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Effect of integrative medicines on 28-day mortality from sepsis: a systematic review and network meta-analysis

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Abstract. – OBJECTIVE: The aim is to perform a network meta-analysis to evaluate the effect of different Chinese medicines combined with Western medicine treatment (WMT) on the 28-day mortality of patients with sepsis.

MATERIALS AND METHODS: We searched multiple databases for randomized controlled trials (RCTs), using keywords such as sepsis, Shenfu, Shenmai, Shengmai, Dahuang Fuzi, Xuebijing, and mortality. The databases we searched included the China Knowledge Network (CNKI), Wanfang database, the Chinese scientific journal database (VIP), the Chinese biomedical literature database (CBM), PubMed, Embase and Cochrane. The collection time was from inception through September 22, 2020. Two researchers independently screened the articles, extracted data, and assessed the quality of the evidence. Stata15 was used for network meta-analysis, and Excel was used to summarize the list of adverse reactions.

RESULTS: Twenty-nine studies with a total of 3201 patients were included in this study. Combined with WMT, Shenfu injection [OR = 0.63, 95% CI = (0.47, 0.83)] and Xuebijing injection [OR = 0.71, 95% CI = (0.52, 0.96)] can significantly reduce 28-day mortality among patients with sepsis, while Shenmai injection [OR = 0.40, 95% CI = (0.16, 1.03)] and Dahuang Fuzi decoction [OR = 1.00, 95% CI = (0.48, 2.10)] cannot significantly improve on the 28-day mortality. The efficacy ranking is as follows: Shenmai group (level of evidence: low) > Shenfu group (level of evidence: low) > Xuebijing group (level of evidence: very low) > WMT group > Dahuangfuzi group (level of evidence: very low).

CONCLUSIONS: Combined with WMT, Shenfu injection or Xuebijing injection can reduce the 28-day mortality among patients with sepsis. The Shenfu group had the best effect on outcomes, and its level of evidence was higher than that of the Xuebijing group.

Key Words:
Integrative medicines, Sepsis, 28-day mortality, Network meta-analysis.

Introduction

Sepsis is a symptom of imbalance in a host's response to infection, which results in life-threatening organ damage[1], and it has a high rate of morbidity and mortality[2]. It is currently believed that inflammatory response combined with immunosuppression is a common factor that causes sepsis[3]; cytokine storms are a direct cause of sepsis[4]; and vascular endothelial injury and microthrombosis directly cause organ dysfunction after sepsis[5]. Therefore, patients with sepsis need bundled treatments, including anti-infection, immune regulation, anti-coagulation, and organ protective interventions, among which anti-infection is the most critical[6]. However, some studies[7,8] have shown that there has been no significant reduction in the mortality rate for sepsis treated by Western medicine in the past 10 years, despite the continuous updating of sepsis diagnosis and treatment.

In China, traditional Chinese medicine combined with Western medicine treatment (WMT) is often used in treating sepsis. Clinical studies[9-12]

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have shown that Shenfu injection, Shenmai injection, Xuebijing injection, Dahuang Fuzi decoction and other traditional Chinese medicine preparations can reduce the 28-day mortality of patients with sepsis, and some conclusions have been supported by meta-analysis[11,12].

Shenfu injection is derived from the ancient formula "Shenfu Tang", which is composed of Renshen and Fuzi and has the effects of recuperating depleted Yang and rescuing patients from collapse, thus replenishing Qi. Dahuang Fuzi Tang is derived from the "Synopsis of Golden Chamber" by Zhang Zhongjing, a medical sage. It consists of Dahuang, Pao Fuzi and Xixin, with the effects of warming up Yang-Qi, dispersing pathogenic cold to resolve masses, eliminating the accumulation of toxins, and alleviating pain. Xuebijing injection uses an effective substance extracted from Honghua, Chishao, Chuanxiong, Danshen and Danggui through modern science and technology and has the effects of resolving blood stasis and detoxification. Modern pharmacology has confirmed that these four prescriptions have anti-shock effects.

However, the existing reports consist of the meta-analysis reporting on the efficacy of two of these treatments in sepsis, while a network meta-analysis that could compare the effects of multiple Chinese medicines on the 28-day mortality of sepsis has not yet been reported. This study uses the network meta-analysis method to rank the efficacy of these integrative medicines used in the treatment of sepsis to reduce 28-day mortality and to provide a reliable evidence-based approach for clinical use.

Materials and Methods

This network meta-analysis was performed according to the Cochrane Handbook for Systematic Reviews of Interventions. The protocol for this study is available in PROSPERO (CRD42020192371).

Inclusion and Exclusion Criteria

The inclusion criteria were identified by the Participants, Interventions, Comparisons, Outcomes, and Study design (PICOS) framework: (1) Participants: adults diagnosed with sepsis. (2) Intervention and Comparisons: The control group was treated with Western medicine treatment (WMT). Each treatment group was treated with one or more Chinese medicines in addition to the WMT of the control group; treatments included Shenfu injection, Shenmai injection, Shengmai injection, Dahuang Fuzi decoction, and Xuebijing injection. (3) Outcomes: Twenty-eight-day mortality was the primary outcome because the impact of adverse reactions was far less than that of death. The secondary outcome was adverse reactions. (4) Study design: RCTs.

The exclusion criteria were as follows: (1) low quality studies (judgement criteria are detailed below, in 2.4. Evaluation method for literature quality); (2) inability to obtain relevant data or the full text; (3) repeated publication; (4) only 1 study was included; and (5) unreliable data.

Search Strategy

The Chinese scientific journal database (VIP), the Chinese biomedical literature database (CBM), the China Knowledge Network (CNKI), the Wanfang database, PubMed, Embase, and Cochrane were searched from inception through September 22, 2020. The language was Chinese or English. The search parameters were as follows (an example from Embase):

1) 'sepsis'/exp OR 'pyemia':ab, ti OR 'pyemias':ab, ti OR 'pyohemia':ab, ti OR 'pyohemias':ab, ti OR 'pyaemia':ab, ti OR 'pyaemias':ab, ti OR 'septicemia':ab, ti OR 'septicemias':ab, ti OR 'poisoning, blood':ab, ti OR 'blood poisoning':ab, ti OR 'blood poisonings':ab, ti OR 'poisonings, blood':ab, ti OR 'severe sepsis':ab, ti OR 'sepsis, severe':ab, ti OR 'septic shock':ab, ti OR

2) 'shenfu':ab, ti OR 'shenmai':ab, ti OR 'dahuang fuzi':ab, ti OR 'shengmai':ab, ti OR 'xuebijing':ab, ti

3) 'mortality'/exp OR 'mortalities':ab, ti OR 'case fatality rate':ab, ti OR 'case fatality rates':ab, ti OR 'rate, case fatality':ab, ti OR 'rates, case fatality':ab, ti OR 'death rate':ab, ti OR 'death rates':ab, ti OR 'rate, death':ab, ti OR 'rates, death':ab, ti OR 'mortality rate':ab, ti OR 'mortality rates':ab, ti OR 'rate, mortality':ab, ti OR 'rates, mortality':ab, ti

4) #1 AND #2 AND #3 AND [randomized controlled trial]/lim

Data Extraction and Assessment

Data were independently extracted and entered into a data-collection form by two reviewers (Chen Huilin and Li Zhen). After extraction, any disagreements were resolved by consulting a third reviewer (Yang Yuedong). For missing data, the author was contacted by email or phone to obtain the information. When the author could not

be contacted, the literature was excluded. Study ID, time of publication, language, sample, gender, age, intervention, disease course, and outcomes were included.

Evaluation Method for Literature Quality

The Cochrane risk of bias assessment was used to evaluate the risk of bias. Trials were considered high quality if they included randomization sequence generation, the blinding of participants and personnel, and the blinding of outcome assessments, which were assessed as having a low risk of bias according to the study parameters of Zhao et al[13]. When 7 risk of bias items in the literature were evaluated as low risk, it was recorded as 0 points; if there was 1 high-risk item among the 7 items, then it was recorded as -2 points; and the rest were recorded as -1 point. This score was used to GRADE each study's evidence level.

Network Meta-Analysis

Homogeneity and similarity were tested from the perspective of clinical (PICOS) and methodology (research design and quality), and homogeneity was tested by statistics (I^2). If the PICOS research design and quality were the same or similar, and if I^2 <50%, then network meta-analysis was performed. Other, heterogeneous literature was identified and excluded. Consistency: If there was a closed loop, the dot method was used to test for inconsistency.

This network meta-analysis was based on the frequency method, and selected odds ratios (ORs) and 95% CIs were used for calculation. Stata 15.0 software was used to evaluate the curative effect of different Chinese medicines on the 28-day mortality of sepsis by using a random effects model and to draw the network evidence plot, the cumulative ranking graph, and the funnel plot.

Network evidence plot: Scattered points represent different interventions, and the size of the points represents their corresponding sample. The line between the two points represents a direct comparison, and the thickness of the line represents the number of corresponding original studies. The yellow line indicates that at least one original study was blinded or a multicentre study, and the green line indicates that the related studies were all unblinded and single-centre studies.

Cumulative ranking probability graph: Surface under cumulative ranking (SUCRA) was used to evaluate the cumulative ranking probability of different treatments. The larger the SUCRA was, the higher its corresponding ranking.

Funnel plot: The horizontal axis shows the difference in the effect value, and the vertical axis shows the standard error of the effect value. If the included studies were symmetrically distributed on both sides of the vertical line at X = 0 and were within 95% CIs, then the publication bias was small. Otherwise, the publication bias was greater. Dots with different colours indicate different types of research, and the number of dots of the same colour represents the number of studies.

GRADE Evidence Level

The GRADE evidence level includes 5 items: study limitations, imprecision, inconsistency, indirectness, and publication bias. Study limitations: The respective literature quality evaluation scores (ROB results) and the corresponding proportions of the network contribution estimates were multiplied to obtain the initial score, and the initial scores were added to obtain the final score, which was then rounded up. The item was not downgraded if it had 0 points, it was downgraded by one level if it had -1 points, and it was downgraded by two levels if it had -2 points. Imprecision: An RR value <0.75 was used as the standard. An item was not downgraded if it met the standard; otherwise, it was downgraded by one level. Inconsistency: I^2 and p-values were used for evaluation. The item was not downgraded if there was no heterogeneity; otherwise, it was downgraded by one level. Indirectness: the consistency of the PICOS among the groups was compared. An item was not downgraded if the groups were consistent; otherwise, it was downgraded by one level. Publication bias: a funnel graph was used to qualitatively assess publication bias. The item was not downgraded if publication bias existed. When publication bias did not exist or the original research included fewer than 10 studies, it was downgraded by one level.

Results

Results of the Search

A total of 915 studies (206 records from CNKI, 265 records from WANGFANG, 227 records from VIP, 201 records from CBM, 5 records from PubMed, and 11 records from Embase) were retrieved from the Chinese and English databases, and 0 were obtained from other sources. After duplicate studies were removed, 330 studies were retained. Ultimately, 29 studies[14-42] were included in the study based on the inclusion and exclusion criteria (Figure 1). In particular, "Shengmai injec-

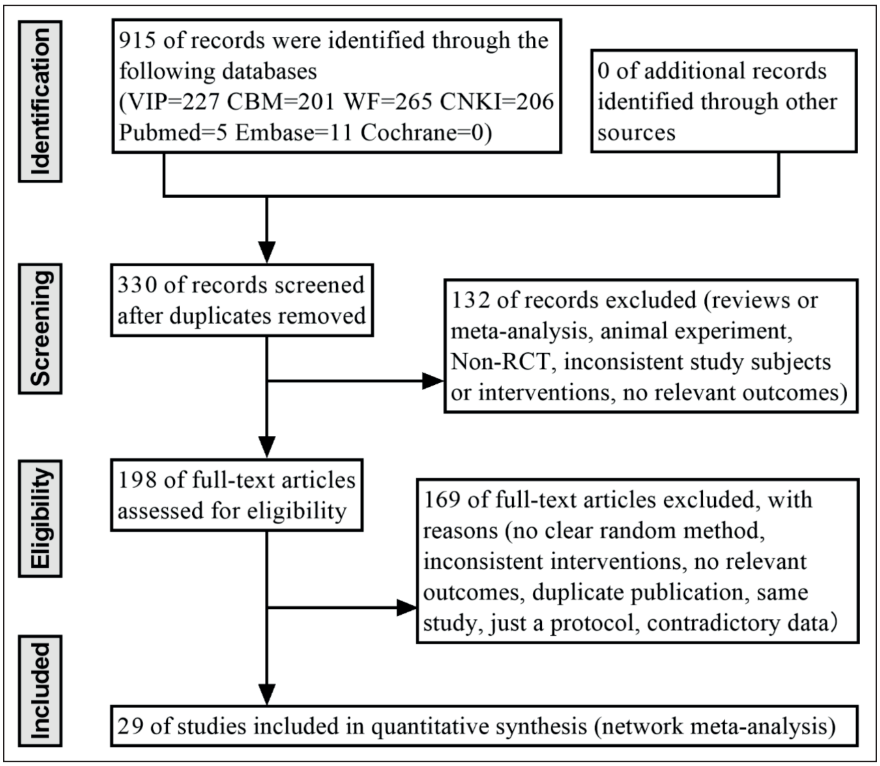

Figure 1. Flowchart of the study-selection process.

tion", "Xuebijing injection combined with Shenfu injection" and "Xuebijing injection combined with Dahuang Fuzi Decoction" were excluded, with only 1 study remaining in the end.

Characteristics of Included Studies

Among the final studies included, there were 27 Chinese studies[14-17,19,20,22-42] and 2 English studies[18,21], both of which were dual-arm studies (Table I). Shenfu injection[14-25], Shenmai injection[26,27], Dahuang Fuzi decoction[28,29], and Xuebijing injection[30-42] were included in these studies.

Evaluation of Study Quality

Randomization sequence generation: All studies had clear, random methods, so all the studies were low risk. Allocation concealment: Only 1 study used allocated concealment, which was low risk[21], and the risks of the other studies were unclear[14-20,22-42]. Blinding: The use of blinding did not affect mortality, so studies that used blinding were low risk. Incomplete outcome data: One study was high risk due to the excessive number of missed follow-ups[21], and the risks of the remaining studies were unclear[14-20,22-42]. Selective reporting: 21 studies were low risk for containing negative results and no commercial cooperation[14,15,18-21,23-32, 35, 36,38-40], and the risks of the other studies were unclear[16,17,22,33,34,37,41,42]. Other biases: Three studies were high risk due to their lack of baseline data comparisons[27,28,37], and the risks of the remaining studies were low[14-26,29-36,38-42]. The risk of bias graph is shown in Figure 2, and the risk of bias summary is shown in Table II.

Homogeneity, Similarity, and Consistency

The PICOS and methodology of the 29 articles included in this study were compared. PICOS: All patients came from hospitals; the inclusion and exclusion criteria were similar; the treatment groups were treated with Western medicine; and the age, gender distribution, dosage, and course of treatment in the studies were roughly the same. Except for Dahuang Fuzi decoction, the rest of the treatment medications were intravenous medications. Methodology: All studies were RCTs of high quality, and the analytic strategy was the same. Statistics: I^2<50%. Therefore, the literature included in this study conformed to the principles of homogeneity and similarity. Since there was no closed loop, the consistency test was not needed.

Table I. Basic characteristics of the included studies.

ID	Language	Sample Total (trt/cont)	Gender (Male/female)	Age (year)	Methods of Treatment	Course (d)	Outcomes
Li et al[14] 2019	Chinese	50 (25/25)	Trt: 13/12 Cont: 17/8	Trt: 67.64±14.49 Cont: 68.84±15.80	Trt: WMT+Shenfu Injection 60 ml/24 h Cont: WMT	7	1
Li et al[15] 2019	Chinese	64 (32/32)	Trt: 18/14 Cont: 19/13	Trt: 49.1±15.7 Cont: 49.2±15.4	Trt: WMT+Shenfu Injection 100 ml/24 h Cont: WMT	7	1
Wang et al[16] 2018	Chinese	102 (51/51)	Trt: 27/24 Cont: 25/26	Trt: 53.16±12.08 Cont: 52.63±12.75	Trt: WMT+Shenfu Injection 60 ml/24 h Cont: WMT	14	1
Zhang et al[17] 2018	Chinese	116 (58/58)	Trt: 31/27 Cont: 29/29	Trt: 58.62±17.37 Cont: 57.46±16.27	Trt: WMT+Shenfu Injection 60 ml/24 h Cont: WMT	14	1
Zhang et al[18] 2017	English	157 (78/79)	Trt: 43/35 Cont: 45/34	Trt: 59.3±16.4 Cont: 58.6±17.2	Trt: WMT+Shenfu Injection 100 ml/24 h Cont: WMT	7	12
Zhang et al[19] 2017	Chinese	71 (36/35)	Trt: 19/17 Cont: 20/15	Trt: 71.43±9.21 Cont: 69.37±10.35	Trt: WMT+Shenfu Injection 100 ml/24 h Cont: WMT	7	1
Wang et al[20] 2017	Chinese	116 (58/58)	Trt: 31/27 Cont: 32/26	Trt: 53.06±5.43 Cont: 52.65±5.55	Trt: WMT+Shenfu Injection 200 ml/24 h Cont: WMT	7	1
Li et al[21] 2016	English	199 (82/83)	Trt: 64/38 Cont: 60/37	Trt: 54.0±16.9 Cont: 54.0±16.9	Trt: WMT+Shenfu Injection 100 ml/24 h Cont: WMT	5	12
Yao et al[22] 2015	Chinese	40 (20/20)	Trt: 12/8 Cont: 13/7	Trt: 63.3±11.4 Cont: 63.2±6.6	Trt: WMT+Shenfu Injection 100 ml/24 h Cont: WMT	15	1
Li et al[23] 2015	Chinese	84 (42/42)	Trt: 28/14 Cont: 25/17	Trt: 54.90±14.70 Cont: 57.50±16.10	Trt: WMT+Shenfu Injection 200 ml/24 h Cont: WMT	7	1
Zheng et al[24] 2014	Chinese	78 (38/40)	Trt: 20/18 Cont: 22/18	Trt: 70.25±19.56 Cont: 69.48±10.13	Trt: WMT+Shenfu Injection 100 ml/24 h Cont: WMT	7	12
Qiu et al[25] 2012	Chinese	68 (36/32)	Trt: 20/16 Cont: 18/14	Trt: 49.3±15.5 Cont: 50.5±17.2	Trt: WMT+Shenfu Injection 100 ml/24 h Cont: WMT	7	1
Zhou et al[26] 2016	Chinese	50 (25/25)	Trt: 14/11 Cont: 19/6	Trt: 71.84±15.17 Cont: 73.40±9.50	Trt: WMT+Shenmai Injection 100 ml/24 h Cont: WMT	7	1
Ren et al[27] 2015	Chinese	51 (26/25)	31/20	Trt: 69.6±13.6 Cont: 68.9±15.1	Trt: WMT+Shenmai Injection 50 ml/24 h Cont: WMT	14	1
Zhang et al[28] 2017	Chinese	72 (36/36)	41/31	47.3±10.3	Trt: WMT+Dahuang Fuzi Tang 2 times/24 h Cont: WMT	3	1
Huang et al[29] 2016	Chinese	68 (34/34)	Trt: 21/13 Cont: 19/15	Trt: 79.90±9.70 Cont: 74.40±8.70	Trt: WMT+Dahuang Fuzi Tang 2 times/24 h Cont: WMT	3	12
Jiang et al[30] 2020	Chinese	190 (95/95)	Trt: 59/36 Cont: 57/38	Trt: 49.40±9.79 Cont: 49.35±9.82	Trt: WMT+Xuebijing Injection 100 ml/24 h Cont: WMT	7-10	1
Sun et al[31] 2020	Chinese	80 (40/40)	Trt: 26/14 Cont: 29/11	Trt: 59.38±12.12 Cont: 57.95±13.64	Trt: WMT+Xuebijing Injection 200 ml/24 h Cont: WMT	7	1

Table continued

Table I. ***(Continued).*** Basic characteristics of the included studies.

ID	Language			Age (year)	Methods of Treatment	Course (d)	Outcomes
Wang et al[32] 2019	Chinese	90 (45/45)	Trt: 28/17 Cont: 25/20	Trt: 53.01±9.24 Cont: 52.59±8.97	Trt: WMT+Xuebijing Injection 200 ml/24 h Cont: WMT	7	1
Dou et al[33] 2018	Chinese	91 (45/46)	Trt: 27/18 Cont: 29/17	Trt: 61.0±14.8 Cont: 58.3±15.6	Trt: WMT+Xuebijing Injection 200 ml/24 h Cont: WMT	5	1
Jiang et al[34] 2017	Chinese	80 (40/40)	Trt: 24/16 Cont: 25/15	Trt: 50.25±12.31 Cont: 50.14±12.22	Trt: WMT+Xuebijing Injection 100 ml/24 h Cont: WMT	7	1
Zhang et al[35] 2017	Chinese	64 (32/32)	Trt: 19/13 Cont: 23/9	Trt: 50.33±12.47 Cont: 49.64±11.92	Trt: WMT+Xuebijing Injection 100 ml/24 h Cont: WMT	7	1
Chen et al[36] 2013	Chinese	731 (392/339)	Trt: 284/108 Cont: 244/95	NR	Trt: WMT+Xuebijing Injection 200 ml/24 h Cont: WMT	NR	12
Cui et al[37] 2012	Chinese	164 (82/82)	91/73	52.7±17.6	Trt: WMT+Xuebijing Injection 150 ml/24 h Cont: WMT	NR	12
Yang et al[38] 2012	Chinese	65 (33/32)	Trt: 20/13 Cont: 21/11	Trt: 60.15±14.93 Cont: 61.08±16.01	Trt: WMT+Xuebijing Injection 100 ml/24 h Cont: WMT	6	1
Liu et al[39] 2011	Chinese	21 (11/10)	Trt: 7/4 Cont: 7/3	Trt: 57.26±16.81 Cont: 58.75±16.24	Trt: WMT+Xuebijing Injection 200 ml/24 h Cont: WMT	NR	1
Yao et al[40] 2011	Chinese	78 (40/38)	Trt: 21/19 Cont: 27/11	Trt: 59.04±18.32 Cont: 52.13±22.21	Trt: WMT+Xuebijing Injection 100 ml/24 h Cont: WMT	7	1
Liu et al[41] 2010	Chinese	142 (72/70)	Trt: 44/28 Cont: 39/31	Trt: 44.3±12.7 Cont: 42.8±13.5	Trt: WMT+Xuebijing Injection 100 ml/24 h Cont: WMT	7	1
Song et al[42] 2010	Chinese	53 (27/26)	NR	NR	Trt: WMT+Xuebijing Injection 200 ml/24 h Cont: WMT	8	1

Note: Trt: treatment group; Cont: control group; WMT: Western medicine treatment; NR: no report; 1: 28-day mortality; 2: Adverse reactions.

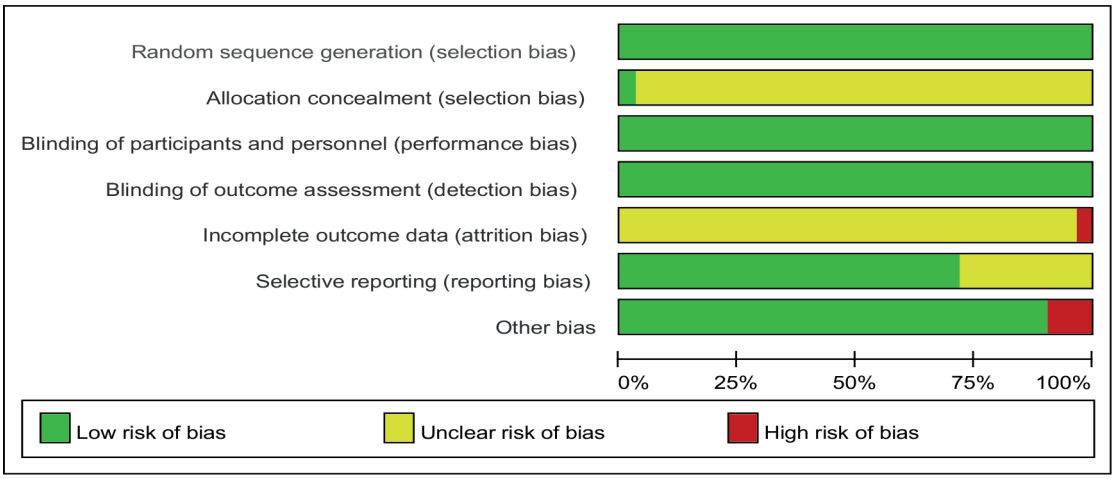

Figure 2. Risk of bias graph.

Table II. Risk of bias summary.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Score
Li et al[14] 2019	Random number table	Unclear	low risk	low risk	Unclear	low risk	low risk	-1
Li et al[15] 2019	Random number table	Unclear	low risk	low risk	Unclear	low risk	low risk	-1
Wang et al[16] 2018	Random number table	Unclear	low risk	low risk	Unclear	Unclear	low risk	-1
Zhang et al[17] 2018	Random number table	Unclear	low risk	low risk	Unclear	Unclear	low risk	-1
Zhang et al[18] 2017	Random number generation system	Unclear	low risk	low risk	Unclear	low risk	low risk	-1
Zhang et al[19] 2017	Random number table	Unclear	low risk	low risk	Unclear	low risk	low risk	-1
Wang et al[20] 2017	Random number table	Unclear	low risk	low risk	Unclear	low risk	low risk	-1
Li et al[21] 2016	Randomize code	Distribution center	low risk	low risk	Too many lost to follow-up without explanation	low risk	low risk	-2
Yao et al[22] 2015	Random number table	Unclear	low risk	low risk	Unclear	Unclear	low risk	-1
Li et al[23] 2015	Envelope	Unclear	low risk	low risk	Unclear	low risk	low risk	-1
Zheng et al[24] 2014	Random number table	Unclear	low risk	low risk	Unclear	low risk	low risk	-1
Qiu et al[25] 2012	Random number table	Unclear	low risk	low risk	Unclear	low risk	low risk	-1
Zhou et al[26] 2016	Random number table	Unclear	low risk	low risk	Unclear	low risk	low risk	-1
Ren et al[27] 2015	Random number table	Unclear	low risk	low risk	Unclear	low risk	Lack of baseline data comparison	-2
Zhang et al[28] 2017	Random number table	Unclear	low risk	low risk	Unclear	low risk	Lack of baseline data comparison	-2
Huang et al[29] 2016	Random number table	Unclear	low risk	low risk	Unclear	low risk	low risk	-1
Jiang et al[30] 2020	Random number table	Unclear	low risk	low risk	Unclear	low risk	low risk	-1
Sun et al[31] 2020	Random number table	Unclear	low risk	low risk	Unclear	low risk	low risk	-1
Wang et al[32] 2019	Random number table	Unclear	low risk	low risk	Unclear	low risk	low risk	-1
Dou et al[33] 2018	Random number table	Unclear	low risk	low risk	Unclear	Unclear	low risk	-1

Table continued

Table II. ***(Continued).*** Risk of bias summary.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Score
Jiang et al[34] 2017	Draw lots	Unclear	low risk	low risk	Unclear	Unclear	low risk	-1
Zhang et al[35] 2017	Random number table	Unclear	low risk	low risk	Unclear	low risk	low risk	-1
Chen et al[36] 2013	Random number table	Unclear	low risk	low risk	Unclear	low risk	low risk	-1
Cui et al[37] 2012	Random number table	Unclear	low risk	low risk	Unclear	Unclear	Lack of baseline data comparison	-2
Yang et al[38] 2012	Random number table	Unclear	low risk	low risk	Unclear	low risk	low risk	-1
Liu et al[39] 2011	Random number table	Unclear	low risk	low risk	Unclear	low risk	low risk	-1

Table III. Comparison results of different interventions.

Shenfu group				
1.56 (0.59,4.15)	Shenmai group			
0.63 (0.28,1.39)	0.40 (0.12,1.33)	Dahuang Fuzi group		
0.89 (0.59,1.34)	0.57 (0.21,1.53)	1.42 (0.63,3.17)	Xuebijing group	
0.63 (0.47,0.83)	0.40 (0.16,1.03)	1.00 (0.48,2.10)	**0.71 (0.52,0.96)**	WMT

Network Evidence Plot

There were 5 medication regimens: conventional WMT, Shenfu injection combined with WMT (Shenfu group), Shenmai injection combined with WMT (Shenmai group), Dahuang Fuzi decoction combined with WMT (Dahuang Fuzi group), and Xuebijing injection combined with WMT (Xuebijing group). The Shenfu

Table IV. Adverse reactions.

Study	Adverse reactions
Zhang et al[18] 2017	Trt: Headache (4/78), Faster heart rate (5/78) Cont: NR
Li et al[21] 2016	Trt: Itching (1/102) Cont: NR
Zheng et al[24] 2014	No obvious adverse reactions in both groups
Huang et al[29] 2016	Trt: Nausea and vomit (7/34), Reflux (8/34), Bloating (12/34), Diarrhoea (2/34), Gastric residue >500 ml (7/34), Hypernatremia (12/34), Hyperchloremia (7/34), Hypokalaemia (12/34), Gastrointestinal bleeding (0/34) Cont: Nausea and vomit (5/34), Reflux (3/34), Bloating (5/34), Diarrhoea (3/34), Gastric residue >500 ml (4/34), Hypernatremia (15/34), Hyperchloremia (12/34), Hypokalaemia (16/34), Gastrointestinal bleeding (1/34)
Chen et al[36] 2013	No obvious adverse reactions in both groups
Cui et al[37] 2012	Trt: Adverse reaction rate (12/82) Cont: Adverse reaction rate (21/82)

Note: Trt: treatment group; Cont: control group; NR: no report.

Table V. GRADE evidence level.

Comparison	Study limitations	Imprecision	Inconsistency	Indirectness	Publication bias	GRADE
Shenfu group	Downgrade	No downgrade	No downgrade	No downgrade	Downgrade	++oo
Shenmai group	Downgrade	No downgrade	No downgrade	No downgrade	Downgrade	++oo
Dahuang Fuzi group	Downgrade	Downgrade	No downgrade	No downgrade	Downgrade	+ooo
Xuebijing group	Downgrade	Downgrade	No downgrade	No downgrade	Downgrade	+ooo

group and Xuebijing group included the largest number of studies. In the Shenfu group, the Dahuang Fuzi group, and the Xuebijing group, at least one of the studies reported blinding or was a multicentre study. There was no closed loop between the studies (Figure 3).

Funnel Plot

The dot on the left was scattered, while dots on the right were concentrated near X=0. There was a dot in the lower right corner, suggesting a small sample effect (Figure 4). The symmetry of the Shenfu group and the Xuebijing group was poor, indicating a certain publication bias. It was impossible to judge publication bias in the Shenmai group and the Dahuang Fuzi group because there were too few studies.

Comparison Results of Different Treatments

The 28-day mortality in the Shenfu group [OR=0.63, 95% CI=(0.47, 0.83)] and the Xuebijing group [OR=0.71, 95% CI=(0.52, 0.96)] was lower than that of the WMT group, and the differences were statistically significant (Table III). The 28-day mortality in the Shenmai group [OR=0.40, 95% CI=(0.16, 1.03)] and the Dahuang Fuzi group [OR=1.00, 95% CI=(0.48, 2.10)] did not change significantly. Compared with each other, the differences among the other interventions were not statistically significant.

SUCRA for 28-Day Mortality

The Dahuang Fuzi group and WMT group had the highest 28-day mortality. The Xuebijing

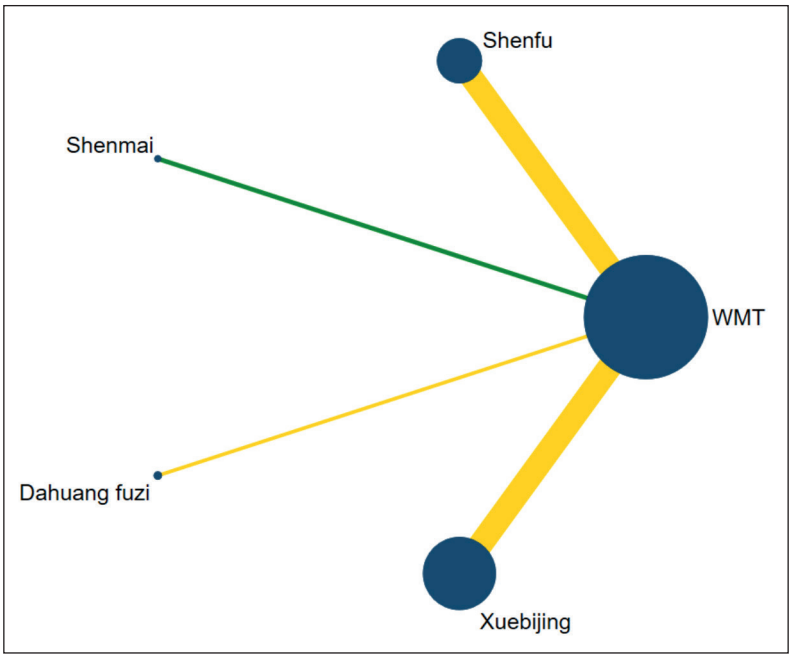

Figure 3. Network evidence plot.

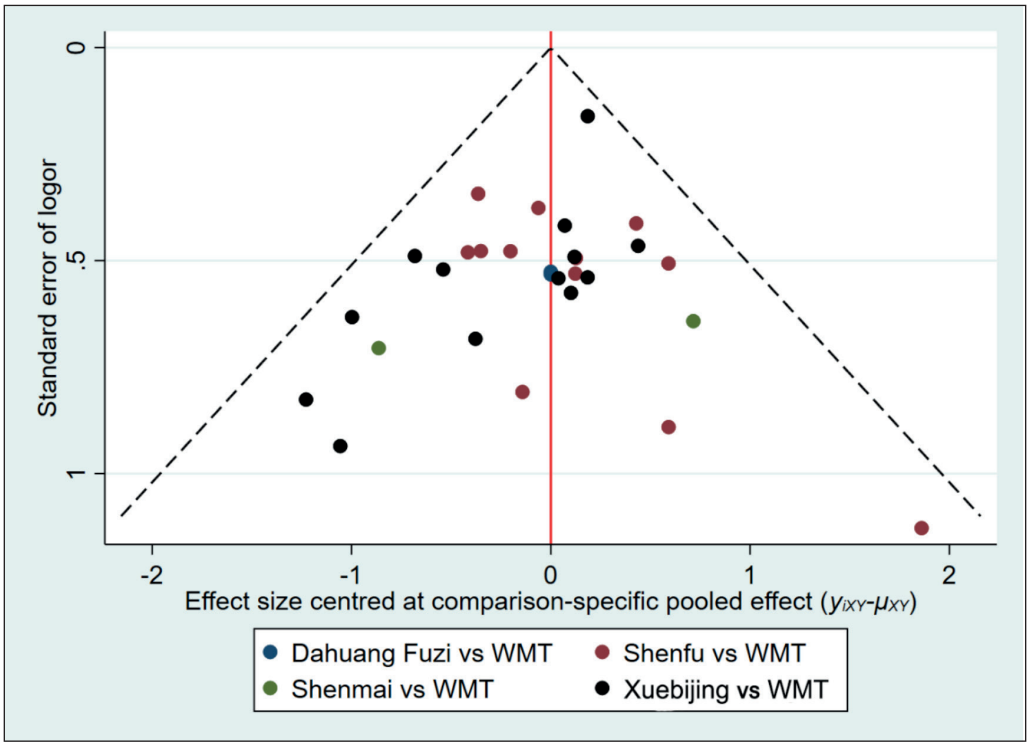

Figure 4. Funnel plot.

group and Shenfu group had lower 28-day mortality. The Shenmai group had the lowest 28-day mortality. The curative effect was ranked as follows: Shenmai group > Shenfu group > Xuebijing group > WMT > Dahuang Fuzi group (Figure 5).

Adverse Reactions

Only 6 studies reported adverse reactions[18,21,24,29,36,37], but the adverse reactions reported in the 6 studies were not consistent; thus, meta-analysis could not be performed. Therefore, adverse reactions are presented as a list only (Table IV).

GRADE Evidence Level

The evidence levels of the Shenfu group and the Shenmai group were both low, and those of the Dahuang Fuzi group and the Xuebijing group were very low (Table V).

Discussion

Sepsis 1.0 provides a novel definition and diagnostic criteria for sepsis. It is believed that sepsis is a systemic inflammatory response syndrome (SIRS) caused by infection, and the diagnostic criterion is infection + SIRS[43]. Sepsis 2.0 maintains the definition of sepsis 1.0 and adds specific diagnostic indicators (a total of 21 diagnostic indicators). The diagnostic criteria are ≥ 2 diagnostic indicators + Sepsis 1.0[44]. In Sepsis 3.0, SIRS is replaced by organ dysfunction. It is believed that sepsis is a life-threatening disease of organ dysfunction caused by host-response imbalance due to infection. The sequential organ failure assessment (SOFA) score was used as diagnostic criteria, that is, infection + SOFA score ≥ 2 points[45]. However, over the past 10 years, the mortality of patients with sepsis has not been significantly reduced despite modern medical treatment[7,8].

The results of the network meta-analysis show that the 28-day mortality of the Shenfu group [OR=0.63, 95%CI=(0.47, 0.83)] and the Xuebijing group [OR=0.71, 95%CI=(0.52, 0.96)] are significantly reduced, while the 28-day mortality of the Shenmai group [OR=0.40, 95%CI=(0.16, 1.03)] and the Dahuang Fuzi group [OR=1.00, 95%CI=(0.48, 2.10)] do not change significantly compared with the WMT group. The possible reasons are as follows: First, only 2 studies on the Shenmai group and the Dahuang Fuzi group could be found. Second, the average age of the patients in the Shenmai group was older. Third, the Dahuang Fuzi group

had a shorter course of treatment, and it was administered via the gastrointestinal tract. The curative effect ranking is Shenmai injection > Shenfu injection > Xuebijing injection > WMT > Dahuang Fuzi decoction. Considering all of the analysis results, it appears that Shenfu injection has the best effect (level of evidence: low), followed by Xuebijing injection (level of evidence: very low). It should be noted that most researchers neglected to monitor for adverse reactions.

It is currently believed that various mechanisms, such as inflammation, immunosuppression, cytokine storm, vascular endothelial injury and microthrombosis, are involved in the pathogenesis of sepsis[3-5]. Chinese medicines have the characteristics of containing multiple components and treating multiple targets, and they are especially good at treating sepsis, which involves multiple mechanisms. Shenfu injection can improve the vascular endothelial function[46] and the immune function[18] of patients with sepsis, thereby reducing the occurrence of multiple organ dysfunction syndrome (MODS). Shenmai injection can reduce the occurrence of inflammatory storms through the NF-κB pathway[47] and thus improve immune function through immune regulation in patients with sepsis[10]. Xuebijing injection can reduce inflammation[48,49], protect vascular endothelial cell function, and improve microcirculation in sepsis[50]. Acute gastrointestinal disorder is one of the important initiating factors of MODS[51]. Dahuang Fuzi decoction can alleviate gastrointestinal dysfunction and reduce inflammation[52,53].

Analysed from the perspective of Chinese medicine, the basic pathogenesis of sepsis is the deficiency of healthy Qi and the intrusion of toxic pathogens, causing channels and collaterals to be blocked by phlegm and blood stasis, which result in a serious imbalance of visceral function. Acute deficiency, blood stasis, and fuqi blockade are common clinical syndromes in patients with sepsis[54]. Shenfu injection is composed of Renshen and Fuzi, which have the effect of recuperating depleted Yang and rescuing the patients from collapse, thus replenishing Qi. Shenmai injection is composed of Renshen and Maidong, which have the effect of replenishing Qi, promoting the secretion of body fluids and astringing Yin and arresting sweating. Patients with septic shock often present with acute deficiency syndrome. Shenfu injection is used to treat patients deficient in Yang, while Shenmai injection is suitable for patients deficient in Yin. Xuebijing injection is composed of Honghua,

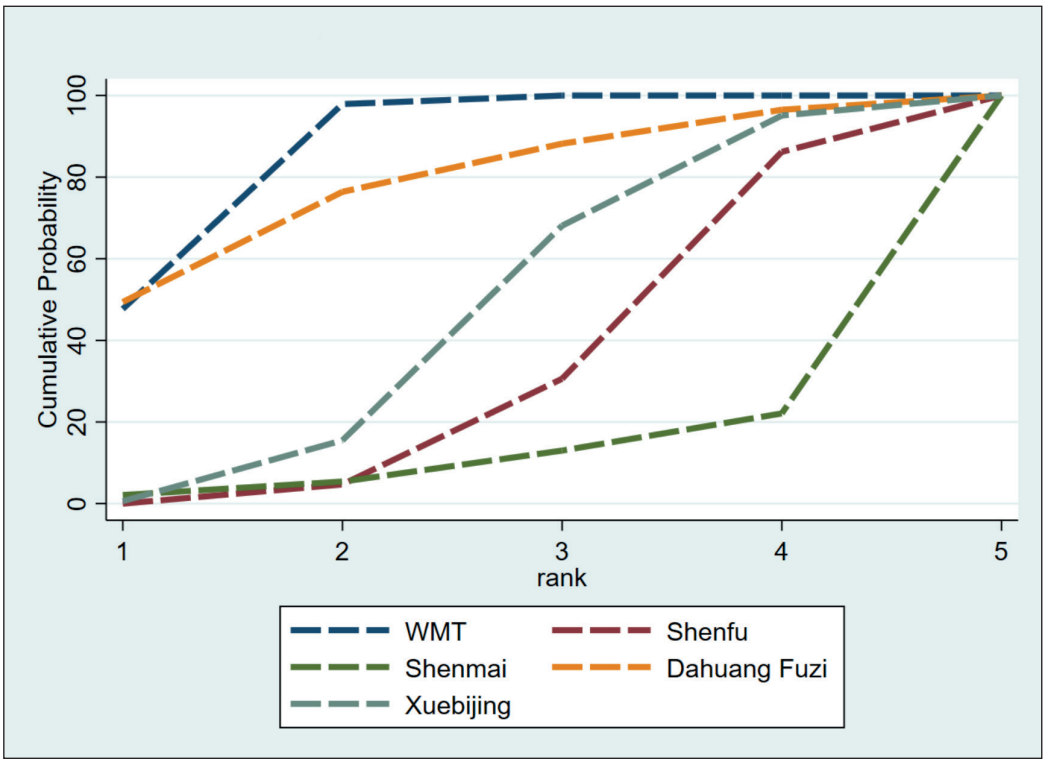

Figure 5. SUCRA for 28-day mortality.

Chishao, Chuanxiong, Danshen, and Danggui, which have the effect of resolving blood stasis and detoxification. Xuebijing injection is used to treat sepsis patients with microthrombosis, which manifests as blood stasis syndrome. Dahuang Fuzi decoction is composed of Dahuang, Fuzi, and Xixin, which warm Yang, dispel cold, unblock fu-organs and relieve pain. Dahuang Fuzi decoction is suitable for patients with sepsis accompanied by gastrointestinal dysfunction, behaving as fu-qi blocking syndrome, which can cause bacterial translocation and accelerate the development of sepsis[55].

Conclusions

Shenfu injection or Xuebijing injection combined with WMT can reduce the 28-day mortality of patients with sepsis. The Shenfu group had the best outcomes, and its evidence level was higher than that of the Xuebijing group.

Conflicts of Interest

The authors declare that there are no conflicts of interest concerning this work.

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