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CLINICAL STUDY

Efficacy and safety of Reduqing granules in the treatment of common cold with wind-heat syndrome: a randomized, double-blind, double-dummy, positive-controlled trial

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Abstract

OBJECTIVE: To assess the efficacy and safety of Reduqing granules in patients with common cold with wind-heat syndrome (CCWHS).

METHODS: A randomized, double-blind, double-dummy, parallel, positive- controlled trial included 72 CCWHS patients was performed. The participants were randomly assigned to two groups, Reduqing (RDQ) group and Lianhuaqingwen (LHQW) group, in a 1∶1 ratio. Patients in RDQ group received Reduqing granules and dummy Lianhuaqingwen capsules three times a day and patients in LHQW group received Lianhuaqingwen capsules and dummy Reduqing granules three times daily. The duration of treatment and follow-up were four days.

RESULTS: There were no statistically significant differences in total markedly effective rate and total effective rate between RDQ group and LHQW group after treatment. Traditional Chinese Medicine (TCM) symptom score was significantly reduced after treatment in RDQ group, as well as in LHQW group. However, the difference of change in TCM symptom score between two groups was not statistically significant ($P > 0.05$). There were no significant differences between two groups in the median time to fever relief [RDQ group (4 ± 8) h *vs* LHQW group (4 ± 5) h] or the median time to fever clearance (RDQ group 47 h *vs* LHQW 36 h). No serious adverse events were reported during the study.

CONCLUSION: Compared with Lianhuaqingwen capsules, Reduqing granules achieved similar therapeutic effect in the treatment of CCWHS and no drug-related adverse events were reported during the study. Therefore, Reduqing granules might be effective and safe in the treatment of CCWHS.

Keywords: Common cold; Symptoms and signs; Reduqing granules; Lianhuaqingwen capsules; Randomized clinical trial

INTRODUCTION

Common cold, also known as acute upper respiratory

infections (AURI), is the most frequently experienced disease among humans and the third most common primary diagnosis in office visits.[1] More than 200 respiratory viruses such as rhinovirus, coronavirus, parainfluenza, respiratory syncytial virus, adenovirus, enterovirus or metapneumoviros are known to cause the common cold and rhinovirus is the most common cause accounting for 30%-50% of all adult related colds.[2-4] These viruses are spread by sneezing, coughing or nose blowing. The symptoms of the common cold include fever, cough, myalgias, headache, nasal congestion, sore throat and usually peak at 2 to 3 days and have a mean duration of 7 to 10 days.[5,6]

Due to the viral mutations and self-limiting aspects of the common cold, it's difficult to make effective treatments. So treatment for common cold is directed at symptom relief rather than treating the infection.[7] Lots of attempts to treat common cold including vitamins, zinc, vaccines, garlic, corticosteroids and others were controversial or ineffective.[8-16] In this case, more and more people start to seek for help from Traditional Chinese Medicine (TCM), a unique and well-established system of medicine. TCM treatment for common cold has unique advantages such as TCM divides colds into three categories: wind-heat syndrome, wind-cold syndrome and summer-heat dampness syndrome. Then different treatments are taken according to different categories, different seasons, and different populations. Besides, TCM treatment for common cold has stable efficacy and few side effects. What's more, TCM is more economical than chemical drugs and people are more likely to accept it. Common cold with wind-heat syndrome (CCWHS) is the most common type and primarily characterized by fever, sore throat, headache and nasal congestion. According to the theory of TCM, CCWHS should be treated by clearing heat and releasing stagnated Lung-*Qi*.

As a pure Chinese medicine, Reduqing granules is manufactured by Zhujiang Hospital, Guangzhou, China. It consists of the following ingredients: Daqingye (*Folium Isatidis*), Lianqiao (*Fructus Forsythiae Suspensae*), Shigao (*Gypsum Fibrosum*), Jingjie (*Herba Schizonepetae Tenuifoliae*), Bohe (*Herba Menthae Haplocalycis*), Gouteng (*Ramulus Uncariae Rhynchophyllae cum Uncis*), Chantui (*Periostracum Cryptotympanae*), Xuanshen (*Radix Scrophulariae*), Lugen (*Rhizoma Phragmitis*), Qianhu (*Radix Peucedani*), Huoxiang (*Herba Agastaches Rugosa*), Shenqu (*Massa Medicata Fermentata*), Danzhuye (*Herba Lophatheri*) and Gancao (*Radix Glycyrrhizae*). Clinical experiences in Zhujiang Hospital showed that Reduqing granules is effective in treating CCWHS by clearing heat, relieving pain and alleviating cough. Further more, no serious adverse events were reported during the clinical experiences.

Lianhuaqingwen capsule, the positive controlled drug, is manufactured by Shijiazhuang Yiling Pharmaceutical Company (Shijiazhuang, China). It developed from Maxingshigan Tang and Yinqiao San. Lianhuaqingwen capsules has been widely used in the treatment of influenza for many years. Its efficacy on influenza by alleviating fever, cough, sore throat and fatigue has been confirmed.[17] Many studies have shown that Lianhuaqingwen capsules also has the antiviral, antibacterial and anti-inflammatory activities.[18,19]

This trial was designed to evaluate the efficacy and safety of Reduqing granules in the treatment of patients with CCWHS by analyzing total markedly effective rate, total effective rate, change in TCM symptom score, time to fever relief, time to fever clearance and adverse events in patients received either Reduqing granules or Lianhuaqingwen capsules.

Reduqing granules has been widely used to treat CCWHS clinically. However, none standardized clinical trial has been conducted to confirm its efficacy and safety. This was the first randomized clinical trial (RCT) conducted in China designed to evaluate the efficacy and safety of Reduqing granules in patients with CCWHS.

METERIALS AND METHODS

Design

This randomized, double-blind, double-dummy, parallel, positive-controlled trial was conducted to evaluate the efficacy and safety of Reduqing granules in the treatment of CCWHS, with Reduqing granules as the study drug and Lianhuaqingwen capsules as the positive control. The clinical trial was conducted in accordance with the Good Clinical Practice Guidelines and the Declaration of Helsinki (2008).[20] In addition, the trial was approved by medical ethics committee in Zhujiang Hospital. All patients had to give their written informed consent before enrollment and were given adequate time to decide whether they wanted to participate.

Participants

All participants were diagnosed with CCWHS in Zhujiang Hospital according to Western Medicine and TCM diagnostic criteria for the common cold. Western Medicine diagnostic criteria for the common cold was established according to Practice of Internal Medicine (2009, Version 13). The TCM diagnosis of CCWHS was based on the Guidelines for Clinical Research of New Chinese Medicine. To be diagnosed with CCWHS, patients should have at least one primary symptom and at least two secondary symptoms. Primary symptoms were adversion to cold, fever and sore throat. Secondary symptoms included headache, cough, sweating, thirsty, nasal discharge and running nose. Signs for the tongue (reddish tongue, greasy tongue coating) and signs for the pulse were also recorded.

Inclusion criteria and exclusion criteria

The inclusion criteria were as follows: (a) diagnosis of common cold according to western medicine; (b) diagnosis of CCWHS according to TCM; (c) body temperature ≤ 39 ℃; (d) TCM symptom score ≥ 8 before treatment; (e) 18-65 years old; and (f) symptom onset ≤ 48 h.

The exclusion criteria were as follows: (a) white blood cell count > 10×10^{10}/L or the percentage of neutrophilic > 80%; (b) known of pregnancy or currently breast feeding; (c) combination with allergic rhinitis, herpangina, pharyngoconjuctivitis, bronchitis, pneumonia, amygdalitis; (d) having received antiviral agent, anti- inflammatory agent, analgesic-antipyretic or any other medicine for colds; (e) with serious primary diseases of the cardiovascular, pulmonary, kidney, and hematological system; (f) psychopath; (g) allergic to Reduqing granules or Lianhuaqingwen capsules; (h) history of drug abuse; (i) participation in another clinical trial within the past one month.

Sample size

Since this trial was the first RCT explored the efficacy and safety of Reduqing granules in the treatment of CCWHS, there is no relevant data can be used for reference. We planned to conduct an exploratory clinical trial with 60 participants to obtain the efficacy rate of Reduqing granules, which can provide a reference to estimate sample sizes for later studies. The participants were randomly assigned to RDQ group and LHQW group in a 1∶1 ratio. Considering a drop-out of 20%, 36 patients were recruited in each group. Consequently, the total sample size was determined to be 72 patients.

Randomization and blinding

A complete randomization method was used to allocate participants by an independent statistician. All eligible participants were randomly assigned to the RDQ or LHQW group in a 1∶1 ratio. The randomization sequence was generated using the SAS (vers 8.2, SAS Institute, Chicago, IL, USA) software. Then the study drugs, positive-controlled drugs and relevant dummy drugs were uniform packaged and numbered. An emergency envelope containing the information of the patient's group and drug number was prepared for each participant. These envelopes were kept by the persons in charge and sponsors in different places and not allowed to open unless there was an emergency. The participants and the clinical pharmacist were blinded to the treatment. Blinding was assessed at the end of the study.

Interventions

Reduqing granules and dummy Reduqing granules were provided and manufactured by Zhujiang Hospital. They were identical in shape, size, color and were 20 g per bag. Lianhuaqingwen capsules was manufactured by Shijiazhuang Yiling Pharmaceutical Company (Shijiazhuang, China). Dummy Lianhuaqingwen capsules was manufactured by Zhujiang Hospital. They were identical in shape, size and color and were 0.35 g per capsule.

Each participant in the RDQ group received a bag of Reduqing granules and four capsules of dummy Lianhuaqingwen three times daily for 4 days. Participants in the LHQW group were administered a bag of dummy Reduqing granules and four capsules of Lianhuaqingwen three times daily for 4 days.

Participants were prohibited receiving therapies that might affect symptoms of CCWHS. However, medications for comorbidities, such as hypertension or diabetes were allowed.

TCM symptom score

The TCM symptom score system used in the study followed the Guidelines for Clinical Research of New Chinese Medicine. In the symptom score system, the primary and secondary symptoms were given graded scores. TCM signs were recorded, but not scored. The change in TCM symptom score used the percentage of symptom score reduction (PSSR), which was calculated according to the following formula:

PSSR = (symptom score before treatment − symptom score after treatment) / symptom score before treatment × 100%.

Treatment efficacy evaluation system

The therapeutic effect of drugs were described as cure (body temperature returned to normal within 3 days, PSSR ≥ 95%), markedly effective (body temperature returned to normal within 3 days, PSSR ≥ 70%), effective (body temperature lower than before within 3 days, PSSR ≥ 30%) and ineffective (body temperature dose not reduce within 3 days, PSSR < 30%). Total markedly effective rate and total effective rate were calculated as follows.

Total markedly effective rate = (number of patients with cure + markedly effective)/all patients × 100%.

Total effective rate = (number of patients with cure + markedly effective + effective) / all patients × 100%.

Time to fever relief and time to fever clearance

Time to fever relief was defined as the time from the first dose of the drug to the body temperature dropped 0.5 ℃. Time to fever clearance was defined as the time from the first dose of the drug to the body temperature dropped below 37.3 ℃ and no longer rose for 48 h.

All patients were be recorded body temperature before treatment. If the temperature was higher than 37.3 ℃, it was recorded per hour for four times in a row within the first 24 h. After that, it was recorded at 10 AM, 2 PM and 8 PM everyday in the next three days. If the temperature was abnormal before treatment, then it was recorded at 2 PM everyday for 3 days in a row.

Safety assessment

Physical examination (temperature, respiration, blood pressure, heart rate and weight), blood biochemical ex-

amination [alanine transaminase (ALT), blood urea nitrogen (BUN), serum creatinine] and blood routine examination (red blood cell count, hemoglobin content, white blood cell count, the percentage of lymphocyte, the percentage of neutrophils, blood platelet count) were conducted before and after treatment to assess the safety of the treatment. During the trial, adverse events were observed in detail and documented in the case report forms.

Statistical analysis

The statistical analysis will be performed by an independent professional statistician using SPSS (vers 20.0, SPSS Inc., Chicago, IL, USA) software. Data are presented as mean ± standard deviation ($\bar{x} \pm s$). The comparison of baseline characteristics between two groups were evaluated by independent *t*-test or χ^2 test. Efficiency between two groups were compared by Pearson's χ^2 test or Fisher's exact test. Change in TCM symptom score before and after treatment was compared in each group by paired *t*-test and between two groups by analysis of covariance (ANCOVA). Time to fever relief and time to fever clearance were estimated by the Kaplan-Meier technique and were compared by the log-rank test. The level of significance was set at $P < 0.05$.

RESULTS

Participants

A total of 72 patients were eligible for our clinical trial. They were randomly divided into the RDQ group and LHQW group in a 1∶1 ratio. Our study procedure was simple and convenient for patients, the duration of treatment and follow-up were only four days, which made patients with good compliance. None was lost or withdrew from the trial. None of the patients discontinued treatment due to adverse events. All the 72 patients completed the 4-day trial and were available for further analysis (Figure 1).

Baseline characteristics

All of the patients were Chinese. There were no statistically significant differences in demographic variables such as gender, age, TCM symptom score, sore throat score, heat syndrome score between the two groups (Table 1).

Total markedly effective rate and total effective rate

8.33% patients were cure after treatment in RDQ group as well as in LHQW group. The markedly effective rate after treatment was 66.67% in RDQ group and 69.44% in LHQW group. There was no statistically significant difference in total markedly effective rate between RDQ group and LHQW group ($P = 0.780$). Similarly, no significant difference in total effective rate between RDQ group (97.2%) and LHQW group (100%) ($P = 1.000$) were observed (Table 2).

Change in TCM symptom score

TCM symptom score was significantly reduced after treatment ($t = 14.34$, $P = 0.000$) in RDQ group, as well as in LHQW group ($t = 15.26$, $P = 0.000$). While, change in TCM symptom score between two groups showed no significant difference ($P = 0.791$). Besides, ANCOVA showed that the influence of TCM symptom score before treatment on change in TCM symptom score is statistically significant ($P = 0.000$) (Table 3).

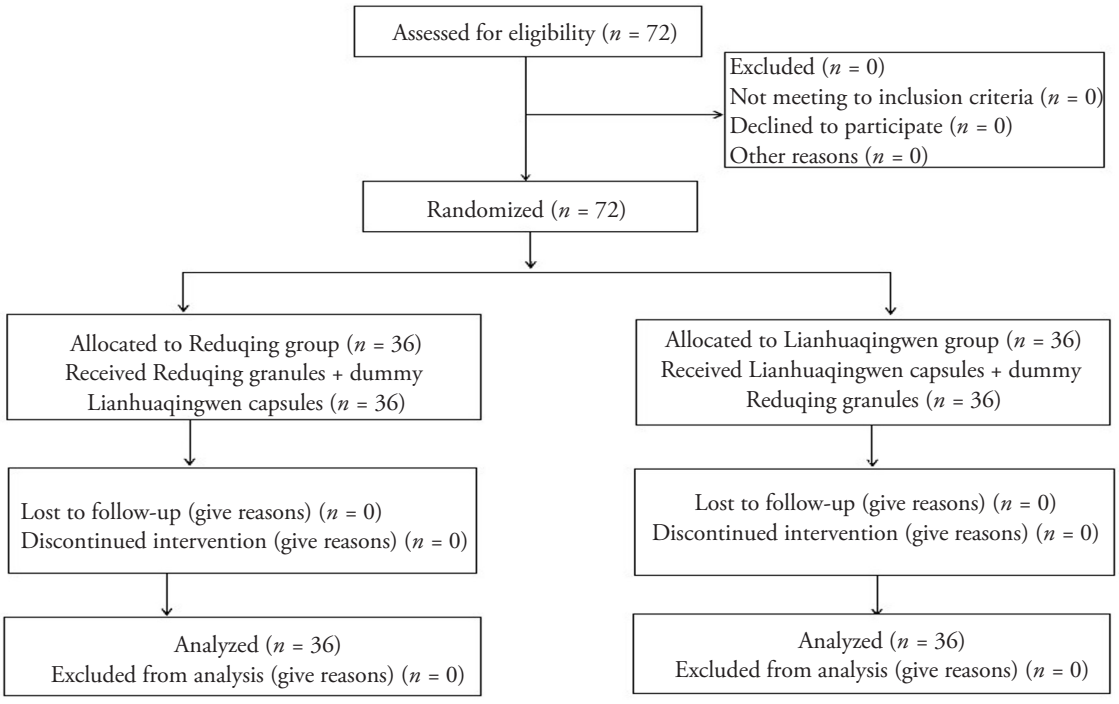

Figure 1 Flow diagram of the trial

Table 1 Baseline characteristics of the participants ($\bar{x} \pm s$)

Characteristic	RDQ group (n = 36)	LHQW grou (n = 36)	P value[a]
Age (years)	36.1±14.0	34.3±13.1	0.580
Height (cm)	164.6±8.3	164.4±5.9	0.922
Body weight (kg)	62.1±12.1	61.4±9.6	0.768
Male/Female (n)	19/17	16/20	0.479
Body Temperature (℃)	37.3±0.6	37.5±0.6	0.140
Pulse rate (min)	71.0±9.1	73.9±11.0	0.226
SBP (mm Hg)	122.2±15.9	1210±9.0	0.704
DBP (mm Hg)	74.6±8.9	73.2±7.1	0.476
Heat syndrome score	3.8±3.2	4.5±3.1	0.333
Sore throat score	3.3±2.5	3.8±2.2	0.369
TCM symptom score	16.3±4.5	18.4±5.2	0.067

Notes: patients in the RDQ group were treated with a bag of Reduqing granules and four capsules of dummy Lianhuaqingwen three times daily for 4 days. Participants in the LHQW group were administered a bag of dummy Reduqing granules and four capsules of Lianhuaqingwen three times daily for 4 days. RDQ: Reduqing; LHQW: lianhuaqingwen; SBP: systolic pressure; DBP: diastolic blood pressure; TCM: Traditional Chinese Medicine. [a] Pearson's χ^2 test or independent-sample t test.

Table 2 Comparison of efficiency for CCWHS

Group	Cure (n)	Markedly effective (n)	Effective (n)	Ineffective (n)	Total markedly effective rate (%)	P value[a]	Total effective rate (%)	P value[b]
RDQ	3	24	8	1	75.0	0.78	97.2	1.00
LHQW	3	25	8	0	77.8	-	100	-

Notes: patients in the RDQ group were treated with a bag of Reduqing granules and four capsules of dummy Lianhuaqingwen three times daily for 4 days. Participants in the LHQW group were administered a bag of dummy Reduqing granules and four capsules of Lianhuaqingwen three times daily for 4 days. RDQ: Reduqing; LHQW: Lianhuaqingwen; CCWHS: common cold with wind-heat syndrome. [a] Pearson's χ^2 test; [b] Fisher's exact test.

Table 3 Comparison of TCM symptom score before and after treatment ($\bar{x} \pm s$)

Group	n	TCM symptom score		Inside group		Between groups	
		Before treatment	After treatment	t value	P value[a]	F value	P value[b]
RDQ	36	16.2±4.5	3.0±2.9	14.34	0.000	-	-
LHQW	36	18.4±5.2	3.2±3.0	15.26	0.000	0.071	0.791

Notes: patients in the RDQ group were treated with a bag of Reduqing granules and four capsules of dummy Lianhuaqingwen three times daily for 4 days. Participants in the LHQW group were administered a bag of dummy Reduqing granules and four capsules of Lianhuaqingwen three times daily for 4 days. RDQ: Reduqing; LHQW: Lianhuaqingwen; TCM: Traditional Chinese Medicine. [a]Paired t-test. [b]Analysis of covariance (ANCOVA). ANCOVA was performed with change in TCM symptom score before and after treatment as dependent variable and score before treatment as covariate.

Time to fever relief and time to fever clearance

There was no statistically significant difference in median time to fever relief between RDQ group and LHQW group [RDQ (4 ± 8) h *vs* LHQW (4±6) h, P = 0.274]. Median time to fever clearance in RDQ group was (47 ± 8) h, which was slightly longer than that in LHQW group (36±7) h. However, Log-rank examination showed no significant difference between the two groups (P = 0.679) (Table 4) (Figures 2, 3).

In order to explore whether the time of defervescence of study drugs was related to the initial body temperature, patients were subgrouped into a ≤ 38 ℃ group and a > 38 ℃ group. In the ≤ 38 ℃ group, median time to fever relief in RDQ group was [(4.0 ± 0.5) h] and [(4.0±6.2) h] in LHQW group. No significant difference was found between the two groups (P = 0.595). There was no significant difference between the LHQW group [(34.0±2.3) h] and RDQ group [(47.0 ± 9.9) h] in the median time to fever clearance in the ≤ 38 ℃ subgroup (P = 0.652). In the > 38 ℃ group, no significant difference was found between the LHQW and RDQ group in the median time to fever clearance and time to fever relief. Median time to fever relief in the >38 ℃ group is higher than that in the ≤ 38 ℃ subgroup when ignoring the types of drugs [(20.0±10.0) h *vs* (4.0±4.7) h], while this difference was not stated as statistically significant (P = 0.776) (Table 5).

Laboratory tests

There were no obvious changes in blood biochemi-

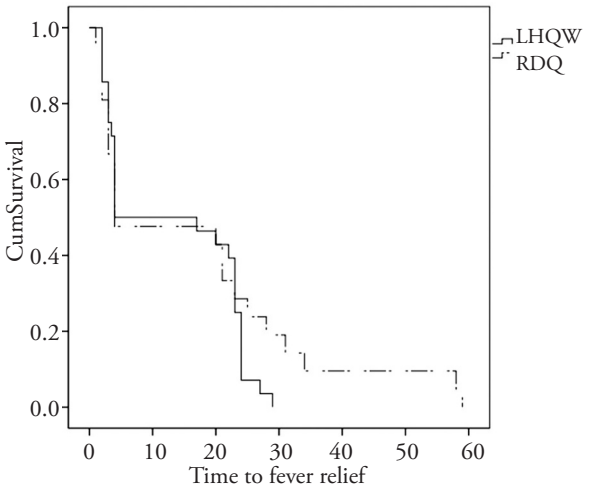

Figure 2 Comparison of time to fever relief (kaplan-Meier survival)
LHQW group: patients received Lianhuaqingwen capsules and dummy Reduqing granules; RDQ group: patients received Reduqing granules and dummy Lianhuaqingwen capsules.

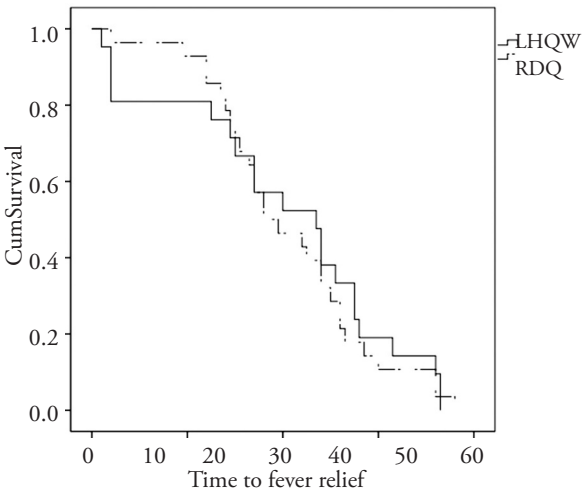

Figure 3 Comparison of time to fever clearance (kaplan-Meier survival)
LHQW group: patients received Lianhuaqingwen capsules and dummy Reduqing granules; RDQ group: patients received Reduqing granules and dummy Lianhuaqingwen capsules.

Table 4 Comparison of time to fever relief and time to fever clearance between RDQ group and LHQW group ($\bar{x} \pm s$)

Item	Group	*n*	Min (h)	Max (h)	$\bar{x} \pm s$	*P* value[a]
Time to fever relief	RDQ	36	1	59	4±8	0.28
	LHQW	36	2	29	4±6	-
Time to fever clearance	RDQ	36	2	73	47±8	0.679
	LHQW	36	4	76	36±7	-

Notes: patients in the RDQ group were treated with a bag of Reduqing granules and four capsules of dummy Lianhuaqingwen three times daily for 4 days. Participants in the LHQW group were administered a bag of dummy Reduqing granules and four capsules of Lianhuaqingwen three times daily for 4 days. RDQ: Reduqing; LHQW: Lianhuaqingwen. [a]kaplan-Meier survival (log-rank test).

Table 5 Comparison of time to fever relief and time to fever clearance between the group of initial temperature ≤ 38 ℃ and the group of initial temperature > 38 ℃ ($\bar{x} \pm s$)

Group	Medicine	Time to fever relief	*P* value[a]	Time to fever clearance	*P* value
T ≤ 38 ℃	RDQ	4.0±0.5	0.595	47.0±9.9	0.652
	LHQW	4.0±6.2		34.0±2.3	
T > 38 ℃	RDQ	25.0±18.8	0.290	40.0±31.0	0.809
	LHQW	20.0±20.9		45.0±7.8	
T ≤ 38 ℃	-	4.0±4.6	0.776	36.0±6.2	0.689
T > 38 ℃	-	20.0±10.0		40.0±4.7	

Notes: patients in the RDQ group were treated with a bag of Reduqing granules and four capsules of dummy Lianhuaqingwen three times daily for 4 days. Participants in the LHQW group were administered a bag of dummy Reduqing granules and four capsules of Lianhuaqingwen three times daily for 4 days. RDQ: Reduqing; LHQW: Lianhuaqingwen. [a]kaplan-Meier survival (log-rank test).

cal examination (include ALT, BUN, serum creatinine), blood routine examination (red blood cell count, hemoglobin content, white blood cell count) and so on.

Adverse events

A patient was found with mild cute liver damage during the treatment in RDQ group. Further investigation showed that it was not caused by the study drug. Therefore, he didn't quit the trial. Later, he was relief without any additional measures were taken.

DISCUSSION

Common cold is mainly caused by viruses (rhinovirus, coronavirus, respiratory syncytial virus, metapneumo virus and so on).[21-23] Thereafter, antiviral drugs are thought to be the most effective measures to treat colds. However, in most cases, treatment for common cold is directed at symptoms relief rather than treating the infection for the viral mutations, self-limiting aspects of the common cold, limitations to antiviral drugs such as viral resistance in some patients and so

on. Lots of attempts to treat common cold were controversial and many uncertainties remain when it comes to prevent and treat the common cold. Such as antihistamines may slightly reduce local symptoms of common cold, but the overall effects were small.[24] Antihistamines as mono therapy were almost ineffective in the treatment of common cold. Decongestants may relieve nasal symptoms, but its clinical significance were still uncertain.[25-27] Nonsteroidal anti-inflammatory drugs were effective in relieving pain and fever in people with common cold, but ineffective in relieving other symptoms.[28] Antibiotics is not useful given the viral etiology of the disease. In this case, the possible availability of an effective and safe treatment could be a useful treatment and TCM is a good choice. TCM has been widely used to treat CCWHS in China. However, the available evidence of the clinical efficacy of these formulas is inadequate.

This randomized, double-blind, double-dummy, parallel, positive-controlled trial demonstrated that Reduqing granules is effective and safe in the treatment of common cold with wind-heat syndrome. All the symptoms were relief after the four-day treatment of Reduqing granules as expected. There were no statistically significant differences in total markedly effective rate and total effective rate between Reduqing group and Lianhuaqingwen group, just as change in TCM symptom score, time to fever relief and time to fever clearance. What's more, no-drug related serious adverse events were reported during the trial. Oral Lianhuaqingwen capsules and Reduqing granules were all well tolerated.

Lianhuaqingwen capsule was selected to be positive-controlled medicine in this trial. This was due to the reason that Lianhuaqingwen capsules had proved to be effective in the treatment of common cold by standard clinical trials.[17] What's more, a systematic review demonstrated that Lianhuaqingwen capsule was more effective than other TCM and western drugs in alleviating flu-like symptoms when treating influenza.[29] Besides, Lianhuaqingwen capsules, which has been listed, has similar indications with Reduqing granules.

Since the difference of the packaging of Lianhuaqingwen capsules and Reduqing granules cannot be overcome, a double-blind, double-dummy trial was conducted. The combination of study drugs, controlled drugs and relevant dummy drugs were identical in shape, size, color and smell. Besides, both the participants and the clinical pharmacist were blinded to the treatment, which guaranteed the validity of the trial.

CCWHS is the most common type. According to TCM therapy, CCWHS should be treated by clearing heat and releasing stagnated Lung-*Qi*. Reduqing granules, manufactured by Zhujiang Hospital, has been widely used in the treatment of CCWHS clinically. It is composed of fifteen herbs include Daqingye (*Folium Isatidis*), Lianqiao (*Fructus Forsythiae Suspensae*) and so on. Given the multiple composition of Reduqing granules, it's not possible to attribute its efficacy in the treatment of CCWHS to a single ingredient. The contribution of the 15 ingredients is not known. The exact mechanism of each herb is also unknown. As a result, more studies are needed to explore the mechanisms of action and properties of the identified components.

This study had some potential limitations. Firstly, this trial was conducted with a small sample size that only 72 participants were involved in the trial, although none was lost or withdrew from the trial. Secondly, the duration of treatment and follow-up was comparatively short, the symptoms of some patients were not resolved completely at the end of study. At last, considering self-limiting aspects of the common cold, a placebo group should have been set, but our study did not. Given above, the conclusion in this trial is not representative. Large scale trials with careful design are needed to objectively evaluate the efficacy and safety of Reduqing granules in CCWHS in the future.

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