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Original Article

Randomized and controlled trials of Sanren Decoction's treatment on upper respiratory infections: a meta-analysis

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Abstract: Objective: This study is to systematically review the clinical efficacy of Sanren Decoction on the treatment of upper respiratory infections (URI). Methods: A systematic literature search of PubMed, EMbase, MEDLINE, Cochrane Library, CNKI, VIP and WanFang databases was performed for randomized controlled trials (RCT) of Sanren Decoction's treatment on URI until October 2015. Two reviewers independently screened articles based on inclusion and exclusion criteria, extracted information and evaluated the methodology quality of all included articles, using RevMan5.2 Meta-analysis software. Results: There were 53 articles identified through the search process, and 7 articles were finally included with 571 patients. It was showed in the meta-analysis that the cure rate [OR = 3.51, 95% CI (2.19, 5.15), P < 0.001] and effectiveness rate [OR = 3.91, 95% CI (2.58, 5.90), P < 0.001] of Sanren Decoction's treatment on URI was significantly higher than that of control group. Conclusions: Sanren Decoction's treatment on URI is effective. However, due to the limited number of studies and low quality of some articles, further study with high-quality evidence is needed.

Keywords: Sanren Decoction, upper respiratory infections, systematic review, meta-analysis, randomized controlled trials

Introduction

Upper respiratory infection (URI) is a common disease, with symptoms of fever, nasal congestion, runny nose, sneezing, and sore throat. Persistent URI can cause severe complications [1]. In traditional Chinese medicine, UPI is considered as "Wind heat syndrome", presented as fever, sweating, wind aversion, thin and white or yellow tongue, coughing, and yellow gel-like phlegm. "Wind heat syndrome" should be treated with cooling and detoxification [2]. The recipe of Sanren Decoction is from "Differential Diagnosis of Warm Disease" by Tang Wu in Qing dynasty. Sanren Decoction is made of almonds, amomum cardamomum, barley, talc, tetrapanax papyrifera, folia bambosae, mangnolia officinalis, Pinellia ternata, and it can be used for treatment of URI with significant clinical efficacy [3]. Articles of randomized controlled clinical trials of Sanren Decoction were systematically searched and reviewed with no restrictions on nationality using Cochrane method, to assess the clinical efficacy and safety of Sanren Decoction's treatment on URI and provide evidence on its future clinical applications.

Methods

Inclusion criteria

We included studies that met the following criteria: 1) clinically diagnosed URI with no restrictions on symptoms, gender, case source, type or duration; 2) Sanren Decoction as primary treatment to study its efficacy and safety; 3) the treatment group received Sanren Decoction only or combined with western medicine, and the control group received western medicine that showed good efficacy; 4) the randomized

Table 1. General characteristics and quality evaluation of all included studies

Included articles	Publication year	Groups	Cases (male/female)	Age (year)	Duration (day)	Intervention	JADAD score
Chongzheng Feng [6]	2011	T	36 (19/17)	53.6 ± 5.8	5.3 ± 1.3	Antibacterials + SD	3
		C	34 (18/16)	54.5 ± 5.1	5.8 ± 1.9	Antibacterials	
Yuan Chen [7]	2011	T	70 (35/35)	2.6	3.3	ACPT + SD	3
		C	35 (17/18)	2.4	3.5	ACPT	
Xiaoli Li [8]	2012	T	34 (21/13)	4.3 ± 1.4	NR*	ACPT + SD	3
		C	34 (23/11)	3.5 ± 2.4	NR	ACPT	
Cong Shen [9]	2013	T	70 (38/32)	1-14	1-12	PCS + SD	2
		C	65 (34/31)	1-13	1.5-13	PCS	
Yundie Wang [10]	2014	T	40 (23/17)	3.03	2.01	Ribavirin + SD	2
		C	40 (26/14)	3.05	1.93	Ribavirin	
Fengli Yao [11]	2014	T	32 (12/20)	6.53 ± 3.31	11.06 ± 9.55	Azithromycin + SD	3
		C	31 (13/18)	6.93 ± 3.52	11.43 ± 9.46	Azithromycin	
Zhenxiao Lei [12]	2014	T	25 (17/8)	55.7 ± 4.5	3	Ribavirin + SD	2
		C	25 (19/6)	54.9 ± 5.1	3	Ribavirin	

*NR = not report; #Antibacterials were selected based on physician's experience and sputum bacterial culture with sensitivity test; ACPT: amoxicillin and clavulanate potassium tablet; SD: Sanren Decoction; PCS: pediatric coughing syrup (Xiao Er Xuan Fei Zhi Ke Ke Li).

controlled study has been published in medical journals with no limitation of nationality or masking method.

Exclusion criteria

We excluded studies that met the following criteria: 1) articles of animals experiments, adverse reactions, or its pharmacology and pharmacokinetics mechanisms; 2) articles without treatment outcomes or with unclear statistical analysis; 3) non-randomized controlled trials; 4) Sanren Decoction was used in control group; and 5) patients with diseases other than URI.

Efficacy standards

Clinical efficacy standards were in accordance with "efficacy standards of traditional Chinese medicine" [4]. Cured case was defined as the disappearance of symptoms, such as dizziness, headache, nasal congestion, runny nose, fever, and chest tightness. Improved case was defined as returning to normal temperature and symptoms decreased such as disappearance of dizziness, headache, nasal congestion, runny nose, and chest tightness. No cure case was defined as not improved or worsened symptoms such as dizziness, headache, nasal congestion, runny nose, fever, and chest tightness. The total number of effective case = total number of cured case + improved case; the cure rate = number of cured cases/total number of all cases; the effectiveness = number of effective case/total number of all cases.

Literature search

Sanren Decoction and San Ren Tang (in Chinese) was searched as key words on China Knowledge Resource Integrated Database (CNKI), VIP Journal Integration Platform, Wanfang database, China Biology Medicine (CBM), PubMed, Embase, MEDLINE and Cochrane Library that have been published until October 2015. Search strategy of combined text and MeSH terms was performed depending on the requirement of databases. Reference lists of all included articles were also reviewed for comprehensive literature search.

Evaluations

All articles were reviewed by two reviewers to independently screen titles and abstracts on the basis of predefined inclusion criteria, and review the full-text of the eligible articles. Two reviewers extracted and compared information of all included articles, and evaluated their quality. When they disagreed with each other, disagreements were either discussed and resolved to reach a consensus between the two reviewers or decided by the third reviewer or professionals. Articles were assessed using modified Jadad quality assessment method [5] to assess their randomization, grouping, blinding, lost of follow-ups and adverse reactions.

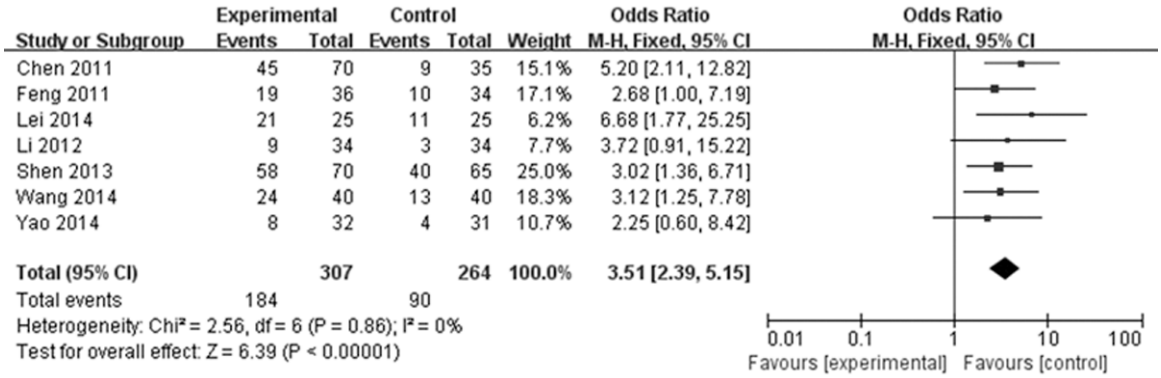

Figure 1. Meta-analysis of cure rate of Sanren Decoction treatment on upper respiratory infection.

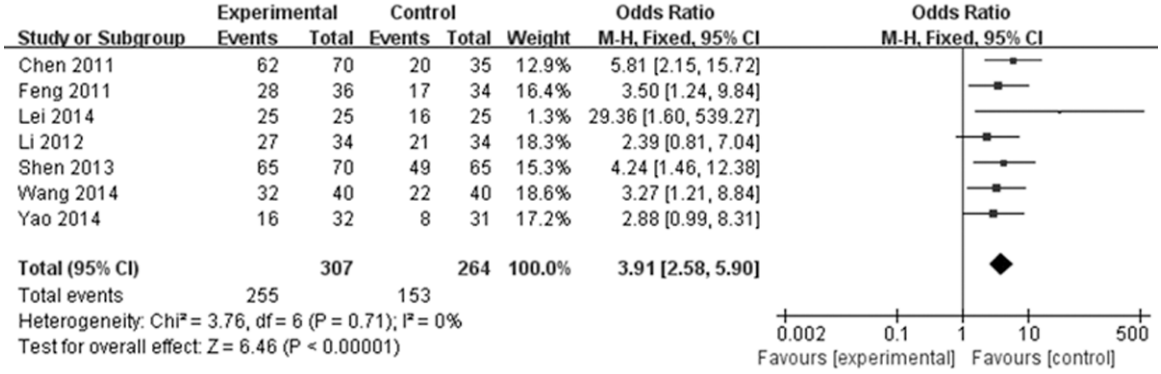

Figure 2. Meta-analysis of effectiveness rate of Sanren Decoction treatment on upper respiratory infection.

Jadad score of 1-3 was considered as low quality, and score of 4 to 7 was considered as high quality.

Statistical analysis

Meta-analysis was performed using RevMan5.2 (Cochrane Collaboration) [6]. χ^2 test and *P* values was used for heterogeneity analysis, and heterogeneity was assessed by I^2. If $P > 0.1$ and $I^2 < 50\%$, the fixed effects model was used; otherwise, random effects model would be used. Continuous variables are presented as mean difference (MD) for effect size, and non-continuous variables were presented as odds ratio (OR) or risk ratio (RR) for effect size, with 95% confidence interval (CI). Funnel plot analysis was used for possible publication bias: symmetric graph indicates the absence of publication bias, and asymmetry graph indicates potential bias.

Results

Characteristics of literature search and included studies

There were 53 articles identified in the search process, and they were managed by NoteExpress. After screening of titles and abstracts and review of full text, there were 7 articles that met all inclusion criteria and were all in Chinese. The treatment group in all articles received Sanren Decoction and regular western medicine treatment, with control group received only western medicine. There were 2 articles using amoxicillin and clavulanate potassium tablet as control, 1 article using ribavirin, 1 article using pediatric coughing syrup (Xiao Er Xuan Fei Zhi Ke Ke Li) and 1 article using azithromycin. There were 3 articles [7-9] with Jadad score of 2, and the others [10-13] of 3. Their general characteristics and quality evaluation were shown in **Table 1**.

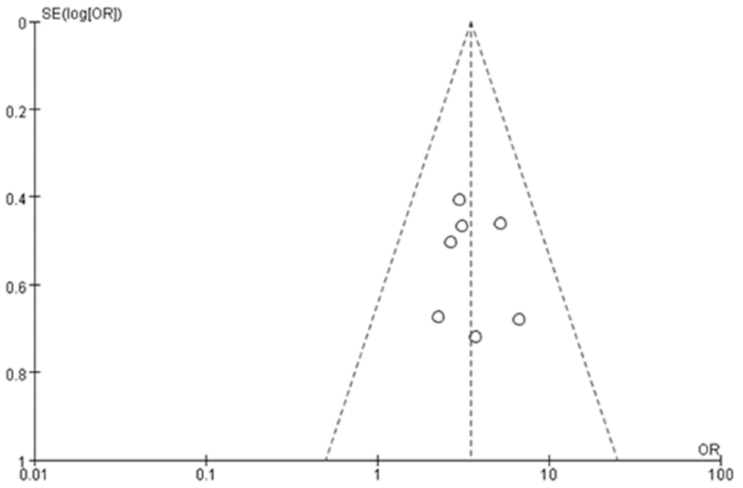

Figure 3. The funnel plot of meta-analysis of Sanren Decoction and control group on the treatment of upper respiratory infection.

Clinical cure rate

To determine the impact of Sanren Decoction on URI's clinical efficacy, the meta-analysis of cure rate comparison between Sanren Decoction group and control group was shown in **Figure 1**. It showed heterogeneity of $I^2 = 0$, indicating no heterogeneity, so fixed effects model was applied. The cure rate of Sanren Decoction group was higher with statistical significance, compared with control group [OR = 3.51, 95% CI (2.19, 5.15), P < 0.001].

To determine the impact of Sanren Decoction on URI's effectiveness rate, the meta-analysis of effectiveness rate comparison between Sanren Decoction group and control group was shown in **Figure 2**. It showed heterogeneity of $I^2 = 0$, indicating no heterogeneity, so fixed effects model was applied. The effectiveness rate of Sanren Decoction group was higher with statistical significance, compared with control group [OR = 3.91, 95% CI (2.58, 5.90), P < 0.001].

Risk of bias

To determine the potential bias of included studies, the funnel plot was generated. The funnel plot made by RevMan5.2 was a scatter plot that composed of treatment outcome (X axis) and sample size (Y axis) of each individual study. The effect estimates of small sample size were in the bottom of the graph with wide distribution, and effect estimates of large sample size were in the upper side of the graph with narrow distribution. The graph was in symmetric inverted funnel shape when without publication bias. This study showed the graph of effectiveness rate between Sanren Decoction and control group on URI treatment was in symmetric inverted funnel shape, indicating low likelihood of publication bias, as in **Figure 3**.

Discussion

URI is a common disease that is most likely caused by virus or by bacterial [14]. Currently there is no effective western antiviral medicine against URI; so Chinese medicine can be advantageous in the treatment [15]. The recipe of Sanren Decoction is from "Differential Diagnosis of Warm Disease" by Tang Wu in Qing dynasty, and it should be used when the body temperature is beginning to rise or in high fever with sweat [16]. The main drugs in Sanren Decoction are Sanren (in Chinese), namely almonds, amomum cardamomum, and barley. Almond is good for the flow and moistening of lung; amomum cardamomum is of aromatic scent that can moisten spleen and stomach, and help the body flow; barley is bitter in taste that promotes the secretion of body fluid thus clear away the bad by urine [17]. Sanren go into Sanjiao that moisten the lung and help the body flow, so clear away the dry, the hot and the bad. The body is moistened and cleared as a whole, the temperature decreased and the cough was ceased [17]. Therefore it is widely used in the treatment of URI.

In addition, Xiaomin Wen et al [18] showed Sanren Decoction could prevent the increased expression of HSP70 in hot and humid environment with high-fat diet or infections, especially caused by Salmonella typhimurium. It could also decrease AQP2 to normal level in urine of rats with syndrome of dampness-heat, indicating that the immune regulation effect of Sanren Decoction [19].

In this study, we had systematically analyzed 7 studies using meta-analysis, including 571 patients. It showed Sanren Decoction was better than western medicine. The cure rate and

effectiveness rate of western medicine combined with Sanren Decoction was better than western medicine alone. However, there are some underlying problems of current clinical studies of Sanren Decoction on URI treatment: 1) design methods lacked overall protocol with no description of detailed randomization or masking methods, thus its appropriateness cannot be determined; 2) no description of inclusion or exclusion criteria; 3) no blinding methods; 4) no published article with negative results; 5) no records of lost of follow-ups or missing cases. The above reasons led to low Jadad scores, and all directly impacted the credibility of study conclusions.

In conclusion, the available evidence indicates that combined Sanren Decoction treatment is more effective than western medicine alone, but high quality study is needed in the future due to the limited number and low quality of the current studies.

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Disclosure of conflict of interest

None.

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