ORIGINAL ARTICLE

Randomized Controlled Trial on Treatment of Bronchial Asthma of Qi-deficiency Cold Syndrome Type by Pingchuan Yiqi Granule (平喘益气颗粒)

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ABSTRACT **Objective:** To evaluate the effect and safety of Pingchuan Yiqi Granule (平喘益气颗粒, PYG) in treating bronchial asthma of qi-deficiency cold syndrome type (BS-QDC). **Methods:** With the randomized, positive agent parallel controlled design adopted, the 80 subjects enrolled were assigned in the ratio of 3:1 to two groups, the 60 patients in the trial group were treated with PYG and the 20 in the control group treated with Ruyi Dingchuan Pill (如意定喘丸,RDP), with the therapeutic course consisting of 7 days for both groups. The clinical effects, effects on TCM syndrome and the changes of lung function after treatment were observed. **Results:** The effect of the treatment on asthma in the trial group: clinically controlled rate was 6.67%, markedly effective rate 51.67%, improved rate 33.33% and ineffective rate 8.33%; and the corresponding rates in the control group were 5.00%, 50.00%, 30.00%, and 15.00% respectively. Comparison between the two groups showed insignificant difference ($P>0.05$). The effect on TCM syndrome in the treated group: clinically controlled rate was 11.67%, markedly effective rate 58.33%, effective rate 21.67% and ineffective rate 8.33%; and those in the control group were 10.00%, 50.00%, 30.00% and 10.00% respectively, also showing insignificant difference between the two groups ($P>0.05$). Lung function test showed that the change on forced expiratory volume in 1 second (FEV1) after treatment in the trial group was of statistical significance ($P<0.05$), but no significant difference was shown in the change of peak expiratory flow (PEF, $P>0.05$); while the changes in the control group were just the opposite, showing insignificance in FEV1 ($P>0.05$) but significance in PEF ($P<0.05$). Comparison of the therapeutic effect on lung function between the two groups showed no significant difference ($P>0.05$). No adverse reaction was found in either group in the course of treatment. **Conclusion:** PYG used to treat BS-QDC is effective and safe, it's effect is similar to that of RDP.

KEY WORDS Pingchuan Yiqi Granule, randomized controlled trial, bronchial asthma, qi-deficiency cold syndrome type

Pingchuan Yiqi Granule (平喘益气颗粒, PYG) is a newly developed Chinese and manufactured cooperatively by the National Supervisory Administration of Foods and Drugs, Zhejiang University, and Zhejiang Research Laboratory of Respiratory Drugs, the Institute of Bioengineering of Huadong Group of Medicine and Drug, and Kangrun Pharmaceutical Co., Ltd., of Huadong Group of Medicine and Drug. It composes of ephedra herb, red ginseng, Japanese Yam rhizome, apricot seed, magnolia bark, common perilla leaf, thorowax root, tangerine peel, and licorice root, etc. Pre-clinical pharmacologic experiment and secondary stage clinical trial proved that it has the actions of opening Fei (肺)-channel, alleviating asthma, nourishing Fei and supplementing qi; toxicologic study showed that it has no evident adverse-toxic effect. It is often used in clinical practice to treat bronchial asthma of qi-deficiency cold (BS-QDC) type. According to the ratification of

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DOI: 10.1007/s 11655-007-0027-7

Chin J Integr Med 2007 Mar;13(1):27-32

National Supervisory Administration on Clinical Research of the number of (1999) ZL-4, the third stage of clinical trial on PYG in treating BS-QDC was conducted by Huaxi Hospital of Sichuan University (as a sub-center), and with randomized, positive drug parallel controlled method adopted, its safety and effectiveness was assessed, so as to provide enough proof for the drug to get permission to come into the market, and to get information for working out an instruction for the drug.

METHODS

Diagnostic Standard

The diagnosis of qi-deficiency cold syndrome (QDC) type was made in reference to the principle of clinical study on TCM new drugs for asthma in "Principle of Guidance on Clinical Study of TCM New Drugs"[(1)]. Bronchial asthma (BA) was diagnosed according to the standard in "Directory of Bronchial Asthma Prevention and Treatment" established by the Branch of Respiratory Diseases of the Chinese Association of Medicine[(2)].

Standard for Inclusion

(1) Included were patients diagnosed by Western medicine to have BA in the attacking stage and of mild or moderate degree, or with clinical manifestation that match the standard for TCM syndrome of QDC type; (2) the onset of attack was within 3 days; (3) those patients who were aged between 18-65 years; (4) who signed on the informed consent and the informed consent acquiring procedure fit with the requirement of good clinical practice (GCP).

Standard for Exclusion

(1) Excluded were patients with BA in the remitting stage or with the syndrome not matching the standard of TCM syndrome of QDC type; (2) their disease was in severe condition; (3) patients with symptoms of dyspnea or labored breathing caused by other diseases than BA; (4) women in pregnant or lactation stage; (5) patients of hypersensitive constitution or allergic to the testing drug; (6) patients complicated with severe primary diseases of liver, kidney and hemopoietic system, cardio-/ cerebralvascular diseases or patients of psychopathy; (7) patients of hypertension.

Standard for Screening

(1) Any patient who was found to unfit the inclusion standard after enrolled; (2) subjects with bad compliance (compliance to the testing drug <80% or >120%), and in need of changing or stopping the prescribed drug or adding other drugs, or in need of using in combination drugs that were forbidden in this program for they influenced the efficacy or safety assessment.

Standard for Dropping-out

Any testee, who had entered into the trial through signing informed consent and passing the screening, has the right to drop out of the trial at any time. In case that the integral course of observation of the clinical trial fail to be completed on any subject, no matter what the reason was or at what time they wanted to drop out, the subjects should be dealt with as dropping-outs and intention-to-treat analysis (ITT) would be applied.

Request of Medical Ethics

This trial program got permission from the ethical committee. Every testee signed the informed consent before enrollment.

General Materials

As shown in Table 1, a total of 80 out- or inpatients of Huaxi Hospital, hospitalized or

Table 1. Comparison on General Materials between the Two Groups ($\bar{x} \pm s$)

Group	Case	Outpatient/ Inpatient	Male/ Female	Age (Year)	Course of illness (Month)	Days of attack (1d/2d/3d)	Severity (mild/moderate)	Score of TCM syndrome	FEV1L (L)	PEF (L/s)
Trial	60	59/1	18/42	49.18 ± 11.72	248.20 ± 189.20	6/29/25	25/35	18.88 ± 5.92	1.64 ± 0.90	3.83 ± 2.13
Control	20	19/1	15/5	46.65 ± 13.50	164.20 ± 131.20	2/13/5	8/12	18.10 ± 5.79	1.85 ± 0.77	4.39 ± 1.95

visiting in the period of Sept. 2001 to Aug. 2003 were enrolled in this trial, who were assigned to two groups in the ratio of 3:1, with the blocking randomized method adopted, 60 in the trial group and 20 in the control group. No case was screened out or dropped out in either group. The difference between the two groups was statistically insignificant in aspects of source, gender, age, course of illness, days of attack, severity, score of TCM syndrome, forced expiratory volume in 1 second (FEV1) and peak expiratory flow (PEF) of the patients (P>0.05), indicating that the materials of the two groups was proportional and the two groups were comparable.

Testing Drugs, Methods of Grouping, Medication and Therapeutic Course

PYG was used for the trial group, which composed of ephedra herb, red ginseng, Japanese Yam rhizome, apricot seed, magnolia bark, common perilla leaf, thorowax root, tangerine peel, and licorice root, etc. with the ratification of National Supervisory Administration on clinical research of the No. of (1999) ZL-4, Batch number 20000901, given orally 3 times daily, 2 packages (6 g) each time.

Ruyi Dingchuan Pill (如意定喘丸, RDP) was used for the control group, consisting of gecko, toad venom, milkvetch root, earthworm, ephedra herb, asiabell root, apricot seed, ginkgo seed, immature bitter orange, asparagus root, schisandra fruit, lilyturf root, tatarian aster root and rhizome, stemona root, barbary wolfberry, prepared rehmannia root, polygala root, pepperweed seed, hindu datura dried flower, gypsum fibrosum and honey grilled licorice root, a product of Huayu Pharmaceutical Factory, batch No. 20010101, given orally 3 times daily, 4 pills each time.

The therapeutic course was 7 days for both groups.

In the trial period, no other drugs (either Chinese or Western drugs) for alleviating asthma and glucocorticoids were allowed to any testee in either group. But other approaches such as fluid supplement, correction of acid-base or electrolytes disorder and oxygen inhalation may be used if necessary; and antibiotics like common penicillin or carbostyrils may be applied to patients with complicated infection.

Items and Methods of Observation

Patients' symptoms (including dyspnea, wheeze, spiritlessness, fatigue, aversion to wind and cold, cough, short breath, no desire to talk, chest stuffiness, expectoration and spontaneous sweating) and physical signs (including wheeze, pictures of tongue and pulse) were observed and recorded before and after treatment, and scored in ranks.

Lung function was examined before and after treatment.

The effect initiation time of asthma and remission time were monitored.

Adverse events and reactions that occurred were observed closely, especially serious events and reactions, time of occurring, degree of symptoms, management and outcome should be recorded. Routine examination on blood, stool and urine as well as liver and kidney function and ECG were determined before and after treatment.

Standard for Efficacy Evaluation

Standard for evaluation of efficacy on bronchial asthma was made in reference to the standard in "Directory of Bronchial Asthma Prevention and Treatment" established by the Branch of Respiratory Diseases of Chinese Association of Medicine[2] in the following manner: (1) Clinically controlled: which means complete remission of asthma symptom, even if a mild attack might occasionally occur, but could be spontaneously remitted without need of medication; FEV1 or PEF increased by 35%, or post-treatment FEV1 or PEF ⩾ 80% of the predicted value; diurnal fluctuation rate of PEF < 20%. (2) Markedly effective: which means the degree of attack got alleviated evidently; FEV1 or PEF increased by 25%-35%, or post-treatment FEV1 or PEF reached 60%-79% of the predicted value; diurnal fluctuation rate of PEF < 20%. (3) Improved: which means symptom of asthma got

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reduced in some degree; FEV1 or PEF increased by 15%-24%. (4) Ineffective: no improvement in clinical symptoms and FEV1 or PEF value, or they got even aggravated.

Evaluation of the therapeutic efficacy on TCM syndrome was conducted according to the nimodipine method, and classified into 4 grades: the efficacy was judged as clinically controlled if the score of TCM syndrome decreased after treatment by ⩾ 90%; it was judged as markedly effective if the score decreased by ⩾ 60% but < 90%; as effective if it decreased by ⩾ 30% but < 60%; and as ineffective if it decreased by < 30%.

The effect initiation time (IT) was defined as the time needed for dyspnea or wheeze to reduce by one grade; the remission time (RT) was defined as the time needed for disappearance of dyspnea or wheeze.

Safety and Adverse Events

The causal relation of adverse events with the testing drug was assessed in five grades, namely, definitely related, very possibly related, possibly related, possibly unrelated and unrelated. If it was assessed as of the former three grades, the events would be regarded as adverse reaction .

Statistical Analysis

Data were analyzed with per-protocol population method. After auditing and proofreading, the clinical data were analyzed with software Stata, χ^2 test for enumeration data, *t*-test for measurement data and Wilcoxon rank test for rank data, and check efficiency α was defined as 0.05.

RESULTS

Efficacy on Bronchial Asthma

See Table 2, the clinically controlled rate in BA in the trial group and the control group was 6.67% and 5.00% respectively, while the markedly effective rate in them was 51.67% and 50.00% respectively, the improved rate 33.33% and 30.00% and the ineffective rate 8.33% and 15.00% respectively, and comparison between the two groups showed insignificant difference (P>0.05), suggesting that the clinical efficacy in the two groups was equivalent.

Table 2. Comparison Efficacy on Bronchial Asthma between the Two Groups [Case(%)]

Group	Case	Clinically controlled	Markedly effective	Effective	Ineffective	Total markedly effective	Total effective
Trial	60	4 (6.67)	31 (51.67)	20 (33.33)	15 (8.33)	58.34	91.67
Control	20	1 (5.00)	10 (50.00)	6 (30.00)	3 (15.00)	55.00	85.00

Efficacy on TCM Syndrome

See Table 3, the clinically controlled rate in TCM syndrome in the trial group and the control group was 11.67% and 10.00% respectively, while the markedly effective rate in them was 58.33% and 50.00% respectively, the improved rate 21.67% and 30.00% and the ineffective rate 8.33% and 10.00% respectively, with comparison between the two groups showing insignificant difference (P>0.05), suggesting that the clinical efficacy in the two groups was equivalent.

Table 3. Comparison Efficacy on TCM Syndrome between the Two Groups [Case (%)]

Group	Case	Clinically controlled	Markedly effective	Effective	Ineffective	Total markedly effective	Total effective
Trial	60	7 (11.67)	35 (58.33)	13 (21.67)	5 (8.33)	70.00	91.67
Control	20	2 (10.00)	10 (50.00)	6 (30.00)	2 (10.00)	60.00	90.00

Efficacy on Score of TCM Syndrome

The score of TCM syndrome in the trial group and the control group before treatment was 18.88 ± 5.92 and 18.10 ± 5.79 respectively, and it got evidently decreased after treatment in the two groups 6.33 ± 4.20 and 6.75 ± 4.98, (P<0.01), but the difference between them showed statistical insignificance (P>0.05).

Changes of Lung Function after Treatment

In the trial group, both FEV1 and PEF increased after treatment but statistical significance only showed in the difference of the former (P<0.05); while in the control group, the two indexes were also increased but showed statistical significance only in the latter (P<0.05); as for comparison between the two groups, no statistical significance was shown in the difference either in FEV1 or in PEF (P>0.05). See Table 4.

Table 4. Changes of Lung Function before and after Treatment between the Two Groups ($\bar{x} \pm s$)

Group	Case	Time	FEV1(L)	PEF(L/s)
Trial	60	BT	1.64±0.90	3.83±2.13
		AT	1.76±0.92*	4.03±2.09
Control	20	BT	1.85±0.77	4.39±1.95
		AT	1.98±0.89	4.70±2.19*

Notes: *P<0.05, compared with the same group before treatment; BT means before treatment, AT means after treatment

Comparison of IT and RT between Groups

The median of IR was 63.0 h and 59.5 h in the trial group and the control group, while the media of RT was 96.0 h and 91.5 h respectively. The differences between the two groups in IT and RT were all of statistically insignificant meaning (Z=0.540, P = 0.589 and Z=0.419, P = 0.675).

Safety Assessment

No evident change after treatment was found in all the testees medicated by PYG in routine tests of blood, urine and stool, or in liver and kidney function and ECG examination. No adverse reaction occurred in the period of this trial.

DISCUSSION

BA is chronic inflammation with the participation of multiple inflammatory cells like eosinophil, mastocyte and T-lymphocyte, and in clinics, it often reveals such symptoms as recurrently attacking dyspnea, gasp, chest stuffiness or cough, and the attack often occurred at night or in the morning. The morbidity of BA is rather high in our country, seriously harmful to people's health and economic development of society. Chinese drugs have served for a long time in the treatment of BA. Though it showed a remitting effect on the symptom of asthma, it was not accepted due to the lack of evidence-based medical proof. For this reason, the authors designed the prospective randomized controlled clinical trial to objectively assess the efficacy and safety of PYG in treating BA-QDC.

In TCM, BA belongs to the category of wheezing syndrome. Among the syndrome types of BS, the cold syndrome type is considered to be caused by invasion of evil wind-dampness, long-term coughing and dyspnea that cause in turn Fei-fluid insufficiency, or by soiling in lung of phlegm that results in accumulation of dampness due to original Pi (脾)-deficiency, which causes Fei (肺)-qi to lose its clean nature, leading to dysfunction in ascending and descending.Thus asthma happens. Further more, repeated attacks of asthma would damage the organism and cause Pi-Shen (肾) deficiency and vital energy asthenia. So the treatment of asthma should be conducted on both superficiality and the essential.

PYG is based on Shenmi Decoction (神秘汤, consisting of ephedra herb, apricot seed, magnolia bark, thorowax root, common perilla leaf and licorice root), with ginseng and Japanese Yam rhizome added. Shenmi Decoction originates from the ancient medical book "Waitai Miyao" (外台秘要) written a long long time ago, in which it is recorded as a recipe for treatment of long-term cough, serious dyspnea during attack, wheezing in the throat, that causes difficulty for the patient to sit or lie down in bed, and that is why it is named originally "the recipe for chronic cough that makes it hard for the patient to sit or lie down". It was said by Mr. Ya Ka Zu, Japan, in his work of "Explanation on the Recipes Used in Clinic": "This recipe is applied on bronchial asthma, with dyspnea as the main symptom, few sputum and accompanied with qi-stagnancy"[4]. There have been some reports in China and Japan dealing with the satisfactory efficacy of applied Shenmi Decoction in treating bronchial asthma[5-7]. In this decoction, ephedra herb is used for dispersing wind-cold, ventilating Fei to alleviate dyspnea; ginseng for consolidating the essential to supplement Fei, ridding off evil elements without consuming vital energy, strengthening the body without causing impediment on qi. The two works together as the prevailing elements. Apricot seed can lower the reversed qi and remove phlegm, Japanese yam rhizome can dispel sputum and calm dyspnea, common perilla leaf can dispel cold and regulate Fei, and magnolia bark can depress qi and dissolve

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sputum. These four drugs work together as the supplements, which help the prevailing elements in performing the function of regulating Fei and relieving dyspnea; thorowax root and tangerine peel act the associative part of dredging Gan (肝)-qi, regulating qi to eliminate sputum; and licorice root harmonizes the effects of all drugs in the recipe, working as the emissary. Combined use of these drugs have the actions of alleviating dyspnea, stopping cough, supplementing qi, warming Fei to achieve the effect of curing the body both at the superficial level and the essential one. Pre-clinical pharmacological study has proved that PYG possesses evident functions of anti-allergy, anti-inflammation, arresting asthma, dispelling sputum and enhancing immunity, while no evident adverse-toxic reaction has been found in the pre-clinical experiments over its acute or long-term toxicity.

It has been shown in this study that PYG has showed an effect in treating BS-QDC that is similar to that of RDP in aspects of clinical efficacy, efficacy on TCM syndrome, effect initiation time, improving score of TCM syndrome and lung function. With no statistical difference found between them ($P>0.05$), it has been suggested that the efficacy of PYG is equivalent to that of RDP. In the trial group after treatment, the score of TCM syndrome lowered significantly, the difference of FEV1 between before and after treatment was of statistical significance ($P<0.05$), suggesting that PYG has effects in improving the symptoms and FEV1 in patients with BS-QDC. However, PEF after PYG treatment changed insignificantly ($P>0.05$), suggesting that the effect of PYG in improving PEF is not so good, but that result may also be due to the small size of samples used in the study. So this needs to be verified with large samples.

Results of this clinical trial indicated that PYG has effects of alleviating dyspnea, stopping cough, supplementing qi and warming Fei, can improve the symptoms and signs as well as lung function in patients with BS-QDC, being safe and effective in treating that disease, and easy for administering, thus providing a new selective drug for clinical application.

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(Received December 2, 2006)
Edited by TAO Bo