverse postoperative complications. If we can have a good control of anaphylaxis, PAIR has shown to be a safe and effective alternative for many patients with suitable cysts of CE. Laparoscopy is most likely to be successful in the setting of anteriorly located hepatic cysts,⁴⁶ whereas exclusion criteria for laparoscopy include deep intraparenchymal cysts, posterior cysts situated close to the vena cava, and presence of > 3 cysts with calcified walls.^{37,47–50} To end the controversy, we need to conduct more high-quality random-controlled trials comparing the 2 therapies and establish evidence-based criteria to allocate the patient to the most appropriate treatment option according to the specific situation.

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