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The Clinical Effect and Mechanism of Kechuan Guben Pills for Blood Stasis Syndrome of COPD in Stable Stage

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Abstract **Objective:** To observe the therapeutic efficacy and possible mechanism of Kechuan Guben Pills (KGP) in patients with blood stasis syndrome of COPD in stable stage. **Methods:** All patients diagnosed with blood stasis syndrome of COPD in stable stage hospitalized in Department of Respiratory and Critical Care Medicine, Linyi TCM Hospital from June 2021 to January 2023, were selected and randomly divided into control group received Budesonide 2 puffs, twice a day and treatment group given KGP on the basis of control group, 9 g, twice a day for six months. The traditional Chinese medicine (TCM) syndrome scores of patients were collected according to TCM Syndrome Diagnosis Criteria of Chronic Obstructive Pulmonary Diseaseand and the serum levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), high-sensitivity C-reactive protein (hs-CRP), transforming growth factor-β (TGF-β) and vascular endothelial growth factor (VEGF) were determined by immunofluorescence assay and latex enhanced immunoscattering turbidimetric assay. **Results:** The taotal effective rate of patients in the treatment group (96.97%) was significantly higher than that in the control group (82.86%), $P < 0.05$. The TCM syndrome scores of patients in the treatment group showed significant improvement compared to the control group ($P < 0.01$). The serum levels of IL-6, TNF-α, hs-CRP, TGF-β and VEGF in the treatment group showed significantly better than those in the treatment group ($P < 0.01$). **Conclusion:** KGP could significantly improve TCM symptoms of patients with blood stasis syndrome of COPD in stable stage by inhibiting the expressions of inflammatory factors and regulating the collagen fiber deposition related factors in the extracellular matrix.

Keywords: *kechuan guben pills, COPD, blood stasis syndrome, TCM syndrome score, inflammatory factor*

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1. Introduction

Chronic obstructive pulmonary disease (COPD) mainly results from small airway remodeling and the development of emphysema, leading to the destruction of the lung parenchyma. Patients of COPD in stable stage have a certain degree of symptoms with little impact on daily life [1]. Decreased lung tissue elasticity, alveolar destruction and fibrosis are further affected the gas exchange and lung function [2]. The treatment goal of stable COPD is to reduce the symptoms and the occurrence of acute exacerbation, and delay the progression of the disease. The treatment plan should be individualized according to the patient's condition, symptoms and the degree of affecting the quality of life, which including relevant targeted drug therapy, glucocorticoid, oxygen therapy, and rehabilitation treatment [3]. According to traditional Chinese medicine, chronic obstruction is mainly caused by the mutual influence of phlegm and blood stasis, loss of lung dispersing, producing phlegm-dampness, chronic disease and blood stasis, and finally phlegm-stasis combined mutually to obstract airflow [4]. "Danxi Heart Method Cough" said that "Phlegm with blood stasis obstructing respiration cursed lung distension and cough and leading to difficultly fall asleep", which suggesting that COPD is mainly caused by phlegm stasis obstructing airflow, therfore, the treatment should be strengthening the body resistance and eliminating pathogens, and addressing both the symptoms and root cause of disease [5]. On the basis of supplementing deficiency, promoting blood circulation could achieve more significantly effective of supplementing deficiency and eliminating solid, and addressing both the symptoms and root cause [6]. This study tries to investigate the clinical efficacy and possible mechanism of Kechuan Guben Pill (KGP) in the treatment for blood stasis syndrome of COPD in stable stage.

2. Research Methods

2.1. Subjects

Total of 80 patients with blood stasis syndrome of COPD in stable stage were selected in Department of Respiratory and Critical Care Medicine of Linyi Traditional Chinese Medicine Hospital from June 2021 to January 2023. According to age, sex, course of disease, etc., 80 patients were randomly assigned to the control group and the treatment group. This study was approved by the Medical Ethics Committee of Linyi Traditional Chinese Medicine Hospital (No. LYZY20240111). All subjects participated voluntarily in the study and signed informed consent document.

2.2. Diagnostic Criteria

2.2.1. Western diagnostic criteria: Refer to diagnostic criteria from "COPD Diagnosis and Treatment Guidelines (2021 Revision)" [7]: Exclude other known causes or airflow restricted diseases with characteristic pathological manifestations. The severity of patients with COPD was comprehensively evaluated, and the treatment plan was selected according to the evaluation results.

2.2.2. TCM diagnostic criteria: Refer to "TCM Syndrome Diagnosis Criteria of Chronic Obstructive Pulmonary Disease (2011 Edition)" issued by Pulmonary Diseases Professional Committee of Internal Medicine Branch of China Association of Traditional Chinese Medicine [8], and exclude other pulmonary diseases and other visceral diseases.

Reference symptoms of TCM blood stasis syndrome: The main symptoms consist of shortness of breath, aggravation of movement, fatigue, weakness, tenderness of waist and knees, easy to catch cold, tongue ecchymosis or purple dark red, pulse astringent or heavy; The secondary symptoms consist of tinnitus, afraid of wind, spontaneous sweating, chest pain, nocturia. To distinguish the syndrome must satisfied the main symptoms and at least 3 secondary symptoms.

2.3. Inclusion Criteria

Patients who met the diagnostic criteria of COPD in stable stage and comprehensive evaluation group B after evaluation were included in the inclusion criteria; TCM syndrome differentiation accords with blood stasis syndrome; 40 years ≤ age ≤ 75 years, no gender limitation; patients with normal movement of both upper and lower limb joints; high compliance.

2.4. Exclusion Criteria

Patients not met any of the above criteria; with poor general conditions or cannot complete well the relevant test content; accompanied by serious other systemic diseases or other serious lung diseases; poor compliance and are not good collaborators.

2.5. Criteria for Shedding and Suspension

Patients who refused to continue the clinical trial and withdraw from the clinical investigation; did not met the above inclusion criteria but were mistakenly included; the condition of subjects worsened during the course of disease.

2.6. Treatment Plan

2.6.1. Control group: All patients were given basic treatments such as smoking cessation, oxygen therapy, breathing training and nutritional support. Budesonide (Astra Zeneca AB, H20160447, Budesonide 320 μg + formoterolfumarate 9.0 μg) / aspirate, 2 aspirate per day for six months.

2.6.2. Treatment group: On the basis of control group, Kechuan Guben Pill (KGP, prepared by Linyi Traditional Chinese Medicine Hospital, Lu Z20090003) was given, 9 g / time, 2 times per day for six months. KGP prescription: *Astragalus* 18 g, *Herba epimedium* 18 g, *Ginseng* 9 g, *Cuscuta chinensis* 9 g, *Gecko* 6 g, *Rehmannia* (raw) 9 g, *Rehmannia* (cooked) 9 g, *Rizoma polygonati* 9 g, *Radix polygonati officinalis* 9 g, *Atractylodes* 18 g, *Medicinal changium root* 18 g, *Chinese yam* 18 g, *Alisma rhizoma* 6 g, *Perilla seed* 18 g, *White mustard seed* 9 g, *Asarum morosa* 2 g, *Bombyx rigidus* (fried) 6 g, *Draba nemorosa* 6 g, *Bitter almond* 6 g, *Fritillaria thunbergii* 9 g, *Peach kernel* 6 g, *Savia miltiorrhiza* 18 g.

2.7. Evaluation Indicators

2.7.1. Clinical efficacy evaluation criteria: Refer to the "Guiding Principles for Clinical Research of Traditional Chinese Medicine New Drugs" [9] and record TCM symptom scores:

Clinical recovery: symptoms disappeared or basically disappeared, syndrome score decreased ≥ 95 %; Significant effective: symptoms improved significantly, syndrome score decreased ≥ 70 %; Clinical effective: all symptoms improved, syndrome score decreased ≥ 30 %; Clinical ineffective: no significant reduction in clinical effect and invalid, syndrome score decreased < 30 %.

Total effective rate = (Clinical recovery, Significant effective and Clinical effective cases) / Total cases × 100 %.

2.7.2. Peripheral blood cytokine levels: Fasting elbow venous blood was extracted from patients before and after treatment, and the serum level of interleukin-6 (IL-6) was detected by immunofluorescence assay, and serum levels of tumor necrosis factor α (TNF-α) and high-sensitivity C-reactive protein (hs-CRP) were detected by latex enhanced immunoscattering turbidimetric assay. Millipore protein detection kits were used to detect the serum levels of transforming growth factor β (TGF-β) and vascular endothelial growth factor (VEGF).

2.8. Statistical Analysis

SPSS 23.0 statistical software was used for data processing. The measurement data were expressed as mean ± standard deviation ($x \pm s$) and the t test for quantified data, x^2 test for counted data. $P<0.05$ was considered as significant difference.

3. Results

3.1. Comparison of Basic Data

Total of 80 patients were randomly divided ito two groups consisting of 40 patients each group, and withdraw 5 patients in control group and 7 patients in treatment group at last. No significant differences in age, sex and course of disease between the two groups ($P > 0.05$). Seen as Table 1.

Table 1. Comparison of basic data between the two groups ($\dot{X}\pm S$)

Groups	Age (years)	Sex (male/female)	Course of disease (years)
Control group, n=35	58.40±10.13	17/18	7.97±1.61
Treatment group, n=33	57.45±8.91	14/19	7.88±1.61
t / x^2	0.41	0.07	0.23
P	0.69	0.79	0.82

3.2. Comparison of Clinical Efficacy

The cases of clinical recovery, significant effective, clinical effective and clinical ineffective were respectively 0, 4, 25 and 6 in the control group while 1, 15, 16 and 1 in the treatment group. The total effective rate of the treatment group (96.97 %) was significantly higher than that of the control group (82.86 %), $P < 0.05$. Seen as Table 2.

Table 2. Comparison of clinical efficacy between the two groups

Groups	Clinical recovery	Significant effective	Clinical effective	Clinical ineffective	Total effective rate (%)
Control group, n=35	0	4	25	6	82.86
Treatment group, n=33	1	15	16	1	96.97

3.3. Comparison of TCM Syndrome Scores

There was no significant difference in TCM symptom scores between the two groups before treatment ($P > 0.05$). After treatment, the TCM syndromes such as expectoration, shortness of breath, wheezing, chills, spontaneous sweating, soreness of waist and knee, five irritability fever and dizziness in the two groups were significantly improved compared with before treatment ($P < 0.01$), and which in treatment group were significantly better than those in control group ($P < 0.01$). Seen as Table 3.

Table 3. Comparison of total score of TCM syndromes between the two groups ($\dot{X}\pm S$)

Groups	Before treatment	After treatment	t	P
Control group, n=35	15.31±1.65	8.74±1.76	22.12	<0.01
Treatment group, n=33	15.42±2.46	4.58±1.79	28.91	<0.01
t	0.21	9.52		
P	0.83	<0.01		

3.4. Comparison of Laboratory Indicators

3.4.1 The serum level of IL-6: Before treatment, there was no significant difference in the serum level of IL-6 between the two groups ($P > 0.05$). After treatment, the serum levels of IL-6 in the two groups were significantly decreased than those before treatment ($P < 0.01$), and which in the treatment group was significantly lower than that in the control group ($P < 0.01$). See Table 4-1.

Table 4-1. Comparison of serum level of IL-6 between the two groups ($\dot{X}\pm S$)

Groups	Before treatment (ng/L)	After treatment (ng/L)	t	P
Control group, n=35	14.46±3.79	9.18±2.84	22.72	<0.01
Treatment group, n=33	15.30±4.09	6.77±1.82	20.13	<0.01
t	0.86	4.08		
P	0.39	<0.01		

3.4.2 The serum level of TNF-α: Before treatment, no significant difference existed in the serum level of TNF-α between the two groups ($P > 0.05$). After treatment, the serum levels of TNF-α in the two groups were significantly reduced than those before treatment ($P < 0.01$), and which in the treatment group was significantly lower than that in the control group ($P < 0.01$). See Table 4-2.

Table 4-2. Comparison of serum level of TNF-α between the two groups ($\dot{X}\pm S$)

Groups	Before treatment (ng/L)	After treatment (ng/L)	t	P
Control group, n=35	25.89±9.23	14.68±7.15	9.38	<0.01
Treatment group, n=33	26.01±9.00	7.71±2.82	15.16	<0.01
t	0.05	5.15		
P	0.96	<0.01		

3.4.3 The serum level of TGF-β: There was no significant difference in the serum level of TGF-β between the two groups before treatment ($P > 0.05$). After treatment, the serum levels of TGF-β in the two groups were significantly decreased than those before treatment ($P < 0.01$), and which in the treatment group was significantly lower than that in the control group ($P < 0.05$). See Table 4-3.

Table 4-3. Comparison of serum level of TGF-β between the two groups ($\dot{X}\pm S$)

Groups	Before treatment (μg/L)	After treatment (μg/L)	t	P
Control group, n=35	26.02±6.48	24.16±5.84	11.63	<0.01
Treatment group, n=33	27.17±4.16	21.31±3.57	31.31	<0.01
t	0.85	2..38		
P	0.40	<0.05		

3.4.4 The serum level of hs-CRP: Before treatment, no significant difference existed in the serum level of hs-CRP between the two groups ($P > 0.05$). After treatment, the serum levels of hs-CRP in the two groups were significantly reduced than those before treatment ($P < 0.01$), and which in the treatment group was significantly lower than that in the control group ($P < 0.01$). See Table 4-4.

Table 4-4. Comparison of serum level of hs-CRP between the two groups ($\dot{X}\pm S$)

Groups	Before treatment (mg/L)	After treatment (mg/L)	*t*	*P*
Control group, n=35	9.25±2.21	6.55±0.83	9.043	<0.01
Treatment group, n=33	9.19±2.01	4.44±0.73	11.22	<0.01
t	0.58	10.96		
P	0.91	<0.01		

3.4.5 The serum level of VEGF: No significant difference existed in the serum level of VEGF between the two groups before treatment ($P > 0.05$). After treatment, the serum levels of VEGF in the two groups were significantly decreased than those before treatment ($P < 0.01$), and which in the treatment group was significantly lower than that in the control group ($P < 0.05$). See Table 4-5.

Table 4-5. Comparison of serum level of VEGF between the two groups ($\dot{X}\pm S$)

Groups	Before treatment (ng/L)	After treatment (ng/L)	*t*	*P*
Control group, n=35	193.17±15.76	175.13±13.86	65.44	<0.01
Treatment group, n=33	192.56±12.97	168.09±17.57	16.43	<0.01
t	0.17	2.81		
P	0.87	<0.01		

4. Discussion

COPD is characterized by persistent respiratory symptoms and airflow restriction, which is not completely reversible and develops progressively, and is related to abnormal inflammatory response of the lungs to harmful particles and gases [10]. In this study, by evaluating the changes of TCM syndrome scores before and after treatment, the scores of symptoms such as expectoration, shortness of breath, wheezing, aversion to cold, spontaneous sweating, tenderness of waist and knee, burning sensation of five centres, dizziness and other symptoms, as well as the overall symptoms in the treatment group were significantly better than those in the control group ($P<0.05$), which indicating that KGP has significant efficacy in the treatment of blood stasis syndrome of COPD in stable stage.

Astragalus, as the main medicine of KGP, belongs to the lung channel and tonify lung qi, while *Herba epimedium* at tonifying kidney Yang. *Ginseng* can reinforce vital energy and *Cuscuta chinensis* tonify kidney Yang; *Gecko* is good at strengthening kidney qi and helping *Herba epimedium* to warm kidney Yang. *Atractylodes*, *Alisma rhizoma*, *Medicinal changium root* and *Chinese yam*, drys dampness strengthens spleen; *Asarum morosa*, *Bombyx rigidus* and *White mustard seed* ventilats airway of lung and warms for resolving cold-phlegm to breath smoothly; *Peach kernel* and *Salvia miltiorrhiza* invigorates blood stasis, and *Peach kernel* moistens intestines and relieves cough to change the stasis of lung collaterals and induce total drugs to the pathogen-nidus. Cai et al. [11] believed that sputum stasis is the main pathogenic factor of COPD, and at the same time, deficiency of COPD should be treated in the stable stage in remission.Yin [12] et al. believed that the pathogenesis of this disease was phlegm stasis and airway obstruction, so the treatment principle should tonify lung to remove stasis and eliminate phlegm.

Previous studies shown that patients with COPD will be accompanied by a significant increase in serum level of IL-6, which is a potential target molecule for the treatment of COPD by promoting collagen synthesis and extracellular matrix deposition, remodeling airway and inflammatory process [13]. Kubysheva et al. [14] reported that TNF-α not only to enhance the inflammatory response in the respiratory tract, but also to play a role in the development of systemic inflammation. TGF-β is the main inducer of extracellular matrix production in lung fibroblasts, which results in the imbalance of extracellular matrix and airway wall fibrosis of COPD patients, and leads to airway stenosis. In addition, TGF-β is also involved in the regulation of immunity, in which the release of IL-1α induced TGF-β releasing and further promoted synthesis of collagen and activation of fibroblast, so that it could exacerbate inflammation and fibrosis of ling tissue [15]. hs-CRP is involved in inducing oxidative stress in COPD patients, which leads to damage to lung tissue and cells, and ultimately leads to severe decline in lung function [16]. In this study, the therapeutic effect of KGP on COPD patients in stable stage was significantly reflected in the changes of several inflammatory indicators, including serum levels of IL-6, TNF-α, TGF-β and hs-CRP. In addition,VEGF is a factor promoting angiogenesis and vascular permeability. In COPD, airway inflammation and injury lead to the process of lung blood vessel damage and repair, and during this process, the expression of VEGF increases to promote the formation of new blood vessels to meet the needs of lung tissue [17]. The results of this study also showed that KGW also had a good improvement effect on VEGF.

Modern pharmacological studies shown that the compatibility and combination of multiple drugs in KGW may have therapeutic effects on COPD. The combination of *Astragalus membranaceus* combined with *Atractylodes* can inhibit inflammation, resist oxidative stress and promote angiogenesis, thus playing a therapeutic role in COPD [18]. The active ingredients of astragalus isoflavanin, luteolin, quercetin and isorhamnetin in the combination of *Astragalus membranaceus* and *Fructus praeparum* can regulate the levels of inflammatory factors through multi-targets and multi-pathways so as to ply an anti-inflammatory activity [19]. Other studies shown that *Astragalus* has an inhibitory effect on inflammatory cytokines IL-6 and TNF-α [20]. The combination of *Ginseng* and *Poria cocos* can inhibit apoptosis through multiple targets to play a role in the treatment of COPD by its antioxidant and anti-inflammatory effects [21]. The compatibility of *Ginseng* and *Tangerine peel* can regulate inflammatory responses through multi-targets and multi-active ingredients of sterols and flavonoids [22]. In addition, the active ingredients of adjuvant medicines such as *Rhizoma Alisma* and *Peach kernel* have anti-inflammatory effects [23]. Epimedium polysaccharide, icariin and other components of *Herba epimedium* can decrease the expression of TGF-β, and then inhibit the

collagen deposition in the extracellular matrix of pulmonary fibrosis [24]. *Gecko* can improve airway inflammatory response and thus play a role in relieving asthma [25]. *Bombyx rigidus* has the effect of anti-histamine and can increase the secretory function of adrenal cortex, thus relieving spasm of airway smooth muscle [26]. Li et al. [27] showed that *Salvia miltiorrhiza* injection can dilate the artery and prevent the plaque formation on the artery wall, so as exerting antioxidant stress and anti-inflammatory effects.

In summary, KGW mighty play a therapeutic role for the patients with blood stasis syndrome of COPD in stable stage by inhibiting the expressions of inflammatory factors and regulating the collagen fiber deposition related factors in the extracellular matrix.

Founding

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Ethics Approval and Consent to Participate

All related experiments were approved by the Ethics Committee of Linyi Traditional Chinese Medicine Hospital (No. LYZY20240111).

Conflicts of Interest Statement

The authors declare that there are no conflict of interest.

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