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Review Articles

Shenmai Injection for Chronic Pulmonary Heart Disease: A Systematic Review and Meta-Analysis

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Objectives: This study sought to evaluate the efficacy and safety of *shenmai* injection for chronic pulmonary heart disease (CPHD).

Methods: A systematic review was conducted of clinical trials that compared *shenmai* injection plus conventional medicine treatment versus conventional medicine treatment alone. Randomized controlled trials of clinical therapeutic studies on CPHD by *shenmai* injection were included. Searches were applied to the following electronic databases: the PubMed (1977–2008), the Cochrane Library, EMBASE, AMED, Chinese BioMedical Literature Database, and CBM. No blinding and language restriction was used. Data were extracted independently by 2 reviewers. All trials included were analyzed according to the criteria of the Cochrane Handbook. Review Manager 5.0 software was used for data analysis.

Results: Thirty-three (33) randomized clinical trials (2617 patients) with low methodological quality were included. Compared to conventional medicine treatment alone, *shenmai* plus conventional medicine treatment showed significant improvement in New York Heart Association classification of clinical status (odds ratio 0.24; 95% confidence interval 0.19–0.30), five studies had reported adverse events. No serious adverse effects were reported in any of the included trials.

Conclusions: While there is some evidence that suggests potential effectiveness of *shenmai* plus conventional medical treatment for CPHD, the results of this study were limited by the methodological flaws, unknowns in concealment of allocation, number of dropouts, and blinding methods in the studies. Long-term and high-quality studies are needed to provide clear evidence for the future use of *shenmai* injection.

Introduction

Pulmonary heart disease is a rising major public health problem worldwide.[1] In China, many traditional Chinese patent medicines (TCPM) are regularly used in patients with chronic pulmonary heart disease (CPHD) in the hospital. Few studies reporting the effectiveness and safety of many commonly used TCPM for cor pulmonale have been published in English.[2] *Shenmai* is a traditional Chinese herbal medicine that has long been used for the treatment of pulmonary heart disease. It is a mixture of two herbal components. Constituent herbs of *shenmai* include ginseng (*Panax ginseng*) and mondo grass (*Ophiopogon japonicus*). Several trials have shown that *shenmai* injection might have a therapeutic effect to improve cardiac function in people with pulmonary heart disease.[3–5] However, the quality of these trials has not been assessed systematically. Furthermore, the spontaneous evolution of pulmonary heart disease is difficult to predict, and a definitive assessment of the effects of treatment requires long-term follow-up. A systematic review will benefit current practice and direct the continued search for new treatment regimens. The objective of this review was to assess the effects (both benefits and adverse effects) of *shenmai* plus conventional medicine treatment versus conventional medicine treatment in all forms of pulmonary heart disease in adults.

Materials and Methods

Eligibility criteria

Administration of *shenmai* injection for the treatment of CPHD was acceptable for inclusion. *Shenmai* injection trials were included regardless of duration of treatment. Trials were included involving patients of any age, sex, or CPHD stage. Excluded were pharmacokinetic studies, nonrandomized evaluations, early results presentations when later results were available, and animal/laboratory studies.

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Search strategy

Two reviewers (S.-y.L. and Z.-w.W.) identified relevant randomized controlled trials independently, in any language, by a systematic search of PubMed (1966–2008), Chinese Biomedical Database (CDROM, 1978–2008), EMBASE (1984–March 2004), AMED (1985–July 2008), Chinese Bio-Medical Literature Database (CBM, 1978–April 2008), The Cochrane Library (Issue 2, 2008), and BIOSIS (1997–2008) with the following terms: (cor pulmonale or chronic pulmonary heart disease) AND (*Shen-Mai* injection or ginseng or *shen* next *mai*). The wild-card term "*" was used to increase the sensitivity of the search strategy. Reviewers scanned the bibliographies of all retrieved trials and other relevant publications, including reviews and meta-analysis, for additional relevant articles.

Study selection and data extraction

Two (2) reviewers (S.-y.L. and Z.-w.W.) extracted data and appraised both quality and content independently. Data extraction was conducted using a standardized form. Initially, abstracts were screened to exclude obviously ineligible reports, and complete primary reports were reviewed for all remaining studies. Trials and abstracts were classified according to study drug under investigation and information was obtained on patient characteristics, study design, and therapy duration. Study design items included methods of sequence generation, allocation concealment, complete description of who was blinded, use of intention-to-treat analysis, and whether the trial was stopped prior to the planned duration, all methodological features capable of impacting effect sizes.

The primary outcome measures included the following:

1. Death
2. Adverse events.

The secondary outcome measures included the following:

1. New York Heart Association classification (NYHA) of clinical status
2. Hemodynamics
3. Partial pressure of oxygen (PaO_2) and carbon dioxide ($PaCO_2$)
4. Quality of life as measured by various instruments.

The data were entered into an electronic database such that duplicate entries existed for each study; when two entries did not match, consensus was reached through discussion and third-party arbitration. To obtain full information regarding conference abstracts, contact was attempted with the study authors for full information through e-mail and telephone communication.

Data analysis

The statistical package (RevMan 5.0) provided by the Cochrane Collaboration was used to analyze the data. Dichotomous data were presented as odds ratio (OR), with 95% confidence intervals (CI). Continuous outcomes were presented as weighted mean difference, with 95% CI. Analyses were performed by intention-to-treat where possible. Otherwise, for dichotomous outcomes, patients with incomplete or missing data were included in sensitivity analyses by counting them alternately as treatment failures or successes. For continuous variables, simple sensitivity analysis was used to test how robust the results were under different assumptions about what might have happened to patients with missing data.

Meta-analysis was only performed within comparisons where individual trials compared similar treatment and control interventions.

Results

Study identification and characteristics

An initial search identified 337 potentially relevant articles. A total of 245 articles were initially excluded because of duplicate publication; then 35 articles were excluded because they did not meet the inclusion criteria. In the identified 57 potentially eligible reports, after the full text was read, 90 articles were excluded for further assessment. The most frequent reasons for exclusion were other types of intervention examined, no clinical outcomes reported, or that it was not a randomized trial. Therefore, a total of 33 studies (2617 participants) were included in the review.[3–35] All studies were published in Chinese. Figure 1 summarizes the search results based on the Quality of Reporting of Meta-Analyses flow diagram. The bibliographic details of these trials are given in Table 1.

The age of patients in the included studies ranged from 43 to 90 years. Most trials included more males (54%–89%) than females; only one trial included more females (55%). All included trials applied standard Western medicine diagnostic criteria for CPHD, although some trials used Traditional Chinese Medicine (TCM) criteria in addition. The dose of *shenmai* injection was from 10 mL to 80 mL, most of which was from 30 mL to 60 mL. *Shenmai* injection was administered as intravenous injection in all included studies. The total duration of treatment varied from 7 to 15 days.

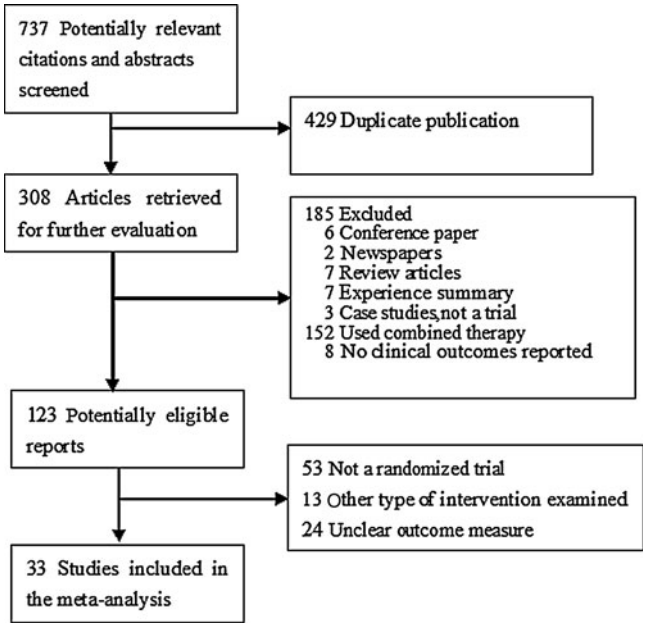

FIG. 1. The Quality of Reporting of Meta-Analyses flow diagram for the meta-analysis.

Table 1. Characteristics of Included Studies

Included studies		*Methods*		*Participants*			*Interventions*		*Outcomes*			
Date of study	*First author*	*Double-blind*	*Settings*	n[a]	*Age (years)*	*Gender*	*Experiment group*	*Control group*	*Death*	*Clinical status*	*Quality of life*	*Adverse effect*
2001	Bao Xiaoyan[31]	Yes	H	32/23	Mean 57	M, F	Conventional medicine treatment plus *shenmai* injection 50 mL qd 10 days	Conventional medicine treatment	No	Yes	No	No
2006	Chen Linqing[18]	Yes	H	30/28	65–80	M, F	Conventional medicine treatment plus *shenmai* injection 50 mL qd 7 days	Conventional medicine treatment	No	Yes	No	Nk
2004	Chen Yunlu[14]	Yes	H	36/36	69–75	M, F	Conventional medicine treatment plus *shenmai* injection 50 mL qd 14 days	Conventional medicine treatment	No	Yes	No	Nk
2003	Chen Hui[3]	Yes	H	40/38	60–89	M, F	Conventional medicine treatment plus *shenmai* injection 40 mL qd 14 days	Conventional medicine treatment	No	Yes	No	Yes
2007	Cui Caimei[25]	Yes	H	40/40	40–79	M, F	Conventional medicine treatment plus *shenmai* injection 50–80 mL qd 14 days	Conventional medicine treatment	No	Yes	No	No
1998	Du Yongyuan[4]	Yes	H	36/34	60–88	M, F	Conventional medicine treatment plus *shenmai* injection 40–60 mL qd 14 days	Conventional medicine treatment	No	Yes	No	No
2001	Gu Jianxia[28]	Yes	H	34/30	Mean 58.43 ± 17.32	M, F	Conventional medicine treatment plus *shenmai* injection 30 mL qd 14 days	Conventional medicine treatment	No	Yes	No	NK
2008	Guo Chengdong[11]	Yes	H	32/30	53–74	M, F	Conventional medicine treatment plus *shenmai* injection 40–60 mL qd 14 days	Conventional medicine treatment	No	Yes	No	Ye
2008	Guo Cuifang[26]	Yes	H	64/51	49–80	M, F	Conventional medicine treatment plus *shenmai* injection 30 mL qd 10 days	Conventional medicine treatment	No	Yes	No	No
2003	Hu Youzhuan[13]	Yes	H	33/33	40–76	M, F	Conventional medicine treatment plus *shenmai* injection 40 mL qd 14 days	Conventional medicine treatment	No	Yes	No	No
2008	Hu Zhen[7]	Yes	H	27/26	62–82	M, F	Conventional medicine treatment plus *shenmai* injection 40–	Conventional medicine treatment	Yes	Yes	No	No

(*continued*)

Table 1. (Continued)

Included studies		Methods		Participants			Interventions		Outcomes			
Date of study	First author	Double-blind	Settings	n[a]	Age (years)	Gender	Experiment group	Control group	Death	Clinical status	Quality of life	Adverse effect
							60 mL qd 14 days					
2003	Jiang Wenjun[24]	Yes	H	40/40	63–90	M, F	Conventional medicine treatment plus *shenmai* injection 40 mL qd 15 days	Conventional medicine treatment	No	Yes	No	NK
2002	Jiang Dan[23]	Yes	H	25/25	55–78	M, F	Conventional medicine treatment plus *shenmai* injection 40 mL qd 15 days	Conventional medicine treatment	No	Yes	No	No
2008	Li Haining[19]	Yes	H	63/50	43–97	M, F	Conventional medicine treatment plus *shenmai* injection 45 mL qd 7–14 days	Conventional medicine treatment	No	Yes	No	Nk
2001	Li Xiang[30]	Yes	H	57/60	Mean 57.3	M, F	Conventional medicine treatment plus *shenmai* injection 30–40 mL qd 7–10 days	Conventional medicine treatment	No	Yes	No	No
1999	Li Guoping[8]	Yes	H	68/62	42–81	M, F	Conventional medicine treatment plus *shenmai* injection 10–20 mL qd 10 days	Conventional medicine treatment	Yes	Yes	No	Yes
2003	Liu Tinggui[10]	Yes	H	66/62	51–85	M, F	Conventional medicine treatment plus *shenmai* injection 40 mL qd 14 days	Conventional medicine treatment	No	Yes	No	Yes
2001	Lu Yihua[9]	Yes	H	57/36	44–82	M, F	Conventional medicine treatment plus *shenmai* injection 30 mL qd 10 days	Conventional medicine treatment	Yes	Yes	No	No
2001	Ma Hongling[15]	Yes	H	37/37	60–86	M, F	Conventional medicine treatment plus *shenmai* injection 20 mL qd 10 days	Conventional medicine treatment	No	Yes	No	NK
2003	Shi Bing[27]	Yes	H	42/36	52–79	M, F	Conventional medicine treatment plus *shenmai* injection 10–60 mL qd 7–10 days	Conventional medicine treatment	No	Yes	No	No
1999	Song Zhenbang[20]	Yes	H	37/37	60–86	M, F	Conventional medicine treatment plus *shenmai* injection 20 mL qd 7 days	Conventional medicine treatment	No	Yes	No	NK
2003	Sun Yanheng[5]	Yes	H	52/48	46–78	M, F	Conventional medicine treatment plus *shenmai* injection 50 mL qd 14 days	Conventional medicine treatment	Yes	Yes	No	Nk
2008	Wang Shenhe[35]	Yes	H	40/40	65–82	M, F	Conventional medicine treatment plus	Conventional medicine treatment	NK	Yes	No	No

(*continued*)

Table 1. (Continued)

Included studies		*Methods*		*Participants*			*Interventions*		*Outcomes*			
Date of study	*First author*	*Double-blind*	*Settings*	n[a]	*Age (years)*	*Gender*	*Experiment group*	*Control group*	*Death*	*Clinical status*	*Quality of life*	*Adverse effect*
							shenmai injection 50 mL qd 15 days					
2003	Wu Quan[16]	Yes	H	39/32	50–81	M, F	Conventional medicine treatment plus *shenmai* injection 30 mL qd 10 days	Conventional medicine treatment	No	Yes	No	NK
2003	Xiang Shengyue[29]	Yes	H	40/38	58–85	M, F	Conventional medicine treatment plus *shenmai* injection 60 mL qd 14 days	Conventional medicine treatment	No	Yes	No	NK
2001	Yang Rongshi[32]	Yes	H	19/19	61–74	M, F	Conventional medicine treatment plus *shenmai* injection 40 mL qd 15 days	Conventional medicine treatment	No	Yes	No	No
2000	Ye Pingxian[17]	Yes	H	50/40	stratified	M, F	Conventional medicine treatment plus *shenmai* injection 60 mL qd 10 days	Conventional medicine treatment	Yes	Yes	No	No
2008	Ye Taiping[12]	Yes	H	40/34	52–85	M, F	Conventional medicine treatment plus *shenmai* injection 30 mL qd 7 days	Conventional medicine treatment	No	Yes	No	Yes
2000	Yun Wu[22]	Yes	H	30/30	61–90	M, F	Conventional medicine treatment plus *shenmai* injection 30 mL qd 7–10 days	Conventional medicine treatment	NK	Yes	No	No
2006	Zhang Xinhua[21]	Yes	H	30/30	55–78	M, F	Conventional medicine treatment plus *shenmai* injection 60 mL qd 14 days (no cardiotonic used)	Conventional medicine treatment (no cardiotonic used)	No	Yes	No	No
1998	Zhang Jinliang[33]	Yes	H	36/34	60–88	M, F	Conventional medicine treatment plus *shenmai* injection 40–60 mL qd 14 days	Conventional medicine treatment	No	Yes	No	No
2005	Zheng Wentao[34]	Yes	H	37/30	45–81	M, F	Conventional medicine treatment plus *shenmai* injection 30 mL qd 7 days	Conventional medicine treatment	No	Yes	No	No
2006	Zheng Qianwen[6]	Yes	H	60/60	48–84	M, F	Conventional medicine treatment plus *shenmai* injection 40 mL qd 14 days	Conventional medicine treatment	No	Yes	No	No

[a]In the *n* column, the number before the slash is the number of subjects in the conventional medicine treatment group and the number after the slash is the number of subjects in the *shenmai* injection plus conventional medicine treatment group.

H, hospital; NK, not known.

No trials assessed ability of daily living after treatment; some trials measured blood gas analysis and hemodynamic parameters.

Only injection was studied in these included trials. No trials were randomized, double blind, and placebo controlled. All included trials were designed comparing *shenmai* injection plus other treatment in the trial group with the same other treatment in the control group.

Study quality

The methodological quality of most included trials was generally "poor." Only one trial reported the method of randomization. No trials were randomized, double-blinded, placebo controlled. No trials on *Shenmai* had grade A level of adequate concealment of randomization. The remaining 31 possible randomized controlled trials (RCTs) did not describe the methods of randomization. No trials blinded the assessment of outcome. No trials reported the number of patients lost to follow-up and whether they had used intention-to-treat analysis. All trials did not mention blinding or intention-to-treat analysis.

Publication bias

Although comprehensive searches were conducted and an attempt was made to avoid bias, all trials found were published in Chinese. Therefore, potential publication bias could not be excluded.

Primary outcomes

Death. Deaths were reported in only five trials.[5,7–9,17] The total duration of treatment varied from 7 to 14 days. No death was reported in the remaining trials. There was a statistically significant difference between two groups (OR 0.33; 95% CI 0.14–0.78; Fig. 2).

Adverse events. The duration of treatment in all included studies was short (7–15 days). Outcomes were measured at the end of treatment. An adverse drug event was any unexpected or dangerous reaction to a drug. An unwanted effect was caused by the administration of a drug. The onset of the adverse reaction may be sudden or develop over time. No obvious adverse events occurred in 18 trials. Eleven (11) trials did not report adverse events. Five (5) trials reported adverse events.[3,8,10–12] These included dry mouth, limbs pain, drowsiness, allergic reaction, anorexia, and erubescence. Most of the adverse events were not severe. They disappeared without special treatment. The adverse events in the *shenmai* injection treatment group were higher than those in the control group; there was no statistically significant difference between the two groups. Although the authors did not find any related information about adverse effects recorded, potential or long-term adverse effects in the included trials could not be excluded.

Secondary outcomes

New York Heart Association classification of clinical status (NYHA class improved <1 class) in 32 trials (2564 patients) measured improvement in heart failure.[3–6,8–35] All the heart function classification systems use the NYHA functional classification. A meta-analysis of data on change of NYHA functional classification showed *shenmai* injection plus conventional treatment had more benefit compared with conventional treatment alone. The summary OR of NYHA class improved <I class, or worsening of heart failure was 0.24 (OR 0.24; 95% CI 0.19–0.30) (Fig. 3).

Hemodynamics. Five (5) trials provided data for Doppler echocardiography hemodynamic change.[3,14,28,32,35] At the end of treatment, *shenmai* injection plus conventional medicine treatment showed a significant increase in cardiac output (weighted mean difference [WMD] 0.91, 95% CI 0.74–1.07).[3,28,32,35] Three (3) trials showed a significant improvement in cardiac index (WMD 0.52, 95% CI 0.39–0.66).[3,28,35] Two (2) trials showed increased ejection fraction (WMD 10.55, 95% CI 8.42–12.68).[3,35] Two (2) trials showed increased stroke volume (WMD 17.48, 95% CI 7.30–27.66).[28,35] Three (3) trials showed a significant decrease in mean pulmonary arterial pressure (WMD 8.02, 95% CI -12.68 to -3.71).[3,14,32] One (1) trial showed a significant decrease on pulmonary vascular resistance (WMD -71.86, 95% CI -79.92 to -63.80) compared with usual treatment.[32]

Partial pressure of oxygen (PaO_2) and carbon dioxide ($PaCO_2$). Five (5) trials with 112 participants provided data for PaO_2 and four trials for $PaCO_2$ at the end of treatment.[6,9,23,25,32] *Shenmai* plus conventional treatment showed a significant increase in PaO_2 (WMD 8.58, 95% CI 7.70–9.46)

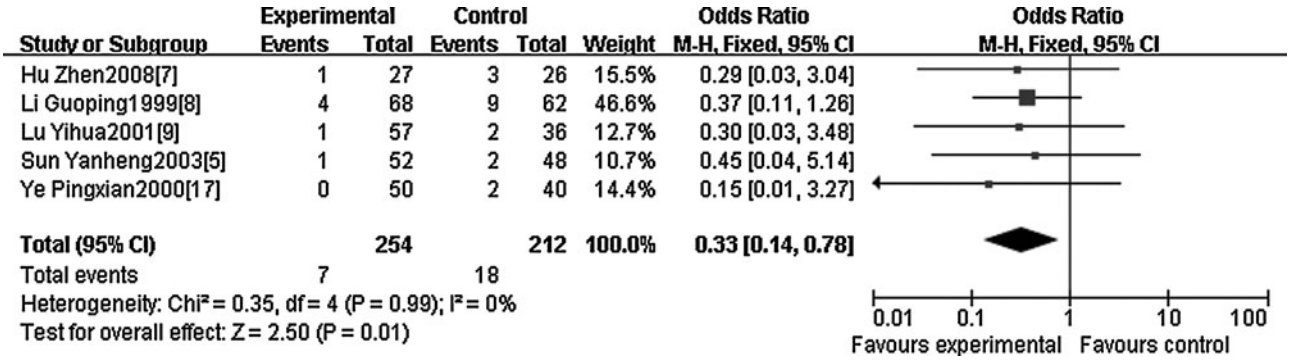

FIG. 2. Death events on five *shenmai* injections versus control. There was a statistically significant difference between two groups (odds ratio 0.33; 95% confidence interval [CI] 0.14–0.78). M-H, Mantel-Haenszel.

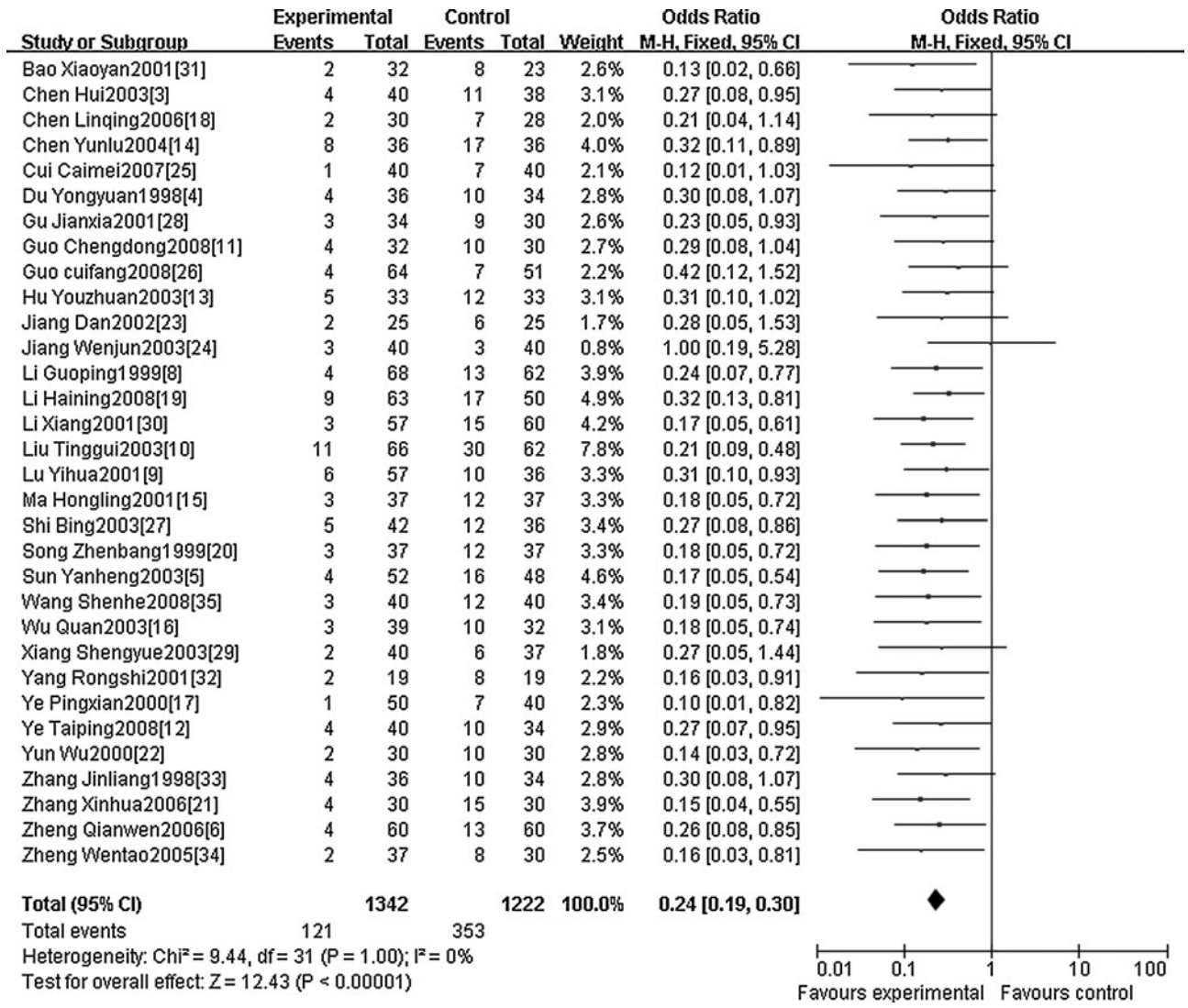

FIG. 3. Lack of improvement in heart failure after treatment by *shenmai* injection plus conventional treatment versus control (New York Heart Association [NYHA] class improved <I class or worsening of heart failure). Meta-analysis of these trials showed that the lack of improvement of NYHA classification of clinical heart function at the end of treatment between the two groups was significantly decreased with *shenmai* injection plus conventional treatment (odds ratio 0.24; 95% confidence interval [CI] 0.19–0.30). M-H, Mantel-Haenszel.

and a significant decrease in $PaCO_2$ (WMD 9.35, 95% CI -10.62 to -8.08) compared with usual treatment.

Quality of life. No trial assessed quality of life.

Discussion

For many years, Western medicine has made great progress and has become the dominating medical treatment worldwide. However, it has been increasingly recognized that Western medicine may sometimes fail to treat an illness, whereas such illness is reportedly improved by the so-called complementary and alternative medicine based on a different theory. This is often difficult to understand for Western doctors. Few relevant articles on TCM for CPHD have been published in the English language medical journals, and the limited evaluation of TCM outside of China reduces its external validity. However, TCM for CPHD is very popular in China, and *shenmai* injection is in regular use, not least because it is an effective, generally accepted, low-cost, specific treatment for the routine treatment of CPHD. Currently, there are more than 50 TCPM used for CPHD. *Shenmai* injection derives from a traditional decoction named *shenmai yin*. It originated from the "Thousand Pieces of Gold Formulae" in the Tang Dynasty, which was prescribed by a famous Chinese traditional medical scholar named Sun Simiao. From then on, it has been used in clinical practice for about 1500 years in China. In the past 30 years, it was made in different dosage forms such as injection and approved by the Chinese State Food and Drug Administration for CPHD. However, few researchers evaluated their effectiveness according to current rigorous international standards. Although there have been a few systematic reviews on other TCPM, no single study has assessed *shenmai* injection for CPHD. This review aimed

to assess the quantity, quality, and overall strength of evidence of *shenmai* injection for CPHD.

In this systematic review, there was very limited evidence from RCTs on the effect of *shenmai* injection on the primary efficacy outcome (death); there were just two truly randomized controlled trials. No definite conclusion can be drawn because of the limited numbers of patients in these two trials. Furthermore, for the other primary outcome, adverse effects, the data were reassuring. Although adverse events in the intervention groups were generally higher than in controls, the adverse reactions were mild and needed no further treatment.

It was found in the review that the recovery from heart failure was similar. The effect could be real or could just be attributable to bias, because lack of randomization or allocation concealment in a trial of a truly ineffective compound could yield similar estimates. Publication bias could also be a factor. However, because the methodological details for many of these trials were lacking, an attempt was made to contact authors to get further information by telephone, letter, or e-mail. Unfortunately, no replies were received from investigators, and it had to be inferred whether the trials were true RCT or not, although there was also no definite evidence to confirm this inference. Therefore, the results should be interpreted cautiously because of the unclear methodology of these trials. Similarly, no definite conclusion can be drawn from these trials.

Also, it was found that the case fatality rate is very low. Though the included patients have many complications, poor cardiac function, and senility, death occurred only in five trials. There are a number of possible explanations: a truly low case fatality rate for CPHD in China; the patients with severe disease were not sent to hospitals (admission bias); a reluctance on the part of physicians to include patients with severe disease in research studies (selection bias); or failure to report major outcome events (reporting bias); and only trials with low mortality rates submitted their results for publication (publication bias). It was not possible to determine which of these factors pertained. The evidence on the effects on death in the small number of trials that reported deaths were not regarded as reliable. The observed positive results on death might be attributable to lack of true randomization and/or chance. Therefore, the general lack of reporting of methodology in the trials publication is not consistent with the Consolidated Standards of Reporting Trials (CONSORT) statement on the reporting of the results of randomized trials; this requirement is being highlighted in many journals around the world but clearly needs additional emphasis in China.

The methodological quality of most included trials was generally "poor" because they did not describe their methods in detail. The limitations of most trials were as follows. In the majority, it was not certain whether or not treatment allocation was truly randomized and well concealed (selection bias); measures at the level of activities of daily living were the primary outcome and the preferred primary outcomes for CPHD trials, yet most trials were focused on effects on improvement in heart failure (the secondary outcome measure), blood gas analysis, hemodynamic parameters, and so on. It was unclear whether most trials had used a blinded method to assess outcome. Finally, some trials did not report the frequency of adverse events.

Conclusions

In conclusion, because of the unclear methodological quality of these identified trials, a definite conclusion on efficacy and adverse events associated with *shenmai* injection cannot be drawn from this review. No evidence was found of a beneficial effect on the primary measure of efficacy to support the routine use of *shenmai* injection for CPHD. However, the agents appeared to be relatively free of major adverse effects, and if the apparently beneficial effects on improvement of heart function were confirmed in methodologically rigorous trials, they would lead to many useful treatments for CPHD being identified and used outside China. Therefore, further high-quality, large-scale, randomized trials of *shenmai* injection for CPHD are justified to confirm or refute the effects reported here. Future trials should overcome the limitations of the trials presented in this review; in particular, they should assure adequate concealment of allocation, blinding of outcome assessors, and use functional outcome as the primary outcome measured at long-term follow-up. Reports of the trials should conform to the recommendations of the CONSORT statement. If such RCTs designed reliably confirmed that *shenmai* injections are beneficial for CPHD, this would contribute greatly to the treatment of CPHD worldwide.

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Disclosure Statement

No competing financial interests exist.

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