Clinical Trial Protocol

Efficacy of Xuanfei Baidu Granules as Add-on Therapy for Hospitalized Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD): A Single-Center, Prospective, Randomized, Open-Label, Parallel-Controlled Trial

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Trial Implementation Institution: Dagang Hospital, Binhai New Area, Tianjin, China

Corresponding Author: Shubin Lv

Department of Respiratory, Dagang Hospital, Binhai New Area, Tianjin

Address: No.1200 South Ring Road, Dagang Area, Binhai New District, Tianjin, P.R.China

Postal Code: 300270;

Email: 83730692@qq.com

Research Team: Jingjing Zhao, Jinling Yang, Changyan Gong, Wei Gu, Lingling Wu, Yaxian Kong, Shubin Lv

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1. Background and Research Rationale

Chronic obstructive pulmonary disease (COPD) is a major global disease causing high morbidity and mortality, imposing heavy economic burden on public health systems worldwide. Acute exacerbation of COPD (AECOPD) refers to acute worsening of respiratory symptoms in COPD patients, which often requires hospitalization, accelerates irreversible lung function decline, reduces long-term survival and impairs health-related quality of life.

Current global clinical guidelines (GOLD 2026) provide standardized Western medicine routine treatment (SOC) including bronchodilators, systemic glucocorticoids and targeted antibiotics. However, a large proportion of hospitalized AECOPD patients still suffer from persistent respiratory symptoms, delayed recovery and high readmission risk, creating an urgent clinical demand for optimized adjuvant treatment.

Traditional Chinese Medicine (TCM) provides unique intervention ideas for inflammatory respiratory diseases. Xuanfei Baidu Granules is an optimized herbal compound developed by multi-target active component screening platform. It integrates five classic ancient prescriptions with added Polygoni Cuspidati Rhizoma et Radix and Verbenae Herba, with multi-component, multi-target and multi-pathway pharmacological effects. Preclinical studies have confirmed that its active ingredients (quercetin, kaempferol, luteolin, etc.) can inhibit the release of pro-inflammatory cytokines (IL-6, TNF-α, IL-1β), regulate Toll-like receptor and NF-κB/MAPK/NLRP3 inflammasome signaling pathways, relieve airway hyperresponsiveness, reduce pulmonary inflammatory exudation and oxidative injury. The overlapping inflammatory pathological mechanism between viral acute lung injury and AECOPD supports its off-label application in AECOPD treatment.

Existing observational studies have suggested clinical benefits of Xuanfei Baidu Granules for respiratory inflammatory diseases, but high-quality prospective randomized controlled trial evidence for its combined use with standard Western medicine in hospitalized AECOPD patients is insufficient. This single-center randomized controlled trial aims to fill this evidence gap, evaluate its efficacy, safety and medical resource consumption as adjuvant therapy, and further screen sensitive applicable population via subgroup analysis stratified by GOLD severity grading, so as to provide evidence basis for integrated traditional Chinese and Western medicine management of AECOPD.

2. Trial Objectives

2.1 Primary Objective

To compare the median time to clinical symptom recovery within 14-day follow-up between AECOPD patients receiving standard Western medicine alone and those receiving standard Western medicine combined with Xuanfei Baidu Granules, to verify whether adjuvant Xuanfei Baidu Granules can accelerate symptom recovery.

2.2 Secondary Objectives

1. Compare the improvement of patient-reported symptom scales (CAT, mMRC, CET) from baseline to Day 14 between two groups;
2. Compare the changes of arterial blood gas indicators (PaO_2, $PaCO_2$) and systemic inflammatory laboratory markers (WBC, neutrophil, CRP) before and after treatment;
3. Evaluate the difference in medical resource utilization: total hospitalization cost, duration of nebulization, systemic corticosteroid and antibiotic treatment;
4. Assess the overall safety and tolerability of Xuanfei Baidu Granules adjuvant therapy,

including incidence and severity grading of adverse events;

5. Explore differential efficacy of the intervention among subgroups stratified by GOLD 1–2 (mild-moderate) and GOLD 3–4 (severe-very severe) airflow limitation.

2.3 Exploratory Objective

Identify the therapeutic window of Xuanfei Baidu Granules in AECOPD intervention, and clarify the population with optimal clinical benefit.

3. Trial Design

3.1 Trial Type

Single-center, prospective, randomized, open-label, parallel-controlled clinical trial.

3.2 Trial Setting

Respiratory Department, Dagang Hospital, Binhai New Area, Tianjin, China.

3.3 Trial Period

Patient screening, enrollment and treatment: 7-day intervention period for all subjects; follow-up observation lasts 14 days after randomization; data sorting and statistical analysis after last subject completes 14-day follow-up.

3.4 Trial Compliance Standards

All researchers shall strictly follow the Declaration of Helsinki and ICH-GCP guidelines; the trial protocol has passed institutional ethics committee approval (Approval No. GYKY-2023-004).

4. Study Population

4.1 Inclusion Criteria

1. Age 40–85 years old, hospitalized patients diagnosed with AECOPD;
2. COPD diagnosis consistent with GOLD 2026 guidelines, with acute exacerbation requiring hospitalization: acute onset of dyspnea, increased sputum volume or purulent sputum exceeding daily fluctuation range;
3. Baseline airflow limitation classified as GOLD Grade 1, 2, 3 or 4;
4. Voluntarily participate in this trial and sign written informed consent form;
5. Able to complete 7-day standardized treatment and 14-day follow-up evaluation, with good treatment compliance.

4.2 Exclusion Criteria

1. Requiring invasive mechanical ventilation due to respiratory failure on admission;
2. Combined with asthma, bronchiectasis or active pulmonary tuberculosis;
3. Severe combined underlying diseases: unstable cardiovascular disease, malignant tumor, end-stage renal or hepatic failure;
4. History of severe allergic reaction to any component of Xuanfei Baidu Granules;
5. Unable to adhere to 7-day oral granule treatment regimen;
6. Participating in other interventional clinical trials within 30 days before enrollment.

4.3 Withdrawal Criteria

1. Subject voluntarily requests to withdraw informed consent;
2. Severe adverse events (≥ Grade 3) related to trial treatment occur;
3. Disease aggravation requiring invasive mechanical ventilation, meeting exclusion criteria during trial;
4. Poor compliance: missing more than 20% of scheduled study drug administration;
5. Lost to follow-up without valid contact information.

4.4 ITT Analysis Population

All randomized enrolled subjects will be included in Intention-to-Treat analysis regardless of treatment completion or withdrawal; missing data will be imputed by Last Observation Carried Forward (LOCF).

5. Randomization and Blinding Management

5.1 Randomization Method

Computer-generated random number table, 1:1 equal ratio randomization to Experimental Group or Control Group. Random sequence is stored by independent data management staff, concealed until subject enrollment.

5.2 Blinding Design

1. Open-label for clinicians and patients: herbal granules have unique taste and appearance, so complete double-blind placebo control cannot be implemented during clinical intervention;
2. Statistical blinding: data management team and statistical analysts are completely blinded to group allocation; subject identification codes are separated from grouping information; grouping code is unlocked only after database lock to complete statistical analysis.

6. Trial Interventions

All subjects receive standardized Western medicine treatment complying with GOLD 2026 and domestic AECOPD diagnosis and treatment guidelines for 7 consecutive days. Other prohibited TCM preparations are specified uniformly.

6.1 Control Group (SOC alone)

1. Oxygen therapy: maintain SpO_2 88%–92%; early non-invasive ventilation for hypercapnia patients;
2. Nebulization therapy: short-acting β_2 agonist combined with anticholinergic agents, administered every 2–4 hours as scheduled;
3. Systemic glucocorticoids: oral prednisone 40 mg/d or intravenous methylprednisolone 40 mg/d, course of 5 days;
4. Targeted antibiotics: stratified by clinical risk and sputum culture results, treatment course 5–7 days;
5. Supportive treatment: mucolytics, postural drainage, nutritional support, venous thromboembolism prophylaxis;
6. Prohibited drugs: other TCM injections, theophylline preparations, oral antitussive Chinese patent medicines within trial period.

6.2 Experimental Group (SOC + Xuanfei Baidu Granules)

Fully consistent standardized Western medicine regimen as Control Group, plus Xuanfei Baidu Granules oral administration:

- Dosage: 1 sachet each time, 3 times daily;
- Treatment course: continuous 7 days;
- Prohibited drugs same as Control Group.

7. Outcome Indicators and Evaluation Timing

All subjects complete baseline assessment on Day 0 (randomization day); follow-up evaluation at Day 7 (end of intervention) and Day 14 (end of observation window).

7.1 Primary Outcome Indicator

Time to clinical symptom recovery (days): from randomization day to the day when stable respiratory symptom state is reached, defined as dyspnea relief, sputum volume returns to baseline,

cough stabilized, assessed by attending physicians. Subjects who do not reach recovery standard by Day 14 are right-censored at Day 14.

7.2 Secondary Outcome Indicators

7.2.1 Patient-reported Symptom Scale Scores

Compare the change value from baseline to Day 14 of three scales:

1. COPD Assessment Test (CAT): evaluate overall COPD-related quality of life;
2. Modified Medical Research Council Dyspnea Scale (mMRC): assess exercise-induced dyspnea severity;
3. Cough Evaluation Test (CET): quantify cough frequency and severity.

7.2.2 Physiological and Laboratory Markers

Detect at baseline and Day 14: arterial blood gas (PaO_2, $PaCO_2$), peripheral blood routine (WBC, neutrophil count), serum C-reactive protein (CRP). Compare intra-group change and inter-group difference of change value.

7.2.3 Medical Resource Utilization Indicators

1. Total hospitalization cost per patient;
2. Duration of nebulization therapy (days);
3. Duration of systemic corticosteroid therapy (days);
4. Duration of antibiotic therapy (days).

7.3 Safety Evaluation Indicators

1. All adverse events (AEs) spontaneously reported or actively observed during 14-day follow-up;
2. Vital signs, routine physical examination, blood/liver/kidney laboratory indexes at baseline and Day 7;
3. Severity grading of adverse events: Grade 1 (mild), Grade 2 (moderate), Grade ≥3 (severe);
4. Causality assessment between adverse events and Xuanfei Baidu Granules.

7.4 Subgroup Analysis Stratification Factor

Stratify all subjects by baseline GOLD airflow limitation grade:

- Subgroup 1: GOLD 1 + GOLD 2 (mild-moderate);
- Subgroup 2: GOLD 3 + GOLD 4 (severe-very severe).

Separate primary endpoint survival analysis and inter-group efficacy comparison for two subgroups.

8. Sample Size Calculation

1. Hypothesis setting: 20% difference in 14-day clinical recovery rate between two groups; bilateral α=0.05, test power=80%;
2. Calculated minimum sample size per group without dropout: 54 cases;
3. Estimated dropout rate 10% during trial;
4. Final planned enrollment: total 120 subjects, 60 cases per group (1:1 randomization).

9. Data Collection, Management and Statistical Analysis Plan

9.1 Data Collection

Uniform case report form (CRF) is used to record all baseline, treatment, follow-up, laboratory, safety and medical cost data. All CRF records are double-checked by two researchers to reduce recording bias.

9.2 Missing Data Handling

Primary endpoint and scale missing data adopt Last Observation Carried Forward (LOCF) conservative imputation method for ITT population analysis.

9.3 Statistical Analysis Software

SPSS Statistics 17.0 software for all statistical testing.

9.4 Statistical Methods

1. Baseline data comparison:
    - Continuous variables conforming to normal distribution: mean ± standard deviation (SD), inter-group comparison Student's t-test;
    - Non-normal continuous variables: median (interquartile range, IQR), inter-group comparison Mann-Whitney U test;
    - Categorical variables: frequency (percentage), Chi-square test or Fisher's exact test;

All baseline indicators compared between two groups, $P>0.05$ indicates balanced baseline.

2. Primary endpoint (time-to-event data):
    - Kaplan-Meier method to draw cumulative recovery curve;
    - Two-sided Log-rank test to compare recovery time difference between groups;
    - Cox proportional hazards regression model to calculate hazard ratio (HR) and 95% confidence interval (CI); HR>1 means intervention accelerates symptom recovery.
3. Secondary continuous outcome indicators (scale score changes, laboratory index changes): inter-group comparison using t-test or non-parametric test as appropriate.
4. Safety and adverse event count data: Chi-square/Fisher exact test for inter-group comparison of incidence.
5. Statistical significance threshold: bilateral $P < 0.05$ is defined as statistically significant.

10. Safety Monitoring and Adverse Event Management

1. Real-time safety monitoring throughout the 14-day observation period: researchers actively inquire about discomfort symptoms and regularly review laboratory results;
2. Any adverse event shall be recorded in CRF immediately, including onset time, severity, duration, treatment measures and outcome;
3. Adverse event severity grading: Grade 1 (mild, no interference with treatment), Grade 2 (moderate, partial adjustment required), Grade ≥3 (severe, need to suspend trial drug and give intervention);
4. For Grade ≥3 adverse events, report to institutional ethics committee within 24 hours, evaluate causality with trial drug, decide whether to withdraw the subject;
5. If serious adverse events related to Xuanfei Baidu Granules occur, the trial will be suspended temporarily for safety assessment.

11. Medical Resource Utilization Assessment

Collect all hospitalization-related expense data of each subject, record the exact days of nebulization, glucocorticoid and antibiotic use, compare the mean duration and total hospitalization cost between two groups, analyze the economic value of adjuvant Xuanfei Baidu Granules.

12. Quality Control and Trial Compliance

1. Uniform training for all researchers before trial launch, unify judgment standard of clinical symptom recovery and scale scoring rules;

2. Specialized personnel regularly audit CRF data to correct logical errors and missing records;
3. Record drug administration records every day to calculate treatment compliance; subjects with compliance <80% will be marked in ITT dataset;
4. All laboratory tests are completed by hospital central laboratory with unified detection standards.

13. Trial Limitations and Risk Control

1. Single-center trial limitation: results need multi-center large sample verification; risk control: strictly standardize enrollment and evaluation standards to reduce single-center bias;
2. Open-label limitation caused by herbal granule characteristics: risk control: data statistics are fully blinded, objective laboratory indicators are used to assist efficacy evaluation to offset subjective bias; future trials will develop matching placebo granules for double-blind verification;
3. Short intervention cycle (7 days): cannot evaluate long-term recurrence and lung function changes after discharge; this trial only focuses on acute phase recovery indicators.

14. Ethical Considerations

1. This trial strictly complies with the Declaration of Helsinki and ICH-GCP; the protocol and informed consent form have obtained formal approval from Institutional Ethics Committee (GYKY-2023-004);
2. All subjects receive full verbal and written explanation of trial purpose, intervention measures, potential risks and benefits before enrollment, and sign informed consent voluntarily;
3. Subjects have the right to withdraw from the trial at any time without penalty, and routine medical treatment will not be affected;
4. All subject personal information is de-identified in CRF and statistical data to protect patient privacy; all original data are stored encrypted.

15. Data Storage and Publication Plan

1. Original CRF, laboratory test reports and randomization records are stored in respiratory department special file cabinet for 5 years after trial completion; electronic data are backed up twice in encrypted hospital server;
2. After statistical analysis is completed, research results will be sorted into academic manuscript for submission to peer-reviewed respiratory or integrated medicine journals;
3. All authors sign data sharing agreement; raw data can be provided to academic institutions for meta-analysis upon reasonable application after de-identification.

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