

• CLINICAL RESEARCH •

Effect of integrated traditional Chinese and Western medicine on SARS: A review of clinical evidence

Ming-Ming Zhang, Xue-Mei Liu, Lin He

Ming-Ming Zhang, Chinese Evidence-Based Medicine Center, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

Xue-Mei Liu, Editorial Department, Chinese Journal of Evidence-Based Medicine, Chinese Evidence-Based Medicine Center, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

Lin He, Library of West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

Correspondence to: Mrs. Xue-Mei Liu, Editorial Department, Chinese Journal of Evidence-Based Medicine, Chinese Evidence-Based Medicine Center, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China. cochrane@mail.sc.cninfo.net

Telephone: +86-28-85422079 **Fax:** +86-28-85422253

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Abstract

AIM: To assess the possible effect of integrated traditional Chinese and Western medicine on severe acute respiratory syndromes.

METHODS: The current available randomized controlled trials of integrated traditional Chinese and Western medicine on SARS were identified through systematically searching literature in any languages or any types of publications. Additional studies of gray literature were also collected. The quality of studies was evaluated by two investigators independently based largely on the quality criteria specified CONSORT. Statistical analysis of the results was performed using RevMan 4.2.0 software developed by the Cochrane Collaboration.

RESULTS: Six studies ($n = 366$) fulfilling the inclusion criteria were found, of which the quality of one study was graded as B, the remaining five were graded as C. Two studies were performed with meta-analysis, the other four studies existed some heterogeneity for which meta-analysis could not be performed, a significant effect on lung infiltrate absorption was found in the treatment groups of these two studies [RR 6.68, 95% CI (2.93, 15.24), $P < 0.01$], there was no significant differences between the mortality [RR 0.86, 95% CI (0.22, 3.29), $P = 0.82$] and the average dosage of corticosteroid [WMD -39.65, 95% CI (-116.84, 37.54), $P = 0.31$]. The other three studies also showed significant differences in infiltrate absorption, including national drug No. 2, 3, 4 in combination with Western medicine [RR 5.45, 95% CI (1.54, 19.26)], compound formulas NO. 1 combined with Western medicine [WMD 0.24, 95% CI (0.02, 0.46)], compound formulas combined with Western medicine [RR 8.06, 95% CI (0.40, 163.21)]. Kangfeidian No.4 in combination with Western medicine had no significant effect on symptom improvement such as loss of dyspnea and cough [RR 1.50, 95% CI (0.41, 5.43)] and [RR 1.29, 95% CI (0.30, 5.43)].

CONCLUSION: Integrated traditional Chinese and Western medicines has some positive effects on lung infiltrate absorption in SARS patients, and is recommended as an adjunct treatment

for SARS. However, its effect on SARS requires further careful study due to limited available randomized control trials.

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INTRODUCTION

Severe acute respiratory syndromes (SARS) is a readily transmissible new disease emerged in the 21st century that imposes a threat to international health^[1-3]. SARS is caused by a novel coronavirus, first identified in Hong Kong, United States of American and Germany. It is due to an infection with SARS associated coronavirus (SARS-CoV). The genome of SARS-CoV is 29 727 nucleotides in length and has 11 open reading frames, and its genome organization is similar to that of other coronaviruses^[4-7]. SARS is an acute respiratory illness with typical symptoms of fever, cough and difficult breathing. Besides, it may be associated with other symptoms, such as headache, muscular stiffness, myalgia, loss of appetite, malaise, chills, confusion, dizziness, rash, night sweat, nausea and diarrhea. SARS can be divided into 5 types and 4 stages. The 5 types are common type (typical type), mild type, severe type and more severe type. The four stages are potential stage (2-10 d), initial stage (1-7 d), developing stage (8-14 d), and recovery stage (1-14 d), which are classified based on the developing process of SARS patient conditions by the criteria of Western medicine. SARS can also be divided as initial stage (1-5 d), acute stage (3-10 d), critical stage (7-14 d) and recovery stage (10-18 d) based on the theory of traditional Chinese medicine^[8-11].

SARS demonstrates dramatically the global havoc that its epidemic had broken out worldwide including mainland China, Taiwan, Hong Kong, Vietnam, Singapore, Macao, North American and Europe when the first case was found in Foshan city, Guangdong Province, China on November 16, 2002. Airborne droplets from SARS patients are the main transmission routes. Based on the data from WHO. SARS epidemic appears to have peaked and is on the wane^[12,13]. A total of 916 SARS patients died in 8 422 cases and the mortality was about 11%. A total of 5 327 SARS patients occurred in mainland China and 349 of them died, the mortality was about 7%. A total of 1 755 SARS patients occurred in Hong Kong Special Administrative Region, China and 300 of them died, the mortality was about 17%. A total of 655 SARS patients occurred in Taiwan, China and 180 of them died, the mortality was 27%. The case fatality ratio was estimated to be less than 1% in persons aged 24 years or younger, 6% in persons aged 25 to 44 years, 15% in persons aged 45 to 64 years, and greater than 50% in persons aged 65 years and older^[14,15].

Western medicine for SARS

The treatment of SARS involves multiple disciplines, and current recommendations are mainly based on the methods of Western medicine including aliment therapy, respiratory

auxiliary ventilation, anti-infection and glucocorticoid therapy. The effectiveness for SARS was limited especially in the first and recovery stages. For example, in severe cases, corticosteroids and ribavirin (antiviral medication) were used, however there was no evidence to support their general or routine use at this stage and to confirm the risks and benefits of Western medicine in the treatment of SARS. Selective therapies included the use of antiviral agents, immunopotentiators and Chinese herbs^[8,9,11,15]

Chinese herbs in combination with western medicine for SARS

Traditional Chinese medicine (TCM) is a useful model for scientific therapies and has been practiced worldwide. Among the components of TCM, herbal agents possess complex biological activities. In the theory of TCM, herbs preparations might resolve toxin, eliminate pathological dampness, disperse the lung, invigorate the blood circulation and resolve the blood stasis, benefit Qi and nourish Yin^[16,17]. Based on this principle, Chinese practitioners suspected that SARS was caused by pestilential toxin, one of the important characteristics of SARS. Nine traditional Chinese patent medicines are optimized for controlling different symptoms of SARS. Compared with the simple treatment of Western medicine, Chinese medicine in combination with Western medicine for SARS may have better effects in that it may reduce the adverse events induced by anti-biotic and anti-virus treatments and other complications, shorten fever period and hospital stay, promote lung infiltrate absorption and decrease damage to the lung^[18-20]. The 5 kinds of herbs are Kangfeidian No.1,2,3^[29,34], compound formula No.1^[32], national drugs No.2,3,4^[31], compound herbs^[30], Kangfeidian No.4^[33]. Unfortunately, no strong evidence is available to demonstrate the benefits and risks of Chinese herbs in combination with Western medicine for SARS.

This review evaluated the possible effect of Chinese herbs in combination with Western medicine for SARS, summarized randomized controlled trials (RCT) and methods of integrated traditional Chinese and Western medicine for SARS, as well as a recommendation for future research.

MATERIALS AND METHODS

Data collection

A comprehensive searching strategy was used to identify all current relevant RCTs regardless of languages or types of publication (published, unpublished, in press, and in progress). We searched MEDLINE for relevant trials (1966 to 2003), EMBASE (1980 to 2003), CBM (Chinese Biomedical Database, 1981 to 2003), Chinese Cochrane Centre Controlled Trial Register (up to 2003), Cochrane Controlled Trial Register in Cochrane Library (issues 1 to 4, 2003), Current Controlled Trials and The National Research Register. The search terms were: "severe acute respiratory syndrome", "acute respiratory syndrome", "randomized-controlled-trial", "random allocation" "double blind method", "single blind method", "placebo", "herbs", "Chinese medicinal".

The references of relevant trials and reviews were identified and RCTs in the Database of Chinese Evidence-Based Medicine Center and in journals not included in this Database were manually searched. We also checked the citations of existing reviews and all studies identified by the above methods. The authors of identified literature and relevant specialists were contacted for additional information.

Types of studies and participants

Only randomized controlled trials of Chinese herbs in combination with Western medicine for SARS were included regardless of blinding, follow up, language or publication status. The followings were excluded such as clinical controlled trials of SARS patients that failed to allocate into either trial, control group, case study or animal experiments.

Only randomized controlled trials of Chinese herbs in combination with Western medicine for the diagnosis of SARS patients with standard criteria of WHO in 2003 were included. Moreover, those SARS patients complicated with other diseases such as diabetes, cardiovascular disease, hypertension, or cancers were also included. The suspected SARS patients and misdiagnosed patients were excluded.

Quality assessment

We screened the titles, abstracts, and keywords of every document retrieved to determine the quality of the papers. We retrieved the full articles for further assessment if the information given suggested that the study included diagnosed SARS patients; compared Chinese herbs in combination with Western medicine with placebo, Chinese herbs, Western medicine or any other active intervention; used random allocation to the comparison groups. Where differences in opinion existed, we would solve them through discussion. If we were unable to solve the disagreement through discussion, we would contact the authors for clarification.

The quality of each trial was assessed based largely on the quality criteria specified CONSORT^[21]. In particular, the following factors were assessed^[22,23] such as minimization of selection bias, minimization of performance bias, minimization of attrition bias, and minimization of detection bias. Based on these criteria, studies were subdivided into the following three categories^[23]: low risk of bias which met all quality criteria graded as A, moderate risk of bias which met one or more of the quality criteria graded as B, high risk of bias which did not meet one or more criteria graded as C.

Statistical analysis

Data were extracted independently by two investigators with a standardized form and analyzed using RevMan 4.2.0 software developed by the Cochrane Collaboration^[23,24]. Heterogeneity was tested using the *Z score* and the *Chi square*. Statistical significance was set at $P < 0.05$. We performed a meta-analysis for the data. The dichotomous data expressed as relative risk (RR). The continuous data expressed as weighted mean difference (WMD). We calculated the overall results based on the random effect model.

Hypothesis

When data were pooled, we hypothesized that all Western medicine interventions used in control and trial groups had the same effect on all the outcome measures indexed in this review.

RESULTS

Studies identified

The initial searching using the electronic search strategy listed above and manual searching yielded 650 studies. After scanned, 48 studies of Chinese herbs in combination with Western medicine for SARS were identified to meet the inclusion criteria. Most of the studies were published in Chinese. Of the 48 studies, one study of clinical report on the suspected SARS patients was excluded upon further scrutiny and the other 28 case reports and 9 case control studies were identified. There were 10 RCT studies identified. Because of some reasons, we did not obtain the complete report of studies. Further exclusion included one study identified as randomized sample, but not randomization allocation^[25], one study which compared Western medicine versus Western medicine for SARS^[26] and the other two studies which were duplicate publication^[27,28]. Finally, 6 RCT studies of Chinese herbs in combination with Western medicine fulfilling the inclusion criteria were identified^[29-34].

Six studies ($n = 366$) were included^[29-34]. The details of the designs of these studies are shown in Table 2. All six studies

were conducted in China. The median time of treatment was 17 d. Four studies reported the number of patients in common type and severe type^[29-31,34]; two studies performed a meta-analysis, the data were sufficient in quality, and similar^[29,34]. One study was Western medicine plus compound herbs^[32]; the other three studies were about Western medicine plus national drugs 2,3,4^[30-32] and Kangfeidian No.4^[33]. The constituents and dosage of Chinese herbs varied. Most of the studies with the heterogeneity of intervention prevented us from doing a meta-analysis and a meaningful subgroup analysis on Chinese herbs.

Study methodology

Most of the included studies had poor quality ('C')^[29-31,33,34] one study was graded as B^[32] (Table 1).

All of the studies claimed as randomization, but none of them described the method of randomization in details, and none of the studies referred allocation concealment. Of the six studies, one described its design in detailed randomization process and the baseline data were reported adequately^[32]. Two

studies were described as stratified randomization^[31,33] and the other three studies only mentioned 'randomization'^[29,30,34]. Withdrawals and loss of follow-up were not reported in six studies and none of the studies reported intention-to-treat analysis.

No adverse events of Chinese herbs were observed in the included studies. Only one study reported the quality of life as result index^[32]. The effect of integrated traditional Chinese medicine and Western medicine for SARS see Table 2.

Mortality

The mortality^[29-31,34] was reported in 4 studies.

National drugs No. 2, 3, 4 in combination with Western medicine did not show a significant difference on mortality compared to simple Western medicine (RR 0.41, 95% CI 0.04, 4.78).

Kangfeidian No. 1, 2, 3 in combination with Western medicine was tested in two studies^[29,34] which used the same dosage and treatment time and had the same outcome. Compared to simple Western medicine, there was no significant effect on mortality [RR 0.86, 95% CI (0.22, 3.29), $P=0.82$, Table 3].

Table 1 Design of the RCTs of traditional Chinese medicine in combination with Western medicine for SARS

Study ID	Grade of method	Participants (case)				Trial interventions	Control interventions	Duration	Follow up	Main results
		Common type		Severe type						
Zhao CH 2003	C	51	26			Western medicine plus compound herbs of kangfeidian No.1,2,3.	Western medicine	14-21d	No	Mortality, lung infiltrate absorption, symptom improvement, dosage of glucocorticosteroids.
Wang BE 2003	C	Trial 13	Control 17	Trial 18	Control 12	Western medicine plus compound herbs.	Western medicine	10-20 d	No	Mortality, lung infiltrate absorption, Secondary infections, dosage of methyprednisolone, SO ₂ ,
Wang RB 2003	C	Trial 5	Control 7	Trial 30	Control 23	Western medicine plus national drug No.2,3,4.	Western medicine	14 d	No	Mortality, lung infiltrate absorption, Secondary infections, symptom improvement
Jiang ZY 2003	B	40				Western medicine plus compound herbs No.1,2,3.	Western medicine	21 d or so	Yes	Lung infiltrate absorption, symptom improvement, quality of life
Zhang SN 2003	C	63				Western medicine plus kangfeidian No.4	Western medicine	7 d	No	Dose of glucocorticoid, lung infiltrate absorption, symptom improvement
Zhang XM 2003	C	Trial 7	Control 9	Trial 24	Control 23	Western medicine plus compound herbs of kangfeidian No.1,2,3.	Western medicine	21 d	No	Mortality, lung infiltrate absorption, symptom improvement, dose of glucocorticoid, length of fever

Table 2 Results of meta-analysis of integrated traditional Chinese and Western medicine for SARS at the end of treatment

Comparison or outcomes	Study	Participants			Statistical method	Effect estimate
		Total	Trial	Control		
National drugs No.2.3.4 combined with Western medicine versus Western medicine						
Mortality	Wang RB 2003	65	1/35	2/30	RR (fixed) 95%	0.41 (0.04, 4.78)
Lung infiltrate absorption		53	25/30	11/23		5.45 (1.54, 19.26)
The secondary infection		65	4/35	7/30		0.42 (0.11, 1.62)
Compound formulas No.1 combined with Western medicine versus Western medicine						
Symptom improvement integral	Jiang ZY 2003	40	7.90 (5.81)	6.50 (3.83)	WMD (fixed) 95%	1.40 (-1.65, 4.45)
Lung infiltrate absorption		40	0.65 (0.35)	0.38 (0.37)		0.24 (0.02, 0.46)
Quality of life integral		40	19.93 (3.69)	22.10 (4.90)		-2.17 (-4.86, 0.52)
Compound formulas combined with Western medicine versus Western medicine						
Lung infiltrate absorption	Wang BN 2003	59	30/30	26/29	RR (fixed) 95%	8.06 (0.40, 163.21)
Kangfeidian No.4 combined with Western medicine versus Western medicine						
Loss of dyspnea	Zhang SN 2003	38	12/20	9/18	RR (fixed) 95%	1.50 (0.41, 5.43)
Loss of cough		30	9/16	7/14		1.29 (0.30, 5.43)

Table 3 Effect of Kangfeidian No.1,2, 3 with Western medicine in SARS patients

Outcome measure	Kangfeidian No.1, 2, 3 combined with Western medicine	Western medicine alone	Relative risk (95% CI)	P	Reference
Mortality	(n/N)				
	4/31	4/32	1.04 (0.24, 4.57)		Zhang XM <i>et al.</i> (2003)
	0/37	1/39	0.34 (0.01, 8.67)		
Overall	4/68	5/71	0.86 (0.22, 3.29)	0.82	
Lung infiltrate	27/31	18/32	5.25 (1.49, 18.53)		Zhao CH <i>et al.</i> (2003)
Absorbing	22/37	6/39	8.07 (2.71, 23.98)		
Overall	49/68	24/71	6.68 (2.93, 15.24)	<0.00001	Zhao CH <i>et al.</i> (2003)
The average Dosage of	N (mean±SD)		WMD(95% CI)		
Glucocorticosteroids	31 (304.13±143.42)	32 (347.40±173.10)	-43.27 (-121.67, 35.13)		Zhang XM <i>et al.</i> (2003)
	15 (1 400.00±685.00)	20 (1 325.00±623.00)	75.00 (-366.27, 516.27)		Zhao CH <i>et al.</i> (2003)
Overall	46	52	-39.65 (-116.84, 37.54)	0.31	

Lung infiltrate absorption

Six studies reported the effect of Chinese herbs in combination with Western medicine on the lung infiltrate absorption^[29,34]. Of the six studies, three reported that Chinese herbs in combination with Western medicine had a better effect than simple Western medicine^[29,31,34].

National drugs No. 2. 3. 4 in combination with Western medicine^[31] showed a significant difference in lung infiltrate absorption [RR 5.45, 95% CI (1.54, 19.26)]. Kangfeidian No. 1. 2. 3 in combination with Western medicine^[29,34] showed a better positive effect on lung infiltrate absorption [RR 6.68, 95% CI (2.93, 15.24), $P < 0.01$] (Table 3). In the original study^[34], $n = 31$ in treatment group, $n = 32$ in control group, 21 d after treatment with Kangfeidian No. 1. 2. 3 in combination with Western medicine, symptoms were improved by 87% in treatment group, and 56% in control group. In the original study, $n = 77$ ^[29], it was reported that the lung infiltrate absorption was less two days in treatment group. In treatment group $n = 22$, the basic absorption time (16 ± 8.8 d) and in control group $n = 6$, the basic absorption time (18.4 ± 8.2 d).

Compound formulas No 1. in combination with Western medicine^[32] showed no significant difference in lung infiltrate absorption between treatment group and control group [WMD 0.24, 95% CI (0.02, 0.46)]. Compound formulas in combination with Western medicine^[31] showed a positive effect on lung

infiltrate absorption [RR 8.06, 95% CI (0.40, 163.21)].

Dosage of glucocorticosteroids

Kangfeidian No. 1. 2. 3 in combination with Western medicine versus Western medicine^[29,34] for SARS showed no significant effect on the treatment group [WMD -39.65, 95% CI (-116.84, 37.54) $P = 0.31$] (Table 3).

Additional results

Kangfeidian No 4 combined with Western medicine versus Western medicine^[33] showed no significant effects on loss of dyspnea [RR 1.50, 95% CI (0.41, 5.43)] and loss of cough [RR 1.29, 95% CI (0.30, 5.43)] (Table 3).

DISCUSSION

Standard treatment and outcome index

To assess accurately any potential benefits and risks in the treatment of SARS, treatment of Chinese herbs must be scientifically evaluated. Standard treatment and outcome index need to be developed, based on the principles used by the Chinese herb practitioners. For example, criteria for the dosage and components of compound herbs, duration of treatment, withdrawal and follow up, treatment protocols should be adjusted according to the conditions of patients^[35,36]. In the six

studies, none of them were standardized and one study described not any details on the dosage and components of compound herbs^[33]. Principal criteria for outcome index are another important issue to be taken into account, such as mortality, symptom improvement, lung infiltrate absorption, quality of life and adverse events. The six studies varied in outcome index.

Treatments to be tested should be selected and standardized so that potentially effective and important treatments are evaluated first. The best evidence should be systematically reviewed, summarized, and disseminated, which in turn would lead to evidence-based decision making in traditional Chinese medicine.

Long term studies

Most of the current studies had a short duration, ranging from 7 to 21 d and a small sample size. All studies did not report data on compliance and follow up. As a new kind of respiratory disease many unknown factors remain to be solved. SARS is likely to require a longer period of follow-up. Based on the current investigation, Chinese herbs may also be considered as an adjuvant treatment to improve the quality of life. Meanwhile, whether herbs have any toxic effects should also be considered and attention should be paid to their long-term adverse events. For example, adverse events should be monitored by a standardized effective reporting system in clinical trials and some severe adverse events should also be studied or observed by epidemiological studies.

Adequate randomization method

SARS is a sudden outbreak disease. It is somewhat difficulty for us to conduct RCT, particularly in acute or critical stage. The current six RCTs conducted suggest that it is a promising work. However, a well designed RCT requires a thorough understanding of randomization so that better research results could be achieved.

Randomization includes 3 important steps: namely sequence generation, allocation concealment and randomization implementation^[37]. Sequence generation is a method used to generate the random allocation sequence, including details of any restriction. Allocation concealment is to implement the random allocation sequence. Randomization implementation is to generate the allocation sequence. Well designed RCTs are required to evaluate Chinese herbs combined with Western medicine versus Western medicine.

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