Efficacy and Safety of Susu Xiao`er Zhike Granules for Treating Acute Cough Due to Common Cold in Children: A Chinese Patent Medicine Study Protocol for Randomized Controlled Trial

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Abstract

Background: Cough is the most bothersome symptom, while more than two-thirds of children with common cold have to endure it for weeks. Susu xiao`er zhike granules (Susu) which used to be a clinical experienced herb formula for treating cough caused by common cold, is reproduced into a patent medicine for meeting market demands as a new drug. This protocol is designed with the aim of exploring the efficacy of Susu on shortening duration and reducing severity of cough, and observe the safety used in children.

Methods/design: This is a protocol for a randomized, double-blind, dose exploration, multicenter clinical trial. A total of 240 children aged 6-14 years old (<14y) with acute cough caused by common cold will be randomly assigned to one of three groups, respectively take Susu of high dose (double-dose), medium dose (recommended dose) and very low dose (5% recommended dose) for 5 days. The primary outcome is clinical cure time of cough. Secondary outcomes will include clinical cure rate, onset time, AUC of cough severity VAS score-time, PAC-QoL, PGA, cure rate of symptoms and efficacy of traditional Chinese syndrome. For safety assessment, adverse events, laboratory tests and vital signs will be observed. Participants will complete the trial after 1-day follow up assessment. We collect the main data from subject diary.

Discussion: The study is a phase II clinical trial that will evaluate the efficacy of a Chinese patent medicine in the treatment of cough in children.

Trial registration: Chinese clinical trial registry, ChiCTR1900028377. Registered 20 December 2019, http://www.chictr.org.cn/showproj.aspx?proj=46643

Background

Common cold is an acute upper respiratory tract infection disease, which mostly caused by a variety of viruses. [1-3] It has a high prevalence during winter and spring, and will last 14 days in children younger than 6 years or 5-7 days in older.[4,5] Clinical symptoms include feverishness, nasal congestion, running nose, cough, headache, etc. However, it varies from patient to patient due to age and virus type, for infants, fever and discharge are predominant manifestations, while cough and nasal symptoms are more common in children. Almost 2/3 of children with common cold are disturbed by cough, which is the main disruptive symptom that people seek help from doctors, and has significant impact on the quality of life for children and their families.[6-8] Cough always last longer than other symptoms, will linger for about 10 days in general.[9] Prescription antitussives or expectorants are not recommended to use when treating cough, considering it may result in retention of secretions and potentially harmful airway obstruction. Existing treatments for acute cough are also limited by their lack of efficacy, [10-12] such as honey, cough drops or fluids, which are commonly used in the home. [13]

Susu used to be a clinical experienced Chinese herb formula prescribed by Zhou Ronghua for treating acute cough caused by common cold. The ingredients includes *Hua Ju Hong (citri grandis exocarpium), Qiao Rui Su(scabbard rui Sue), Zi Su Ye(perillae folium), Jie Geng(platycodonis radix), Gan Cao(glycyrrhizae radix et rhizonma),*which relieving cold and cough, resolving phlegm in traditional Chinese medicine theory. Its pharmacodynamical research showed that Susu could significantly prolonged the cough latent period, decreased frequency of cough induced by SO_2, and promote phenolsulfonphthalein excretion in mice. It was also found to suppress ear swell induced by xylene, and decrease the pain-like twisting number in mice. To standardize the quality and make it easier to take, we reproduced it into a patent medicine and design this trial for evaluating it.

Methods/design

Trial design

This study designed as a randomized, double-blind, and parallel dose-exploring, multicenter clinical trial.

Participants

Recruitment

7 clinical research centers in different provinces of China will conduct this trial: First Teaching Hospital of Tianjin university of TCM(leader center), Affiliated Hospital of Chengdu University of Traditional Chinese Medicine, Hubei Provincial Hospital of TCM, Shanghai Hospital of Traditional Chinese Medicine, The First Hospital of Hunan University of Traditional Chinese Medicine, Xiamen Hospital of Traditional Chinese Medicine and Yunnan Provincial Hospital of TCM. Recruitment information will be advertised by internet, roll screen or news board in pediatric department of hospitals.

Inclusion criteria

1.Patients with symptom of cough should meet the diagnostic criteria of common cold[13,14] and wind-cold syndrome[15];

2.Aged 6-14 (<14) years old;

3.The VAS score of day-time or night-time cough ≥40mm;

3.The cough duration ≤48 hours;

4.Maximum axillary temperature within 24 hours before visit ≤38℃;

5. All patients(≥8 years old) or their statutory guardians should signed the informed consent form(ICF) first at the very begin of entering the study.

Exclusion criteria

1. Accompanied by swelling and pain of pharynx and obvious heat image;
2. White blood cell count, absolute value of neutrophils and c-reactive protein≥1.2 times of normal value, so that the investigator considers patient has more possibility of bacterial infection;
3. Complications (such as otitis media, sinusitis, acute bronchitis, pneumonia) have occurred;
4. Patient had acute bronchitis or pneumonia, and it cured less than 8 weeks;
5. Having medical history of seasonal or perennial allergic rhinitis, chronic sinusitis, chronic otitis media, bronchial asthma, chronic cough, or recurrent respiratory tract infection;
6. Severe malnutrition;
7. Presenting with respiratory system, circulatory system, hematopoietic system disease, or mental disorder;
8. Allergy to any component of study drugs;
9. Received antihistamines, antitussive agents or steroid drug(oral or inhaled) the day before visit;
10. Other situations that difficult to complete the study.

Subject's exit criteria

The investigator can decided the patient to withdraw, when patient: having an allergic reaction, or serious adverse events(SAE); with new feverish or hyperpyrexia during study; occurring complications (such as otitis media, sinusitis, acute bronchitis, pneumonia); with compliance < 80%, or > 120% ; adding or changing unallowable drug according to the protocol; breaking blindness; found to have seriously violated the inclusion and exclusion standards after randomization. Patients have right to withdraw for any reason during the study.

Randomization, allocation concealment and blinding

240 subjects will be randomly allocated into three groups according to a randomized list produced by statistician who will not participate in the final statistics using SAS V9.2. Block randomization method will be used with search center as the stratified factor. 240 subjects are divided into 40 blocks with the block size as 6.The documents of random process and randomized list will be enclosed in an opaque envelop.

Participants, investigator, clinical research coordinator, clinical research associate and statistician are blinded in this study. To conduct, we will dilute or concentrate the drugs to make all different dosage experimental drugs are in same specifications when producing. Flavorings and colorants will be added for ensuring the taste and appearance consisted. All drugs will be repacked into medicine boxes with same appearance and drug ID on the label outside. Investigators enroll participants who meet the criteria and login EDC system to get the drug ID according to the allocation sequence which has imputed in EDC. Pharmacist of central pharmacy will dispend drugs by drug ID to make sure all participants are in blinding.

We prepared the blind codes as 2 levels. The first-level only lists the groups that patient in which can be uncovered for analysis after database locked. The second-level blind codes tell the dosage that the group used, and should not be uncovered before summarizing.

E-emergency envelope will be used by electronic data capture system. All search center will receive an opaque envelop with EDC and safety information in it. Investigator should open the E-emergency envelope online under the following conditions: patient occurs SAE or serious infection; patient`s condition worsened and need for necessary emergency treatment.

Interventions

All drugs of different dosage groups will be packaged as 9g granule per bag. Drug of high dose, medium dose, and very-low dose of Susu contains 20.25g, 10.13g and 0.51g crude herbs respectively. Very-low dose is considered as placebo in this study considering the difficulty in preparation of placebo for chinese herb medicine.

All patients should take one bag medicine each time, twice a day (7-9AM and 5-7PM) for five days. To make sure everyone takes 10 times of medicine and can fill the diary regularly and synchronously, we rule that the first dose time should be 5-7PM on Day 1, and the final dose time is 7-9AM on Day 6.

Drugs with therapeutic effects on cough should not be combined during the study, including antihistamines, antitussive, expectorants, bronchodilators, antibiotics, antiviral drugs and any traditional Chinese treatment. The participants will be required to report all experimented and combined treatments in diary, and that information will be recorded on case report form (CRF).

Outcome measures

Primary outcome

The primary outcome measure will be clinical cure time of cough. Clinical cure is assessed based on VAS score of cough severity, and defined as both VAS scores of day-time and night-time cough reduce to 17mm or less, and last for 24 hours. Day-time refers to 6AM-10PM, night-time refers to 10PM-6AM.[16,17]

The cough VAS is a 100mm line segment, its length represents cough severity (both cough frequent and tense should be considered). 0mm=no cough, 100mm=worst cough, seriously impacting life quality such as playing, going to school, sleeping.[18] Day-time and night-time VAS are assessed independently on baseline (Day1) and Day 2-Day 6 to assess the severity of last 24 hours (Table 1). Children will be trained to use this assessment tool after randomized, and will recorded it by themselves via dairy with the assistance of their parents, they draw “×” on the most representable point of the line, then the investigator measure length from 0 to "×" and noted the results on CRF after diary back.

Secondary outcome

The secondary outcome measures will include clinical cure rate, onset time, AUC of cough severity VAS score-time, Parent-proxy Children's Acute Cough-specific QoL Questionnaire (PAC-QoL), Parent Global Assessment (PGA), cure rate of symptoms and efficacy of traditional Chinese syndrome.

Clinical cure rate and AUC of cough severity VAS score-time are assessed around the primary outcome for supporting main result and showing details of the change of cough severity. They also based on VAS score of cough severity. The clinical cure will be assessed on the last 24 hours of treatment.

The onset time aims to assess when the drug active. Onset is defined as the day-time or night-time cough severity VAS score change from baseline≥17mm.[19]

PAC-QoL is a 16-iterm parent-proxy questionnaire to reflect the frequency of particular feelings and concerns or worries of parents, developed by team of Sophie Anderson James in Australia.[20] 7 points Lkiert-type scale (very consistent, consistent, some consistent, general, some non-consistent, non-consistent, and very inconsistent, scoring 1-7, respectively) is used to assess the quality of life of past 24 hours. Lower scores shows greater frequency, concerns, or worries, with higher scores therefore reflecting better quality of life.

PGA is a tool for measuring the global change in cough severity. It is assessed by parents, with the question of "How is your child`s cough severity changed after treatment?" (compared with 6 days ago). The response includes much better, better, no difference, worse, much worse. It will be record on Day 6. PGA will also be used as an anchor for calculating the MID of VAS for acute cough in child as a continue research.

The clinical manifestation of wind-cold TCM syndrome includes feverish, cough, intolerance of cold, headache, body ache, nasal congestion, sneezing, runny nose, pharyngeal itching. We will assess the cure rate of symptoms respectively and the total efficacy of traditional Chinese syndrome on Day 6 via the TCM syndrome scale (Table 2).[15,21] Cure is defined as the score of the independent symptom decreased to 0. Efficacy means the change from baseline of total score≥50%.

Safety assessment

Preclinical safety information

The acute toxicity test and long-term toxicity test showed that there was no death or toxicity. The maximum tolerated dose of Susu for mice is 120g crude drug/kg·d, which is equal to 178 times of the recommended dosage in this trial. The no observed adverse effect level of male mice is 15g crude drug/kg·d, while the NOAEL of female is 30 crude drug /kg·d, they are 22 and 44.5 times of recommended dosage, respectively.[22]

outcome measures

For the safety assessment, outcome measures include adverse events (AE), Laboratory tests and vital signs. All unnormal safety measure should be followed up until recover or return to pre-medication levels.

AEs is the primary safety outcome measure. The occurrence will be asked on every visit by investigators. Reports of all AEs, truthfully filled in "adverse events record" on study case, including occurrence time, end time, duration, severity, therapeutic measures, outcome, relationship with experimental drug. Severity of AE is assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NGI-GTCAE) V.5.0. If its standard is not applicable for special condition, 5 level criteria will be considered.[23] Relationships between AE and experimental drug can be divided into definitely related, probably related, possibly related, probably not related, need further evaluated and unknown. The first 4 cases will be considered as adverse drug reactions.[24]

Laboratory tests include blood routine examination, C-reactive protein test, urine routine, liver and kidney function test and electrocardiogram. Vital signs refers to axillary temperature, heart rate, respiration and blood pressure. Patients will be tested before and after the treatment.

Sample size

This clinical trial is in phase Ⅳ, therefore a prospective sample size calculation was not performed. According to the *Provisions for Drug Registration* issued by the NMPA[25], we determined the sample size as 240 with the consideration of 20% drop-out rate. 80 cases for each group.

Study schedule

There is no run-in period. All participants will receive intervention for 5 days, and be followed up for 1 more day after that. If occurs AE, child should be followed up for safety till recover or return to pre-medication condition. (Table 3)

Data collection, management, and monitoring

Study case and diary were designed for original data collection. When recording the study case, investigators or clinical research coordinator (CRC) should collect related information timely, completely and accurately. In this protocol, day-time and night-time cough VAS will be assessed by children themselves via diary for reducing recall bias. Investigators should train children and their parents in proper way to evaluate at the very beginning, and check and sign the diary with parent on the last visit to ensure the data are real and available.

Electronic CRF is the statistical source. CRC is authorized to input original data from study case and diary within 1 week after subject finishing this trial. During the study, independent clinical research associate is hired for data monitoring. Data manager will clean and verify the database according to the data verification plan previously written after finishing data collection, and sent query form of questionable data to investigators circularly till all questions are answered. The database will be locked after data

verification meeting, investigator, statistics and data manager will have access to the final trial dataset, but modify is not allowed since then.

Statistical analysis

Data of subject will allocated to full analysis set (FAS), per-protocol set (PPS) and safety set (SS). Data form FAS and PPS will be analyzed for efficacy, while data from SS is the source of safety analysis.

SAS V9.2 will be used for analysis. All hypothesis tests are two-sides with a significance level of 0.05. Last observation carried forward (LOCF) approach will be adopted for missing data of primary effective outcome.

Data of enrollment distribution, baseline information, efficacy and safety outcomes, drug combination and medication compliance are in analytical range in this study.

Continuous data will be expressed by mean, standard deviation, minimum, maximum, median, upper and lower quartiles. Analysis of variance or Kruskal-Wallis rank sum test will be used for comparison among groups. Covariance analysis is performed when considering covariates. Dichotomous and categorical data will be expressed as frequency, percentage, or constituent ratio, and analyzed by c^2 test or Fisher`s exact test. CMHc^2 test and logistic regression model will be used if center or confounding factors are considered. For survival data, median time and its 95% confidence interval will be estimated by Kaplan-Meier method, and its difference between groups will be analyzed by log-rank test and COX proportional hazard regression model or accelerated failure time model.

There is no interim analysis. Considering the short research period and the safety of toxicity test, DMC is not needed for this study.

Ethics and dissemination

This protocol had been approved by ethics committee of First Teaching Hospital of Tianjin university of TCM, and has reached a consensus by ethics committees of other research centers.

All guardians and child ≥8 years old who has had civil liability need to sign the ICF prior to entry to the study. Investigators should make children aware that participation is strictly voluntary, and they have the right to withdraw from the study at any time. The manufacturer has purchased insurance for subjects and can make compensation if there occurs SAE. To avoid a conflict of interest, they will have no access to privacy information of patient.

If there is important protocol modification, relevant parties (investigators, IRBs, participants, etc) will be informed.

Discussion

Compound preparations for common cold on the market are generally focused more on feverish and nasal symptoms than cough. Susu which is a patent Chinese medicine for treating acute cough composed with 5 herbs. It is supposed to have the efficacy of shorten cough duration because of its multiple-targets and diverse active ingredients supported by preliminary animal experiments. The following points were considered when designing this protocol.

Age of the included population

The preliminary toxicity tests of Susu only supports it to use in children over 6 years old, because we did not use the neonatal rat limited by experiment condition.

Exploration of dose

As a compound formula, Chinese patent medicine always has complicated active ingredients, which makes it difficult to get a clear pharmacokinetic result to support the determination of clinical dose. In view of this situation, we respect the clinical experience of the prescription provider and calculated the equivalent dose for patent medicine from the practical dose of crude herbs. Double-dose are explored in this study, take into account the loss of active ingredients in the production process. As for the very-low dose, because the Chinese patent medicine is very difficult to simulate for its characteristic odor and taste, it will replace the placebo in this study with the consideration that 5% dose can be considered as non-active. This method is often used in clinical trials of traditional Chinese medicines or European botanical drugs, but it may interfere the safety assessment in a way.

Assessment of cough

There is a difference between day and night in severity of cough in upper respiratory infection, generally it gets worse at night, so they are evaluated separately. Though cough is an objective symptom which can be observed by parents or cough frequency monitors easily, the severity also depends on subjective feeling, such as trying to constrain from cough in public, muscular pain or poor-quality sleep caused by cough. VAS is more sensitive and intelligible compared with cough diary, which makes it appropriate for use as children`s self-report i n this study. Foreign studies suggest that children more than 6 years old can use VAS correctly.[26] To verify, we also do an easy test in clinic before designing this protocol. There is no MID for VAS of acute cough in children[27], so when defined onset, we referent the threshold of adults, which is one of the reasons that we included PGA as a secondary outcome.

TCMcharacteristics

“Syndrome” differentiation is the center of TCM theory. Patients diagnosed with same disease, in addition to the similar main symptoms, there are some different manifestations of associated symptoms which have high degree of association and often appear together. The group of those associated symptoms is called syndrome. When designing clinical trials of traditional medicine (herb formula or patent medicine),

disease-syndrome pattern is used commonly. Participants are limited to a certain type of syndrome in inclusion criteria, and their associated symptoms also need to be assessed as a secondary outcome.

At present, there are still different views on the evaluation method of traditional medicine. The publish of CONSORT Extension for Chinese Herbal Medicine Formulas[28] is a big progress. It is hoped that the methodological research can also come into focus and get more consensus in the future.

Trial status

Date and protocol version identifier V1.0, 04/09/2019. Recruitment is scheduled to occur from January 2020 until December 2022.

Abbreviations

AE: adverse events;

AUC:area under the curve;

CRF: case report form;

CRC: clinical research coordinator;

FAS: full analysis set;

ICF: informed consent form.

LOCF: Last observation carried forward

MID: minimal important difference;

NGI-GTCAE: national cancer institute common terminology criteria for adverse events;

NMPA:national medical products administration;

PAC-QoL: Parent-proxy Children's Acute Cough-specific QoL Questionnaire;

PGA: Parent Global Assessment;

PPS: per-protocol set;

SAE: serious adverse events;

Susu: susu Xiao`er Zhike Granules;

SS: safety set;

TCM: traditional Chinese medicine;

VAS:visual analogue scale;

Declarations

Ethics approval and consent to participate

This protocol has been approved by the ethics committee of First Teaching Hospital of Tianjin university of TCM, and a consensus has been reached among research centers. Informed Consent Form should be signed by subject or their guardians(under 8 years old) at the very first.

Consent for publication

Not applicable.

Availability of data and material

The results will be published in a peer-reviewed journal. Data sets generated or analyzed in this study will be provided by the corresponding authors upon reasonable request.

Competing interests

Rui Liu is from TASLY pharmaceutical group co. LTD which is the sponsor of this study, he has helped to hold meetings, and did not participate in the plan making. Other authors declare that they have no competing interests.

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Authors' contributions

Siyuan Hu is responsible for the overall protocol, and organized expert team. Qiuhan Cai draft this protocol. Xinmin Li who is the primary investigator of pediatric department of leader center joined the discussion and gave suggestions for modification with Youpeng Wang, Yongbin Yan. Chengliang Zhong and Shengxuan Guo provided statistical plan and will be the statistician of this study. Rui Liu organized the expert meeting and provide financial support. Xuan Li and Qiuhan Cai co-wrote this manuscript. Methodology support was from National Science and Technology Major Projects for "Major New Drugs Innovation and Development"(2020ZX09201-008).

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Tables

Due to technical limitations, table 1 to 3 is only available as a download in the Supplemental Files section.

Supplementary Files

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- tables.docx
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