Binafuxi Granules in the treatment of common cold with heat syndrome based on traditional Uighur medicine: study protocol for a multicenter randomized controlled trial

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Method Article

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Abstract

Background: Common cold is a highly prevalent illness with significant impact on society and health care. Common cold with heat syndrome (CCHS) is one of most common type based on traditional Uighur medicine (TUM) syndrome differentiation, which is widely used in Central Asia. The study is designed to explore the efficacy, safety and optimal therapeutic dosage of Binafuxi Granules in treating CCHS.

Methods: This is a multicenter, randomized, double-blind, placebo-controlled, phase II clinical trial. 240 participants will be enrolled from 5 centers across China and randomly assigned to the high-dose group, low-dose group or placebo control group in a 1:1:1 ratio. All eligible patients will receive test drugs twice daily for 3 days. The primary outcome is the time to fever relief. Secondary outcomes include the time to fever clearance, duration of primary symptoms and each symptom, change in TUM symptom score.

Discussion: This is the first placebo-controlled randomized clinical trial for a Uighur medicine in treating common cold. It will provide robust evidence on the efficacy and safety of Binafuxi Granules in the treatment of CCHS.

Trial registration: The registration number is ChiCTR-IIR-17013379, which was assigned by the Chinese Clinical Trial Registry on 14 November 2017.

Background

The common cold is a highly prevalent upper respiratory tract infectious disease, mainly caused by more than 200 viruses [1]. Varying among different viruses, the symptoms of the common cold often include sneezing, runny nose, nasal congestion, sore throat, coughing, fever and general malaise [2, 3]. The duration of these symptoms is generally 3–7 days, but occasionally up to several weeks [1]. Despite generally mild, the common cold still has a significant impact on society and health care [4]. According to previous data, the common cold is the third most common diagnosis in office visits [5]. It even can be a trigger for severe and even fatal illness in individuals with chronic respiratory diseases or other underlying conditions [6].

So far, the treatment of common cold is aimed at symptom relief. The complementary and alternative medicine (CAM), primarily herbal and nutritive remedies, has become very popular recently [7]. Many clinical studies of CAM, such as Echinacea, Vitamin D, Vitamin C, Probiotics, Ginseng and Chinese herbal medicine, have showed the efficacy and safety for common cold [8-14]. Traditional Uighur medicine (TUM) is the common traditional medicine in Xinjiang Uygur Autonomous Region, China. With a history of more than 2,500 years, it's based on the ancient Uighur medicine theory, combined the theories of traditional Chinese medicine (TCM), ancient Greece medicine, Egyptian medicine, Arabian medicine, and Indian medicine. The humorism, one of the most important TUM theories, is based on the Four materials (fire, air, water, and earth) and the four Mizaj (temperaments) (hot, cold, moist, and dry) [15]. And the Humorae theory indicates that the Hilit (body fluid) is composed of Kan (blood), Belghem (phlegm), Sapra (yellow bile), and Savda (black bile) [16]. Based on humorism, the common cold, which is also called as

Zukamu in TUM, can be divided into heat syndrome and cold syndrome. The common cold with heat syndrome (CCHS) is generally related to the imbalance status and abnormal change of Kan (blood) and Sapra (yellow bile) in the four body fluid [17]. CCHS primarily characterized by fever (the body temperature >38 degrees Celsius), sore throat, nasal congestion, nasal discharge, cough and headache.

The Uighur herbal medicine Binafuxi prescription, derived from the Uighur medicine ancient books, including “Mahzinul Murakkibat (Uighur Combination Medicine)” and “Karabadin Azam”, has been used for CCHS over 300 years. The prescription is mainly composed of Tianshanjincai (Viola tianshanica Maxim), Heguotenggen (Roots of Operculina Turpethum), Gancaojingao (Extractum Glycyrrhizae), Meiguihua (Flos Rosae Rugosae), Sikamoniyazhi (Resina Scammoniae) and Alihong (Sclerotium Fomitis Officinalis). Binafuxi granules is based on Binafuxi prescription and has been approved by the State Food and Drug Administration of China (SFDA) for a clinical trial (Approval Number: 2014L01342). Unpublished pharmacologic experiments demonstrated that Binafuxi Granules had the effects of relieving fever, alleviating cough, sweating and reducing inflammation. The data showed that Binafuxi Granules can significantly reduce endotoxin-induced fever in rabbits administered clinical equivalent doses (0.52g/kg) of Binafuxi Granules. Additionally, there was no chronic toxicity found in rats administered different doses of Binafuxi Granules (30x, 15x and 7.5x normal dose) for 1 months except some diarrhea cases occurred in the 30x group.

TUM has benefited many patients with common cold since ancient times. However, high quality clinical study of TUM on common cold has not been found. In conformity with the Drug Administration Law of the People’s Republic of China and Good Clinical Practice (GCP) issued by SFDA, we designed this randomized clinical trial to evaluate the efficacy and safety of Binafuxi Granules in patients with CCHS and to detect the optimal therapeutic dosage.

Methods/design

This trial is a multicenter, double-blind, placebo-controlled and randomized phase II clinical study, which has been authorized by the SFDA (Approval Number: 2014L01342) and registered with the Chinese Clinical Trial Registry (ChiCTR-IIR-17013379). The study is financially supported by Xinjiang Yinduolan Uighur Medicine Co. Ltd., Xinjiang, China, which had or will have no role in the study design, study conduct, data management, or decision to submit study results. This trial will be conducted in five trial sites in China. A total of 240 patients will be enrolled and randomly allocated to the high-dose group, low-dose group or placebo control group in a 1:1:1 ratio. Binafuxi Granules and placebo will be provided for 3 days to subjects in three study groups, respectively. The study flow chart is shown in Fig. 1.
The trial protocol has been approved by the Ethics Committee of Clinical Trials and Biomedicine of West China Hospital of Sichuan University (Number: IRB-2017-5). All eligible patients have to provide their signed informed consent prior to enrollment. The privacy of all subjects will be properly protected. The personal information of eligible patients will be concealed by identification codes and all records will be stored in a locked location.

Recruitment

By means of advertisements and recommendations, we recruit participants at the following 5 research sites across China: 1) West China Hospital of Sichuan University, 2) Shanghai Traditional Chinese Medicine Hospital, 3) Xinjiang Traditional Chinese Medicine Hospital, 4) Ruikang Hospital Affiliated to Guangxi University of traditional Chinese medicine, 5) Lishui People's Hospital. Each site will recruit patients equally.
Eligible participants in above 5 sites will be enrolled by the investigators who have been well-trained. The investigators will talk with eligible patients about the study and obtain informed consent from them. The principal investigator is responsible for subject recruitment in each site.

Inclusion criteria

The inclusion criteria are as follows: (1) meet the diagnosis of common cold according to Western medicine; (2) meet the diagnosis of CCHS according to traditional Uighur medicine; (3) with fever and body temperature between 38 degrees Celsius and 39 degrees Celsius; (4) symptom presenting within 24 hours; (5) age between 18 and 65 years old; (6) voluntarily participate and sign the informed consent.

Exclusion Criteria

The exclusion criteria are as follows: (1) with influenza, acute or chronic rhinitis, acute sinusitis, suppurative tonsillitis, pneumonia and tuberculosis; (2) white blood cell count 11.0×109/L and/or neutrophils percentage > 75%; (3) taking any medication to treat common cold; (4) liver function levels (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) 1.5 times higher than the upper limit of normal, abnormal serum creatinine; (5) with serious primary diseases of the cardiovascular, pulmonary, kidney, liver, neurological and hematological system; (6) pregnant or in lactation or plan to get pregnant; (7) allergic or might be allergic to ingredients of the study drug; (8) participating in or have participated in other drug clinical trials within the last 3 months; (9) identified by the investigator as inappropriate to participate in this study.

Diagnostic criteria

The diagnosis for the common cold in Western medicine is established according to the diagnostic criteria for the common cold of acute upper respiratory tract infection of Internal Medicine (2013, Version 8) [18]. The typical clinical symptoms of common cold include sneezing, nasal congestion, nasal discharge, fever and sore throat.

The TUM diagnosis of CCHS is based on the Clinical Research Guidelines for Treatment of Common Cold with New Uyghur Medicine (2017) [17]. The TUM diagnostic criteria for CCHS include primary symptoms, secondary symptoms, signs for the tongue and signs for the pulse. The primary symptoms include fever, nasal congestion, nasal discharge and sore throat. The secondary symptoms include cough, headache, thirsty, sore limbs and sweating. The signs for the tongue are red tongue and yellow thick tongue coating. The signs for the pulse are hard and rapid. To meet the diagnosis of CCHS, patients should have at least

two of the primary symptoms in which fever is essential, and at least two of the secondary symptoms, as well as the TCM signs for the tongue and pulse.

Interventions

Binafuxi Granules (Batch No. Y170521) and Placebo Granules (Batch No. Y170520) are manufactured by Xinjiang Yinduolan Uighur Medicine Co. Ltd., Xinjiang, China. The minimum effective dose of Binafuxi Granules is 2.75 g. According to preparation of Chinese herbal medicine placebo, the placebo is made of 20-fold dilution of 2.75g of Binafuxi Granules and maltodextrin with adding artificial pigment and flavoring agents [19]. Patients in placebo group will be administered Placebo Granules which are almost identical to the Binafuxi Granules in appearance, smell and taste. All test drugs are concealed in unified and sealed packages and each package contains 2.75g dosage. In each site, an independent drug administrator is responsible for dispensing, reclaiming, storing and recording of all test drugs. Patients in the high-dose group, low-dose group or placebo group will receive Binafuxi Granules 2 packages (5.5g) twice daily, Binafuxi Granules 1 package (2.75g) plus placebo 1 package (2.75g) twice daily, or placebo 2 packages (5.5g) twice daily, respectively. All test drugs will be dissolved in warm water and taken orally 2 times daily for 3 days. Throughout the trial, participants will be visited at baseline and the 4th day post baseline. The study procedures comply with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Checklist (see Fig. 2). We will not regularly follow up all patients except for experiencing an adverse event.

Concomitant treatments and forbidden drugs

During the study, if the body temperature of a patient rises to higher than 39.0°C and/or the body temperature do not drop significantly at 48h post administration, paracetamol can be used to bring down a fever following doctor's advice. Patients can continue their treatments for underlying conditions, such as diabetes or hypertension. Any rescue treatment for drug adverse events is also permitted in this study. Besides, considering the related impacts on the study results, the patient with drug adverse event may be withdrawn from this trial. All concomitant medications or treatments in the study must be recorded carefully in the case report form (CRF). Any other medication or therapy for common cold is not allowed during the study.

Randomization and blinding

According to a stratified block randomization method, 240 patients are stratified by study center and randomly assigned to the high-dose group, low-dose group or placebo control group in a 1:1:1 ratio. The random sequence and the randomization list of each center will be generated by the independent specialist, using the PRCO PLAN function of the analysis system of SAS software (SAS, Cary, NC, USA). The independent drug administrator will assign numbered packs of study drugs to eligible patients in order by randomization list. The randomization sequence will be concealed in a lightproof sealed envelope, which will be kept by the leader and the sponsor

Treatment allocation will be blinded to the participants, investigators and statisticians throughout the study. Test drugs and placebo will be ensured identical in appearance, color and taste. All drugs are

concealed in uniform packages with the number labels. During the study, the blinding envelope will not be allowed to reveal unless for the medical emergency purposes. An emergency letter including random sequence and assignment has been prepared in each center. In any emergency medical situation, such as serious adverse event or deteriorative condition, unblinding process will be started after contacting the sponsor and the primary investigator. The investigator should record the details of urgent unblinding and make sure the corresponding patient is excluded.

Outcome measures

Primary outcomes

The primary outcome of the study is the time to fever relief, which is defined as the time (number of hours) from the first dose of the test drug until the axillary temperature dropping at least 0.5°C. All patients are required to record their axillary temperature in the subject diary every 1 hour within the first 6 hours. And then, if the temperature is ≥37.3°C, it should be recorded every 2-4 hours, and if the temperature is lower than 37.3°C, it should be recorded at 8 am. and 4 pm. every day. If the temperature is below 37.2°C and no longer rises for 24 hours, it doesn't need to be recorded. Investigator will check and collect the subject diary, in which the data will be acquired and evaluated at the 4th day.

Secondary outcomes

Secondary outcomes include the time to fever clearance, duration of primary symptoms and each symptom, change in TUM symptom score.

Time to fever clearance

The time to fever clearance is defined as the time (number of hours) from the first dosing to the axillary temperature dropping below 37.2°C and no longer rising for 24 hours.

Duration of all symptoms and each symptom

The duration of all symptoms is defined as the number of hours from enrollment to the time that all symptoms completely disappear. Each patient is required to record any change in symptoms in the subject diary. Investigator will assess the duration of all symptoms and each symptom.

Change in TUM symptom score

Currently, there is no grading evaluation standard for Uygur medicine. In this trial, the TUM symptom graded score system follows the Guidelines for Clinical Research on New Drug of Chinese Medicine [20] (see Table 1). The primary symptoms are given a graded score (none = 0, mild = 3, moderate = 6, severe = 9). The secondary symptoms are given a graded score (none = 0, mild = 1, moderate = 2, severe = 3). TUM signs will also be assessed, but not scored. The total score of TUM symptoms (including primary and secondary symptoms) will be summed on baseline (symptom score before treatment) and the 4th day (symptom score after treatment). The sum of all symptom scores is the cumulative TUM symptom score.

The change in cumulative TUM symptom score is assessed by the percentage of symptom score reduction (PSSR), which is calculated according to the following formula:

PSSR
Based on the therapeutic effect evaluation system, the improvement of TUM symptoms will be categorized into clinical recovery (PSSR≥70%) and invalid (PSSR< 70%). .

Table 1 Symptom Scoring system and TUM sign.

TUM Symptoms	Score			
Primary	**0**	**3**	**6**	**9**
Fever	None	37.3℃-37.9℃	38℃-38.5℃	≥38.5℃
Nasal congestion	None	Mild	Moderate	Severe
Nasal discharge	None	Occasionally	Sometimes	Frequently
Sore throat	None	Dry throat with slight pain	Significant with obvious pain when swallowing	Sore and swollen throat with severe pain
Secondary	**0**	**1**	**2**	**3**
Cough	None	Occasionally in daytime	Occasionally day and night	Frequently day and night
Headache	None	Slight and occasionally	Slight and lasting	Severe and affect working
Thirsty	None	Dry mouth	Moderate	Severe and drink plenty of water
Sweating	None	Mild	Moderate	Severe
Sore limbs	None	Slight	Moderate	Severe
Cumulative symptom score	**Primary symptom scores + Secondary symptom scores**			
TUM sign	**Unscored**			
Tongue proper	□Red □Others:			
Tongue coating	□Thick and yellow □Others:			
Pulse condition	□Hard and rapid □Others:			

Safety assessment

Safety assessment, including physical examination and laboratory tests, will be performed at baseline and the 4th day. Physical examination includes vital signs (temperature, respiration, heart rate, and blood pressure) and conventional examination (chest, abdomen, nervous system, etc.). Laboratory tests include

routine blood test, urine analysis, stool test, blood electrolytes, liver function test (ALT, AST, ALP, TBil, and GGT) and renal function test (BUN, serum creatinine, microalbuminuria, urinary nag enzyme and serum cystatin C). In addition, before treatment, all patients are required to undergo a chest X-ray and electrocardiogram, and female patients of reproductive age are required to take a urine pregnancy test. All adverse events (AEs) should be truly recorded in detail on the adverse event form (AEF) and followed up to completion. The patient experiencing an AE will be treated appropriately until recovery from it. The serious AEs (SAEs) is defined as an adverse event resulting in death, a life-threatening event, an illness requiring hospitalization or severe disability, and it should be recorded and reported to the principal investigator, SFDA, ethics committee and the sponsor within 24 hours.

Quality control

As the Monitoring center, Beijing QiHuang Clinical Drug Research Center is in charge of monitoring implementation of trial protocol, data of CRFs and safety of participants, as well as contacting and coordinating the various units. The center will assign the Clinical Research Associate (CRA) to regularly review CRFs and monitor the row data every week. The CRA is blind to trial assignment. Monitoring results should be presented to the principal investigator in each site. The principal investigator will be responsible for the implementation of the trial, which should be following the standard operation procedure (SOP) for quality assurance and quality control. Any protocol modification should be documented with appropriate justification and approved by the sponsor, primary investigator in each unit and statisticians. Then the final version should be presented to the Ethics Committee, and the SFDA if required.

Sample size calculation

Using “One-Way Analysis of Variance F-Tests using Effect Size” in PASS (version 15.0.5), we estimate the sample size with a significance level of 0.05. To our knowledge, no previous study reported the effective size related to the time to fever relief in our target population (patients with common cold). Thus, we used η2 as an alternative measure of effect size (calculated by $\sigma m^2 / (\sigma m^2 + \sigma^2)$ to estimate the sample size [21-23]. Generally, the effect size can be defined as follows: An $\eta^2 = 0.0099 \approx 0.01$ is a small effect. An $\eta^2 = 0.0588 \approx 0.06$ is a medium effect. And, an $\eta^2 = 0.1379 \approx 0.14$ is a large effect [21-23]. In the study, we would like to determine the sample size required to detect a medium effect when the power is 0.90. Therefore, total sample of 204 subjects (68 for each group) would be required. Assuming an overall 15% drop-out rate of subjects, 80 subjects should be recruited in each group. Finally, the total sample size is determined to be 240 patients.

Data management

All CRFs in triplicate will be reviewed by the investigators and CRA. The completed CRFs will be securely stored in a locked location and finally sent to two independent data administrators, who will responsible for data entry, inspection and management in a specified statistics center. Once the trial is completed, the principal investigator, the sponsor, data administrators and statisticians will perform a blind review to

confirm the dataset. The final database will be locked and analyzed in line with the statistical analysis plan.

Statistical analysis

The independent statistician will conduct the data analysis using SAS 9.4 software (SAS, Cary, NC, USA), in accordance with the statistical analysis plan for this trial. The primary analysis set for efficacy is the full analysis set (FAS) with an intention-to-treat (ITT) principle, in which all patients treated with at least one dose of study drug and clinical observation record should be involved. According to an ITT principle, the last-observation-carried-forward (LOCF) imputation method will be used to approach for missing data. Patients who fulfil the protocol without any major deviations will be involved in per-protocol set (PPS). And all participates who are treated at least one dose of the study drug and have the safety data will be included the safety set (SS). Baseline characteristics of all subjects will be analyzed using descriptive statistics for continuous variables and categorical variables. Time to fever relief, time to fever clearance and duration of all symptoms will be estimated by the Kaplan-Meier technique and compared by the stratified log-rank test. Comparisons among three groups of TUM symptom scores will be conducted by an analysis of variance (ANOVA) and Bonferroni method. Covariates designated as potential confounders will include: age, gender, Body Mass Index (BMI), and duration of symptomatic illness prior to enrollment. The improvement of TUM symptoms will be estimated with descriptive analysis for number and proportion of patients achieving clinical recovery. Prespecified subgroup analysis and sensitivity analysis involving covariance analysis will evaluate the primary outcomes according to the age and gender. In the multicenter trial, the Cochran-Mantel-Haenszel (CMH) test will be performed to analyze stratified variables. A 2-sided P-value of <0.05 is considered as statistically significance.

Discussion

To date, this study is the first randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of Uighur medicine in common cold. In Central Asia, TUM is one of the most common traditional medicines, which has benefited many people in China and the other countries. So far, most of TUM researches have referred to skin disease, urogenital disease, rheumatism, digestive system disease and respiratory system disease [24]. To our knowledge, few of standardized clinical trials designed for TUM has been reported.

Binafuxi formula has been used in Xinjiang Uygur Autonomous Region of China for over 20 years and been proven effective in treating CCHS based on local clinical experiences. Refer to five different regions in China, the results of our study will provide a stronger evidence for popularization of Binafuxi Granules. We designed this study to practice methodology of syndrome differentiation for clinical research in TUM. According to grading standard for TCM, we will first perform the TUM symptom graded score system in this trial, and then verify that would be feasible. It will provide a scientific quantitative standard to estimate the efficacy of TUM for CCHS. In the light of TUM theory for CCHS and characteristics of Binafuxi, the time to fever relief and the duration of fever will be primarily observed in this study [17]. Both

Western and TUM efficacy evaluation will be performed, so as to provide more powerful evidence for TUM therapy on common cold.

Nevertheless, there are two potential limitations in this study. In screening period, we will not perform culture examination for excluding patients with potential influenza. Due to spending more time on culture detection, participants may miss the best time to enroll in the study. In order to avoid mistakenly recruiting, all physicians involved in this study will carefully screen patients. Accordance with inclusion criteria and exclusion criteria, we will strictly exclude any participates who have a body temperature higher than 39 degree centigrade and severe symptoms. Patients with chill and/or other flu-like symptoms will be excluded or advised to detect influenza virus. Besides, in this study, we do not explore the mechanisms underlying CCHS and potential pathways through which Binafuxi can work in treating common cold, which may need further research.

In conclusion, this protocol is rigorously designed for exploring the efficacy and safety of Binafuxi Granules on the common cold with heat syndrome. As we know, this study will be the first multicenter, double-blind, placebo-controlled and randomized clinical trial for a Uighur medicine in treating common cold. In addition, it will provide robust evidence for assessment of efficacy and safety of Binafuxi Granules in treating CCHS, and may help selecting optimal therapeutic dose for the next phase III clinical trial.

Trial Status

The study is currently in the process of recruiting participants. Recruitment of participants commenced on 5 February 2018 and will be completed in early May 2019. The protocol version number and date is Z-BNFX-GR-□-2017-YDL-01 and 22 May 2017.

Abbreviations

AEs: Adverse events; ALP: Alkaline phosphatase; ALT: Alanine transferase; ANOVA: Analysis of variance; AST: Aspartate transferase; BMI: Body Mass Index; BUN: Blood Urea Nitrogen; CAM: Complementary and alternative medicine; CCHS: Common cold with Heat syndrome; CRF: Case report form; ECG: Electrocardiogram; FAS: Full analysis set; GGT: Gamma-glutamyl transpeptidase; GCP: Good Clinical Practice; ITT: Intention-to-treat; LOCF: last-observation-carried-forward; PPS: Per-protocol set; PSSR: Percentage of symptom score reduction; SFDA: State Food and Drug Administration; SOP: Standard operation procedure; SS: Safety set; TBil: Total bilirubin; TCM: Traditional Chinese medicine; TUM: Traditional Uighur medicine; USA: United States of America.

Declarations

Acknowledgments

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Funding

The study is financially supported by Xinjiang Yinduolan Uighur Medicine Co. Ltd., Xinjiang, China. The sponsor had and will have no role in the study design, study conduct, data management, and decision to this manuscript.

Availability of data and materials

The data will be available to other investigators.

Authors' Contributions

JM, BS, XZ, YC and BM contributed to the design and development of the study protocol ethics, trial registration, and the manuscript draft. XZ was responsible for statistical design. BM was the general supervisor for this research. BS and YC participated in the coordination of the trial and recruiting patients. All authors reviewed the content and approved the final version.

Ethics approval and consent to participate

The trial protocol has been approved by the Ethics Committee of Clinical Trials and Biomedicine of West China Hospital of Sichuan University (Number: IRB-2017-5). All eligible participates have to provide their signed informed consent prior to enrollment. The trial results will be disseminated through scientific journals or presentation at scientific conference.

Consent for publication

Not applicable.

Conflicts of Interest

The authors declare that they have no competing interests.

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Figures

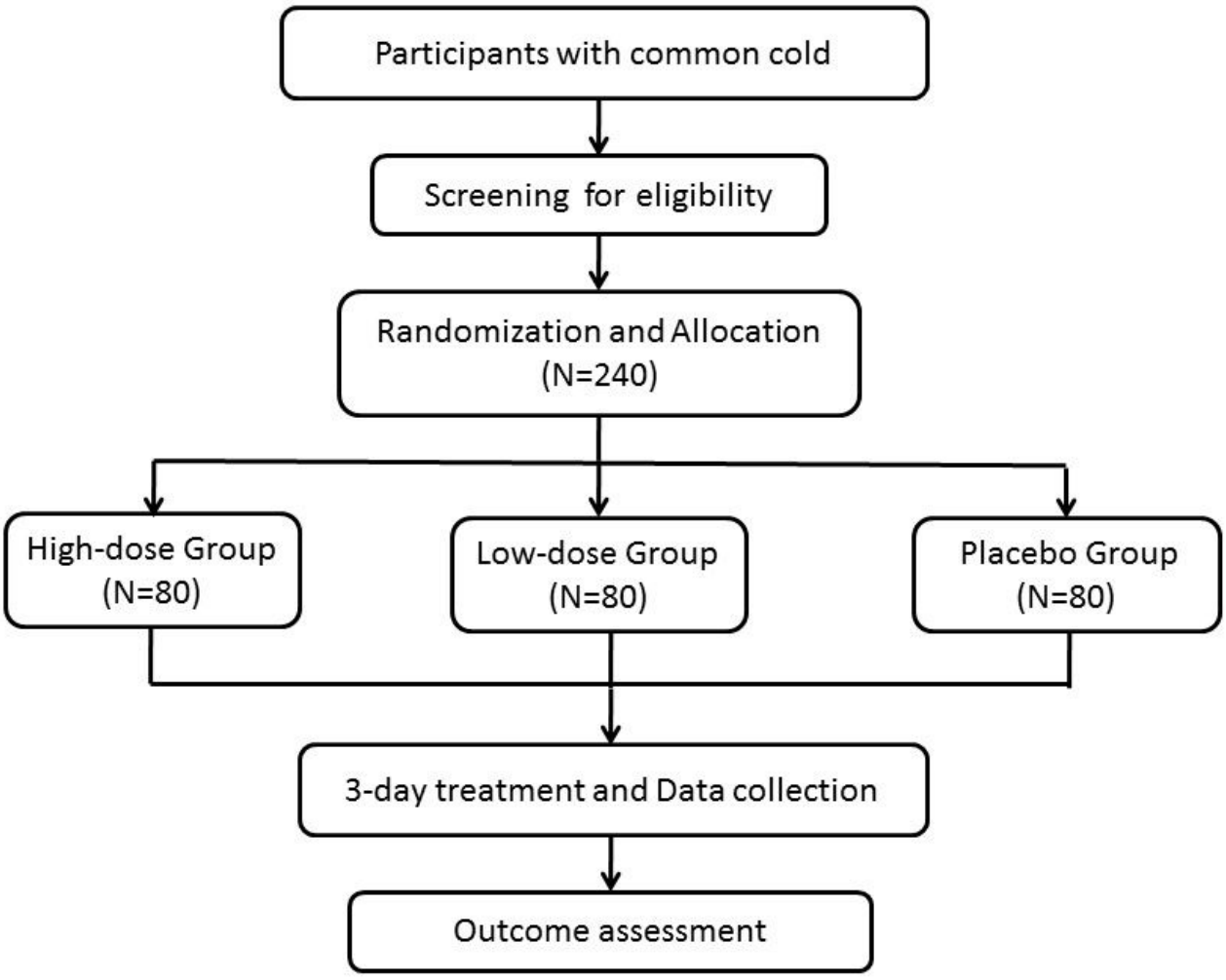

Figure 1

Flowchart. 240 patients will be recruited and randomly allocated to one of three groups (high-dose group = 80; low-dose group = 80; control group = 80). After 3 days, we will analyze the data and make assessment.

	Study Period		
	Enrollment	Allocation	Close-out
Visits	Visit 1	Visit 2	Visit 3
Time point	Day 0	Day 1	Day 4
Basic medical record			
Informed consent	×		
Demographic information	×		
Medical history	×		
Comorbidity	×		
Combined medication	×	×	×
Physical examination	×	×	×
Eligibility screen	×		
Efficacy assessment			
The time to fever relief			×
The time to fever clearance			×
Duration of symptoms			×
TUM symptom score		×	×
Safety assessment			
Vital signs	×		×
Routine blood test	×		×
Urinalysis	×		×
Stool routine	×		×
Liver function test	×		×
Renal function test	×		×
Electrocardiogram	×		×
Chest X-ray	×		×
Urine pregnancy test	×		×
Adverse event record			×
The Others			
Drug distribution		×	
Drug recycling and count			×

Figure 2

Study schedule and SPIRIT figure

Supplementary Files

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