

Anerning Granule for Community Acquired Pneumonia: Protocol for Randomized, Double-Blind, Single-Dummy, Parallel Control of Placebo, Multicenter Clinical Trial

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Study protocol

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Abstract

Background: Community acquired pneumonia (CAP) in children is one of the common clinical diseases and infectious diseases threatening the health of the population. CAP has complicated causes, closely related to region, season, age, and primary disease. It is the most common cause of children being hospitalized and the first cause of death for children under 5 years old. At present, the clinical treatment is mainly antibiotics, but abuse and non-standard combination of antibiotics have led to increasing antibiotic resistance. Anerning Granules have the functions of clearing away heat and removing wind, reducing phlegm and relieving cough, and improving cough symptoms and lung signs. Thus, this study aims to evaluate the efficacy and safety of Anerning Granules (AEN) in the treatment of community-acquired pneumonia in children, and to explore whether AEN can reduce the use of antibiotics and have a good effect on the clinical treatment of CAP.

Methods and analysis: this study, a randomized, double-blind, single-dummy, parallel control of placebo, multicenter clinical study will be established in 7 hospitals in the same period. A total of 216 patients with community-acquired pneumonia will be randomly allocated at a ratio of 2:1 to two groups: experimental group, control group. The experimental group receives Anerning Granules plus ceftriaxone sodium; the control group receives AEN placebo plus ceftriaxone sodium. Each group will be treated for ten days, and a stage effect evaluation will be conducted on the sixth day. The primary outcome is the end of antibiotics in frequency (DDDs) and effective rate. Secondary outcome measures of effectiveness are the full fever time, sore throat onset time, and safety assessment. Outcomes will be assessed at baseline and after treatment. In addition, adverse events will be monitored throughout the trial process and must be traced to be resolved.

Discussion: This study protocol will provide the research data regarding the efficacy and safety of AEN for the treatment of community-acquired pneumonia in children. The first aim is to determine whether Anerning Granules can reduce the use of antibiotics; the second aim is to evaluate the effectiveness of Anerning Granules combined with ceftriaxone sodium in the treatment of children with community-acquired pneumonia. The third aim is to observe the safety of clinical application of Anerning Granules. The results of this study will improve the rational use of drugs, especially the rational application of antibiotics. It will also enable safety evaluation from laboratory indices of adverse events, which will provide reliable evidence for clinical treatment.

Trial registration: Clinicaltrials.gov identifier: NCT03675178, registered on 16 September 2018.

Background

Community-acquired pneumonia in children (CAP), in the case of otherwise healthy children in the hospital for infectious pneumonia, including those infected by pathogens, have clear incubation periods and the latent period of onset of pneumonia after admission is relative to hospital-acquired pneumonia (HAP), and pathogens including bacteria, viruses, mycoplasma, chlamydia, fungi, protozoa, etc.¹ CAP is

the acute infection of lung parenchyma and/or interstitial parts, which causes the body to experience varying degrees of hypoxia and infection and poisoning symptoms. CAP usually includes respiratory signs such as fever, cough, increased breathing, difficulty breathing, inspiratory depression in the chest wall, wet gurgling and tubular breath sounds in the chest, and abnormal changes in chest x-rays.

CAP belongs to the category of traditional Chinese medicine "cough" and "wind temperature and lung heat". Traditional Chinese medicine (TCM) has shown excellent efficacy in improving patients' clinical symptoms, improving patients' immunity and sterilization, and playing an increasingly important role in the clinical treatment of CAP.^{2 3} Anerning Granules is a modern Tibetan medicine preparation produced by Jinhe Tibetan Medicine Co., Ltd. (Z20025878). The prescription was originally derived from the classic prescription "Sanchen San" of Tibetan medicine, which has been continuously improved and perfected by later generations of physicians, forming the classic prescription of pediatrics of Tibetan medicine "Nine West is better". It is currently published in "Tibetan Medicine Clinical Notes" by Yundan Jiacao, a well-known Tibetan medical scientist, and has been in clinical use for more than 300 years. The medicine is composed of safflower, sandalwood, tianzhu yellow, artificial bezoar, short-tube rabbit ear grass, rock cabbage, alpine horseradish, aconite, and licorice with the function of clearing heat and removing wind, phlegm, and cough. It is clinically applied to children with wind, heat, cold, cough and phlegm, fever and sore throat, and upper respiratory tract infections.

Anerning Granules also have a certain basis for early work. The pharmacodynamics experiments showed that Anerning Granules could significantly prolong the incubation period of pneumonia-induced cough in mice and reduce the number of coughs.⁴ It can significantly increase the amount of phenolic red secretion in the trachea of mice and the amount of tracheal secretion in rats, thus showing good expectorant effect.^[4] The antipyretic effect of Anerning Granules on dry yeast-induced rat fever model is obvious, and its antipyretic effect can continue until four hours after administration, but its antipyretic effect has no obvious dose-dependent relationship^[5]. The content of evanilan in the peritoneal fluid of mice with increased capillary permeability induced by acetic acid was significantly decreased, indicating that evanilan had good anti-inflammatory effects.⁵ In addition, the toxicological test results of Ma Wenjun⁶ suggest that Anerning granules have a high safe dose range and are safe for clinical use.

From November 2013 to July 2014, a children's hospital affiliated with the capital institute of pediatrics was carried out by Anerning Granule treatment of infantile acute bronchitis (phlegm cough) clinical study,⁷ the results show that Anerning Granule treatment of infantile acute bronchitis curative effect, especially for cough and lung signs of improvement, and no obvious adverse reactions worthy of clinical promotion. The DiErWuYi Hospital of the Chinese People's Liberation army at the same time carried out clinical observational studies, mainly involving children with upper respiratory tract infection, the wind hot cold, infantile cough, exogenous fever; the results showed curative effects and no obvious adverse reactions.

Aim

The aim of this study is to present the experimental protocol of a trial aimed at evaluating the efficacy and safety of Anerning in reducing antibiotic application in the treatment of community-acquired pneumonia in children, and thus to clarify the role of Anerning Granules in clinical practice in the medical field.

Methods And Analysis

Study design

This is a stratified randomized (random assignment), double-blind, single-dummy, parallel control of placebo, multicenter superiority test clinical study. The study will be conducted at the first Affiliated Hospital of Tianjin University of Traditional Chinese Medicine; Oriental Hospital of Beijing University of Chinese Medicine; the first Affiliated Hospital of Henan University of Traditional Chinese Medicine; the first Affiliated Hospital of Hunan University of Traditional Chinese Medicine; Affiliated Hospital of Shandong University of Traditional Chinese Medicine; Shanghai Hospital of Traditional Chinese Medicine; and Tianjin Children's Hospital. Ethical clearance for the trial was obtained from the respective ethics committees of the seven hospitals. Children with community-acquired pneumonia will undergo a standardized baseline evaluation before treatment, comprising detailed history taking, physical examination, and laboratory testing. All included patients are randomly divided into two groups: an experimental group and control group. The experimental group receives Anerning Granules plus ceftriaxone sodium; the control group receives AEN placebo plus ceftriaxone sodium. Each group will be treated for ten days, and a stage effect evaluation will be conducted on the sixth day. The trial is conducted in accordance with the World Medical Association Declaration of Helsinki and Good Clinical Practice of Pharmaceutical Products.^{8 9 10} After a full explanation from the clinicians, written informed consent will be obtained from the participants before intervention.^{11 12} Strict data management and quality control will be conducted in this trial.^{13 14} The study design is shown in Figure 1. The protocol follows the recommendations of the SPIRIT initiative (see additional file 1),¹⁵ and the trial results will be reported according to the latest version of the CONSORT statement.¹⁶

Patient and public involvement

Patients were not involved in the research question, design, conduct, outcome measures, or data analysis of the study. Only medically trained clinicians carried out patient recruitment and management in the study. The clinicians will describe the purpose, burden of the intervention, procedure, and potential risks of this trial to the participants themselves or their designated representatives before recruitment. We will disseminate the results of this study to participants through patient organizations and open lectures.

Participants and recruitment

Diagnostic criteria of Western medicine and traditional Chinese medicine

The Western medicine diagnostic criteria of community-acquired pneumonia in children will refer to the Guidelines for the Management of Children's Community-Acquired Pneumonia (2013 Revision)¹⁷ and will be formulated with reference to the 8th edition of "Zhufutang Practical Pediatrics".¹⁸ The traditional Chinese medicine (TCM) diagnostic criteria of community-acquired pneumonia in children will refer to the Guidelines for the Diagnosis and Treatment of Common Pediatric Diseases of the Chinese Medicine Society of China (2012)¹⁹ and the "Twelfth Five-Year Plan" textbook "Pediatrics of Traditional Chinese Medicine".

Inclusion criteria

Inclusion criteria are as follows: (i) age > 1 and < 5 years; (ii) meet the Western diagnostic criterion of community-acquired pneumonia in children that the disease duration does not exceed 48 hours and consider bacterial infections; (iii) the syndrome differentiation of TCM is wind-heat closed lung and phlegm-heat closed lung; (iv) sign the written informed consent form for the clinical trial.

Exclusion criteria

Exclusion criteria are as follows: (i) chest X-ray film showed obvious lung tumors and tuberculosis; (ii) people with acute infectious diseases such as measles, whooping cough, or influenza; (iii) acute upper respiratory tract infection, wheezing bronchitis, bronchial asthma, bronchial foreign bodies or other respiratory diseases; (iv) children with severe malnutrition and immunodeficiency; (v) in combination with severe cardiopulmonary disease, liver and kidney disease, advanced tumors, and other serious or progressive diseases; (vi) those who meet the diagnostic criteria for CAP (severe) Western medicine for children; (vii) patients with clinical diagnosis or clinical consideration of viral pneumonia and mycoplasma pneumoniae pneumonia; (viii) people with an allergic constitution or allergy to penicillin, cephalosporin antibiotics, Anerning Granules and their components; (ix) researchers think it is inappropriate to join the group.

Exit criteria

Patients will leave the trial when one of the following criteria is met: (i) incorrectly included; (ii) are poorly compliant; (iii) no medication or any follow-up records; (iv) occurrence of allergic reactions or serious adverse events (AE); (v) participants have other complications or special physiological changes during the trial; (vi) patients have been treated with other medicines during the trial; (vii) not alleviated or the symptoms are aggravated; (viii) poor patient dependence; and (ix) breaking blind cases for various reasons. Participants may withdraw from the study at any time for any reason.

Interventions

All researchers are clinical doctors and receive standardized training in diagnostic interviewing before the start of the trial. The 216 qualified subjects are divided into an experimental group of 144 cases and a control group of 72 cases. The experimental group was given oral Anerning Granules: 1 to 5 years old, 1

bag / time, 3 times / day; the control group was given oral Anerning Granules placebo: 1 to 5 years old, 1 bag / time, 3 times / day. Both groups were treated with intravenous ceftriaxone sodium (50mg / kg / time, 1 time / day, the total amount does not exceed 2 grams per day), and the experimental drug and its simulation agent are consistent in appearance, smell, and taste. The Anerning Granule Simulator is composed of sucrose, caramel color, lemon yellow, and bitter melon extract. The drugs are provided by Jinxian Tibetan Medicine Co., Ltd. Ceftriaxone sodium is arranged by each clinical unit and is not provided uniformly. If clinical recovery is reached during this period, the treatment will be terminated.

Criteria for clinical cure and withdrawal

After treatment, the body temperature is normal, the signs of cough, sputum, and lungs basically disappear, and the symptoms and signs score and improvement are $\geq 90\%$; the body temperature (axillary temperature) is less than 37.3°C , and is maintained for 24 hours or more. Regarded as clinically cured, although the treatment period is less than 10 days, the drug can be discontinued. For details, please refer to the quantification standard table of TCM syndromes and signs on the CRF form (see additional file 2).

Drug allocation

The participant patients were randomly divided into 2 groups according to the 2:1 ratio. The divided test drugs are sent to each test center according to the random layered center number. Observation doctors should issue medicines according to the order of each patient's visit and the medicine number, and no medicines should be selected. The drug number remains unchanged throughout the trial. The distribution of medicines is conducted by nurses who have been professionally trained in standard operating procedure, one box at a time, containing 9 sachets (a 3-day dose). After the test, the drug administrator is responsible for the centralized destruction of the remaining drugs, according to procedures. If a blind bottom leak caused by any unspecified situation occurs and affects the objectivity of the test result, the test will be considered invalid. In the event of an emergency (such as a serious adverse event), or when the patient needs to be rescued and must know what treatment they received, the main investigator decides whether to unblind the blindness urgently according to the condition. Cases withdrawn due to efficacy reasons must not be broken. Once the blinding is urgently released, the numbered subjects will withdraw from the trial, and the investigator should record the reason for withdrawal on the case report form.

Test medication compliance

In clinical trials, the compliance of the subjects is mainly compliance with the test medication so that the subjects fully understand the importance of taking the medication on time and in quantity and avoiding adding other drugs or treatments. This test mainly uses the drug counting method, combined with the inquiry method when necessary, to judge the compliance of the test drug. Test medication compliance = (the amount of test drug taken / the amount of test drug that should be taken) $\times 100\%$.

Test process

Before conducting any experimental procedure, the subject and / or its agent must have read and signed the informed consent form approved by the ethics committee. The test procedure shall be carried out within the specified visit time window. The test process is shown in Table 1.

- a. Observation period: 10 days.
- b. Visiting points: observe every day.
- c. Safety follow-up: the patients were followed up to normal or pre-treatment levels.

Table 1: Overview of the test process

| Phase | The baseline period | Therapeutic observation period | | follow-up(security) |
|---|---------------------|--|--------------------|---------------------|
| | -1~0day | Intermediate viewing point~Day 2 ~ day 9 | End point (day 10) | |
| Project | | | | |
| Sign the informed consent form | √ | | | |
| Cases to be included in the | √ | | | |
| Demographic data | √ | | | |
| Medical history | √ | | | |
| Always use | √ | | | |
| randomized | √ | | | |
| Distribution of experimental drugs | √ | | | |
| Distribute the subject diary card | √ | | | |
| Vital signs | √ | √ | √ | |
| The doctor of traditional Chinese medicine syndrome | √ | √ | √ | |
| Lung signs | √ | √ | √ | |
| Physical check | √ | √ | √ | √* |
| X-ray chest radiograph | √ | | √ | |
| Blood, CRP, urine routine, stool routine | √ | | √ | √* |
| Liver and kidney function | √ | | √ | √* |
| Mycoplasma pneumoniae IgM | √ | | | |
| Electrocardiogram (ecg) | √ | | √ | √* |
| Antibiotic use record | | √ | √ | √* |
| Drug combination | | √ | √ | √* |
| Adverse events | | √ | √ | √* |

Recall drug and subject log
card

√

Note: * is the test when necessary.

Outcome measures

Primary outcome measure

Antibiotic frequency at the clinical endpoint (DDDs): evaluation at the end of the test.

Secondary outcome measures

- i. The total effective rate of the disease: 5 and 7 days after the treatment and the record of the end point of the test, and the evaluation will be completed after the test.
- ii. Clinical recovery time: evaluation after the end of the trial, calculated in days.
- iii. Time for complete fever remission, time for onset of fever, cough, sputum, and sore throat; severity-time AUC of fever, cough, sputum, and sore throat symptoms, observed once every 24 hours (1 day) after treatment.
- iv. The curative effect of TCM syndromes 5 or 7 days after treatment and recorded at the end of the trial, the evaluation of the end of the trial.
- v. Single symptoms (fever, daytime cough, nighttime cough, sputum quality, sputum volume, etc.) and the curative effect of lung signs are observed daily after treatment, and the trial is concluded.
- vi. Effectiveness of chest X-ray is inspected and evaluated at the baseline and the end of the test.
- vii. Incidence of conversion to CAP (severe) is evaluated at the end of the test.

Safety assessments

Safety measurements included laboratory indices and AEs. All patients will undergo laboratory examination before enrollment and at the end of the clinical trial. Changes in laboratory indices before and after the clinical trial will be compared to conducting a safety analysis. Laboratory indices are: (i) routine blood and urine testing; (ii) liver function (AST, ALT, TBIL, DBIL, γ -GT, ALP) and kidney function (Scr, BUN); and (iii) ECG. The occurrence of any AEs in trial participants such as subjective discomfort of patients or abnormal laboratory results will be recorded in the CRF during the whole trial process. We will withdraw patients who have severe AEs, as it will be unsafe for them to continue the trial. Meanwhile, we will give them relevant medical care and follow up with them until the reaction has terminated.

Informed consent

Before enrolling patients in the trial, the investigating doctor will completely and comprehensively describe the purpose, procedure, and potential risks of this trial in writing to the patients themselves or their designated representatives. Patients will be informed that they have the right to withdraw from the

trial at any time. Each patient must provide written informed consent before participating in this study; this consent will be kept in the study file.

Quality control

Quality assessment will be conducted in terms of the following aspects: the progress of the trial; the qualifications of the investigators; the mastery of the program; the authenticity, accuracy, and completeness of the CRF; archival preservation; program implementation; AEs; drug preservation and storage; written informed consent; participant compliance; and laboratory examination data. In particular, the authenticity and accuracy of the CRF, program implementation, and determination of AEs will be strictly examined.

Data management

The patients in this trial will be recruited. Therefore, the original data will include the CRF, patient log card, original laboratory examination, and written informed consent. The inspector will regularly visit all centers to conduct a data quality inspection. The authenticity and accuracy of the data will be checked by original laboratory comparison, telephone follow-up with patients, and examination of the integrity, timeliness, and normalization of the data. The paper form of the data will be collected after approval and inspection. The researcher who is responsible for data entry will build a database with double-recorded data entry by two people, and consistency testing will be carried out to ensure accuracy.

Statistical analysis

Statistical analyses will be performed by professional statisticians using SPSS 22.0. Three datasets will be conducted: intention-to-treat; per-protocol set; and safety dataset. The intention-to-treat refers to the patients who have been randomized; an intentional analysis will be conducted for curative effect. The per-protocol set refers to all cases that do not violate the protocol and complete the trial; per-protocol set analysis will be conducted for curative effects. The safety dataset refers to the randomized cases that have taken a tested drug at least once with safety evaluation data after treatment. We use mean \pm standard deviation (SD) for continuous variables and percentages for categorical variables. In measured indices, an independent t-test will be used for hypothesis testing of the normal variables, while the Wilcoxon rank sum test will be used for hypothesis testing of the skewed variables. The χ^2 test will be used for hypothesis testing of the counted indices. The statistical analyses will use the two-sided hypothesis test. $P \leq 0.05$ will be set as the significance level.

Discussion

Children's community-acquired pneumonia is one of the most important diseases that cause children's death worldwide.²⁰ Millions of children die of pneumonia every year, and the situation in China is not optimistic, where about 20 million children suffer from pneumonia every year. The incidence of pneumonia among children under 5 years old ranks second, seriously affecting the health of Chinese

children. About 350,000 children under the age of 5 die of pneumonia, which is the leading cause of infant death in China. Therefore, for pediatric medical workers, reducing the incidence of pneumonia and increasing its cure rate should be urgent problems to be solved.²¹ At present, antibiotics are the mainstay of clinical treatment. However, antibiotic abuse and irregular combinations of drugs have led to increasingly severe antibiotic resistance. Chinese medicine may provide an effective and safe treatment for CAP. This study was designed to provide diagnostic evaluation of the use of AEN in the treatment of community-acquired pneumonia in children and the use of antibiotics, as well as observational indicators of therapeutic effects, and to provide research data regarding its efficacy and safety. The first aim is to determine whether AEN can reduce the use of antibiotics; the second aim is to evaluate the effectiveness of AEN combined with ceftriaxone sodium in the treatment of children with community-acquired pneumonia. The third aim is to observe the safety of clinical application of AEN. The results of this study will help promote the rational use of the drug, especially the rational use of antibiotics. To facilitate high validity and reliability, strict quality control and high-quality methodology are indispensable. We describe in detail the method of randomization, allocation concealment, blinding, interventions, recruitment, and data collection.

The results of this trial may provide a basis for the effectiveness, safety, and reduction of antibiotic application of Anerning Granules and help promote the rational use of the drug, especially the rational application of antibiotics, and provide reliable evidence for the clinical treatment of CAP.

Strengths and limitations of this study

- a. The results of this randomized, double-blind, single-dummy, parallel control of placebo, multicenter clinical trial will provide new evidence of the efficacy and antibiotic use of AEN for community-acquired pneumonia in children and guide rational application of antibiotics.
- b. This trial will be implemented in seven hospitals in Chinese patients; this can strengthen its generalizability.
- c. One limitation is the results of participant symptom evaluation scales having subjective factors.
- d. Another limitation is that because the participants are children, the patient's dependence on combined medication is relatively poor.

Trial status

This trial was registered in the Clinical Trials USA Registry (registration no. NCT03675178) on 16 September 2018. Recruitment will begin in October 2018, and it is anticipated that enrollment will be completed in December 2020. We will publish the results of this study in peer-reviewed journals to ensure widespread dissemination.

Abbreviations

CAP: community acquired pneumonia; DDDs: defined daily doses; HAP: hospital acquired pneumonia; GCP: Specification for quality management of drug clinical trials; AEN: Anerning Granules.

Declarations

Authors' contributions

SMH wrote the first draft of the manuscript, revised the final manuscript and contributed to the research design. XYM, and CY concept research, revised and approved the final manuscript. LJ, ZYL, WX, ZLD modify the manuscript and make comments. All authors revised the protocol critically for important intellectual content and approved the final manuscript.

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Ethics and dissemination

The protocol has been approved by the Ethics Committee of the First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine (identifier TYLL2018 [K] Word 018); the Committee of Oriental Hospital of Beijing University of Chinese Medicine (identifier TYLL2018 [K] Word 018); the Ethics Committee of the First Affiliated Hospital of Henan University of Traditional Chinese Medicine (identifier 2018HL-070); the Ethics Committee of the First Affiliated Hospital of Hunan University of Traditional Chinese Medicine (identifier HN-LL-KY-2018-004-01); the Ethics Committee of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine (identifier (2018) Lunshen No. (011) -KY); the Ethics Committee of Shanghai Hospital of Traditional Chinese Medicine (identifier TYLL2018 [K] Word 018); and the Ethics Committee of Tianjin Children's Hospital (identifier TYLL2018 [K] Word 018). This trial was registered in the Clinical Trials USA registry (registration No. NCT03675178) on 16 September 2018. Based on the Declaration of Helsinki, written informed consent will be obtained from all study participants. Any modifications to the protocol that may impact the conduct of the study, the potential benefits to the patients, or patient safety will require a formal amendment to the protocol, which should

be approved by the ethics committee prior to implementation. Protocol modifications will be communicated to all centers involved through regular meetings and telephone conversations. All staff will be notified, trained, and qualified before conducting the trial.

All patient-related information including case reports, laboratory specimens, and evaluation forms will be kept strictly confidential. All records will be kept in a safe, locked place and secured with password-protected access systems. To protect confidentiality, identification information will be deleted from all study documents.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

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Protocol version

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Figures

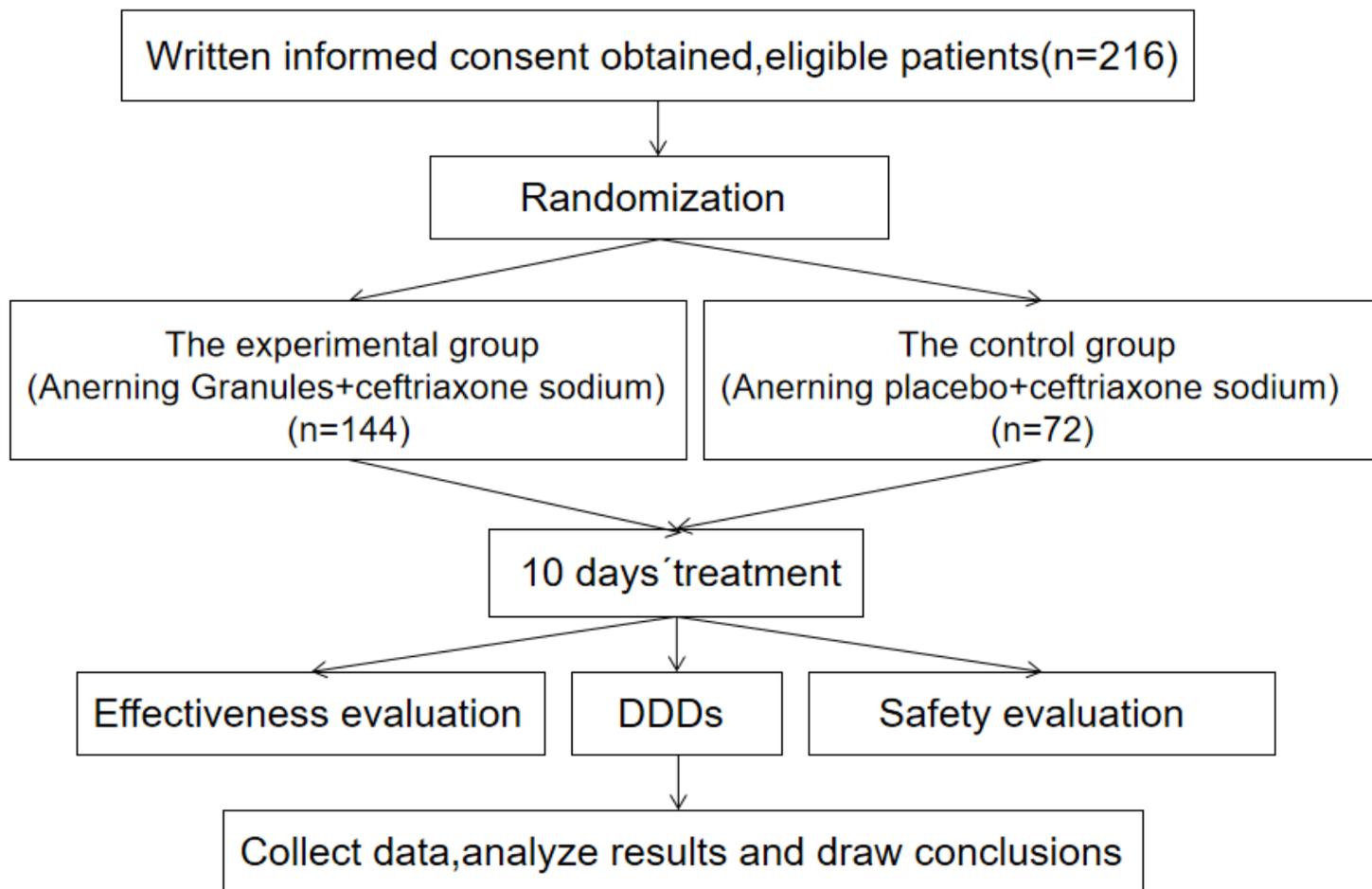


Figure 1

Flow diagram

Supplementary Files

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