Clinical Effects of Chinese Medicine ,Ping Chuan Chong Ji , Composition for Treatment of Bronchial Asthma

Short Title : Chinese Medicine Treat Asthma .

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Abstract

Traditional Chinese medicine have been used for centuries in the of treatment asthma . The current study aimed at studying the effects of Ping Chuan Chong Ji (PCCJ), which is used in the treatment of asthma patients.

After a run-in period, we randomly assigned 28 subjects(age range 18 to 68 years PCCJ 41±12 ; Placebo 46±15) to receive either PCCJ or placebo . 2 grams , 3 times per day for 12 weeks . For the first four weeks of the study , the subjects continued the conventional medication they had received before enrollment . During the following four weeks , the doses of conventional medication were tapered in an effort to discontinue this therapy . The primary outcome measure were lung function , IgE level and an improvement in the asthma symptom score at 12 weeks , according to a 5 point scale , with 0 indicating no symptoms and 5 incapacitating symptom .

Results: 15 subjects were assigned to receive PCCJ and 13 were assigned to received placebo. At base line in PCCJ group , the mean symptom score was 3.1±1.35 . After 12 weeks of therapy, the mean score were 0.600±0.737. At base line in placebo group , the mean symptom score were 2.85±1.28 . after 12 weeks of therapy , the mean score were 2.6±1.6. FVC , FEV1 , PF were significantly improvement in PCCJ group with no improvement in placebo group . Patients treated with conventional medicine had greatest reductions 65- 82 percent in PCCJ group with only 3- 7 percent in placebo group . PCCJ reduced IgE in the blood which placebo had no effects .

Conclusions : PCCJ improves symptoms of asthma , lung function and regulates IgE , and which reduces the need dose of conventional medication . The results showed that the patients were able to replace their oral steroid with PCCJ .

INTRODUCTION

Despite important progress in our understanding the pathogenesis of asthma , morbidity and even mortality from the disease in the developed countries have not decreased [1-3]. At present preventive therapy for the asthma is mainly based on topical or systemic corticosteriods, agents that raise concern about long term safety . Therefore patients often express an interest to explore non conventional approaches to relief symptoms of asthma . In China, herbal therapy has been used for several centuries as therapy for asthma with an apparent beneficial effect . Studies has been done in the last 10 years in China and Japan which have suggested that herbs can have some deferrable effects such as regulate T cell subgroups[4], decrease IgE [5] and enhanced cAMP. However , it has been difficult to assess the benefit of herbal therapy using scientific methods . This difficulty results mainly from the fact that the concentration and dose of the apparent pharmacologically active components of the herbs are not well known or standardized . Furthermore , according to the traditional Chinese therapy , the mixture of herbs has to be individualized for each patient . We therefore decided to study a fixed combination of herbs , Ping Chuan Chong Ji (PCCJ) . This combination (it's components are listed in the appendix), is a modification of an ancient mixture assigned to the Ming Dynasty . Preliminary animal and clinical research has suggested that these herbs may improve symptoms , induce a measurable effect on lung function , on IgE levels , the degree of bronchial reactivity and thereby may enable reduction the dose of steroids. We therefore conducted a double blind placebo controlled study ,in which we evaluated the short term effect of this fixed composition of herbs on symptoms, need for rescue medication , lung function and IgE levels in patient with mild to moderate asthma.

METHODS

Patients

Patients , 18 to 68 years old with mild -moderated disease who had asthma for at least three months and had been treated with an inhaled steroid for at least three months or ≤ 5mg prodnison, were enrolled . Thirty consecutive patients from the pulmonary clinic of the Sheba medical center were approached, and 28 patients were randomly divided into two groups , 15 to receive PCCJ and 13 to placebo . Patients data is presented in table 1 . The differences in base-line characteristics between the two groups were minor and non significant.

table 1. Base-Line Characteristics of the Study Groups (mean±SD)

Characteristics	PCCJ N =15	Placebo N =13	P value
Age (yrs)	41±12	46±15	0.3876
Gender (M/F)	3/12	6/7	
Duration of disease (yrs)	19.8±15.6	18.5±14.9	0.8401
Dose of inhaled salbutamol (ug /day) *	340± 250	340±280	>0.05
Dose of Fluticasone (ug/day)	417±417	292.±257	0.4627
Dose of salmeterol (ug/day)	127± 57	107±45	0.961
Dose of Budesonide (ug/day)	333± 269	160±203	0.0783
Symptom score during days +	3.2±1.5	2.85± 1.28	0.6364
Symptom score at nights +	1.9±1.8	1.9±1.6	0.8556
Lung Function**			

FVC liters	3.5± 0.8	3.9 ±1.1	0.3501
FEV1 liters	3 ± 0.6	3.3± 0.9	0.3352
PEF morning (liters/min)	250± 57.2	299 ±126	0.187

* Rescue medication for day and night . one puff = 100 mcg .
**Abbreviations FEV_1 denotes forced expiratory volume in one second , and PEF peak expiratory flow.
+Symptoms were scored from 0 (no symptoms) to 5 (very serious symptoms)

Study Design

This was a double -blind, randomized, placebo controlled parallel-group study that was consisted from 3- 4 phases (depending on the assigned treatment), A: during the first 2 phases the conventional therapy was continued, 2 weeks of run-in period ,B: 4 weeks treatment with herbs or a matched placbo, C: 4 weeks in which dose reduction of the conventional medicine was attempted according to a standard protocol after which the treatment code was broken. D: 4 weeks of open treatment with herbs, this last phase was offer only to those who received placebo during the treatment period.

Evaluation
Diary-Card

Patients filled in a daily diary that included morning and evening peak flow (best of two attempts),each before meditation ; Day and night score of syptoms (according to a 5 point scale .with 0 indicating no symptoms and over 3 incapacitating symptom); number of awakening due to asthma ; use of rescue inhaled therapy and the dose of conventional therapy . (Table 2)

Clinic Visits

During the study patients attended the clinic every two weeks, during which they underwent physical examination, review of the diaries and siprometry. Blood tests for IgE, and liver function were done at end of the run-in period and after two weeks each the treatment. During each visit the patients answered a questions on cough ,phlegm, dyspnea(each on 1-3score). Patient withdrawal from the schedule due to declination or need for oral steroid were also recorded. Table 2 .

Table 2 Asthma Quality of life Questionnaire and clinic examine

Domains
1. Symptoms : shortness of breath , cough , phlegm, wheeze ,night symptoms : number of awaking due to asthma attack ;day symptoms : 0-5 score. Use of Inhalators .
2. Manifestations : rales ,stridor, BP, HR.
3. Medication : Flixotide, Severant, Ventolin ,Budicort , Prednisone others .

4. Lung function: FVC, FEV1, FV1/FVC, PEF.
5. laboratory Examine: IgE , Eosinophilia,

The patients answers are based on experience during previous two weeks . Coughing, Phlegm, Shortness of breath , wheeze are grade on a 3 point scale : 1= mild ,2 moderate , 3=serious . The day symptoms on a 6 point scale .0=normal ,1= mild , 2 =2 brief attack , 3=persistent symptoms for many hours ,4 = persistent symptoms for a full day , 5 = severe symptom.

Episode-free Days

Declined as an episode-free day was a day in which there no need for rescue therapy with inhaled β_2-agonists, symptom score of 0, a morning peak expiratory flow that was 80 percent and no adverse events .

IgE Measures

Serum concentrations of free and total IgE were measured by the AlaSTAT Total IgE immunoenzymometric assay using enzyme -labeled murine monoclonal anti-IgE antibody and ligand-labeled goat anti-IgE antibody [6].

Treatment

In the test group ,the patients took Ping Chuan Chong Ji orally. The ingredients are Radix Ephedrae , Prunus Armeniaca , Licoric . Codonopsis pilosula etc. The treatment contained of 5 capsules (2 grams) each time , 3 times daily. One course of treatment consists of 2 months daily treatment. The control group patients took placebo , 5 capsules each time , 3 times daily of two months. Steroid were used for severe asthma symptoms.

Statistical Analysis

The date analysis followed a factorial design. All variables were analyzed with use of ANOVA and t-test , with base-line variables for comparison . For data from the diaries, mean values for the last 14 days before each visit were used. The analysis included all randomized patients. Data for patients who withdrew or discontinued therapy were included up to the time of their withdrew. The number of days during which treatment was received was entered as a covariate.

RESULTS

All patients who were randomized completed the study, and two patients in placebo group required oral perdnsion due to worsening of asthma .

Symptom scores

Symptom scores are shown in table 3. Only in the PCCJ group the improvements was significant. (table 3).

Table 3. Clinical Outcomes in treatment and control groups (mean±SE)

Groups	phase	run-in	treatment	titration	open
PCCJ	daily score	3.1333±0.350	0.600±0.190*	0.400±0.214*	
	Night score	1.933±0.483	0.333±0.187*	0.133±0.091*	
	Cough score	1.600±0.235	0.333±0.126*	0.200±0.145*	
	Phlegm score	1.533±0.236	0.400±0.131*	0.200±0.107*	
	Short breath score	2.200±0.175	0.733±0.248*	0.53±0.256*	
	Salbutmaol(pull/day)#	3.667±0.583	1.267±0.396*	0.667±0.252*	
	Symptom free day	6%	19%	20%	
Placebo	daily score	2.846±0.522	2.615±0.595	2.923±0.680	0.571±0.202**
	Night score	1.714±0.606	1.286±0.522	2.714±0.606	0.571±0.369**
	Cough score	1.154±0.249	1.385±0.385	1.462±0.386	0.500±0.189**
	Phlegm score	1.231±0.231	1.154±0.274	1.231±0.303	0.286±0.184**
	Short breath score	2.077±0.178	1.769±0.201	1.846±0.274	0.286±0.184**
	Salbutmaol(pull/day) #	3.417±0.811	3.167±0.878	3.33±0.762	1.143±0.553*
	Symptom free day	7%	9%	10%	25%

Notes: * p < 0.0001, **P<0.05 compared with period 1(run-in period). # one puf Salbutmaol=100mcg.

The need for rescue medication was reduce significantly in the treatment group during both the day and the night . The four patients in this group stopped the conventional medication completely . The treatment patients reduced prednisone easily and was associated with a increased number of episode-free-days . This change did not occur in placebo group (the table 4)

The table4 The change of medication (mean±SE)

Phase measurement	PCCJ		Placebo		
	run-in	titration	run-in	titration	open
Fluticasone (ug)	714.3±101	250±77.2**	318.2±76.060	386.4±91.476	187.5±78.348
Budesonide(mg)	0.455±0.061	0.127±0.041***	0.218±0.063	0.273±0.078	0.80±0.053
Salmeterol (ug)	23.00±3.391	15±1.5*	15.3±4.253	14.4±4.285	10±3.162

Note: * p< 0.0661, ** p <0.0038 , *** p < 0.0001.Compared with period 1 (run-in period).

Lung Function

FVC and FEV1 in the two groups remained unchanged during the run-in period, but they increased only with the addition of PCCJ (table 5). FVC and FEV1 have remained higher during the titration than during the run-in period. (table 5)

Table 5 The changes of FVC(L%) and FEV1(L/S%)PF(LPM) (mean±SE)

Group	phase	run-in	treatment	titration	open
PCCJ	FVC	64.867±4.412	79.600±3.169**	79.800±3.468**	
	FEV1	51.800±5.170	64.133±4.634*	65.87±4.895*	
	PF	250±14.768	330.667±19.085***	336±18.434***	
Placeblo	FVC	75.154±22.407	76.385±23.243	74.467±20.769	89.22±16.98
	FEV1	63.231±26.398	64±26.957	61.615±23.361	61.62±23.36
	PF	299.231±126.258	294.614±110.067	294.615±110.575	363.3±125.89*

Notes :*p<0.0015; **p<0.0003. ***P<0.0001, Compared with run-in period.

Changes in peak expiratory flow were significantly in PCCJ group and the open period of placebo group.(table5).

Serum IgE Concentration

With PCCJ treatment serum concentration of free IgE dropped rapidly and the difference was close to significance . While it has not significant changes in the control group .(table 6).

Table 6 The changes of IgE (mean±SE)

Groups	n	run in period IU	treatment period IU
PCCJ	14	193.931±41.4	120.380 ±24.93*
Placebo	10	286.702±68.142	304.229±71.699

Nots :* $p < 0.0676$ Compared with run-in period .

Adverse Events

All treatments were well tolerated throughout the study . one patient received prednisone for asthma exacerbation and one patient report had constipation both in the placebo group . one patient improve SGPT to normal and one patient improve lithium to normal , one patient stomach upside for 2 days ,no influence to blood pressure and heart beat and smoothly withdraw the conventional medication in the PCCJ group.

DISCUSSION

The study showed that the PCCJ can improved asthma-symptom scores , lung function and reduced the need for rescue medications and enabled reduction of the dose of inhaled steroid; In the meaning time of the improvement was clinically significant and also in lowing the IgE . The improvement in the control of symptoms is in agreement with the results of other studies . Many study already did in China, Dr Li et al clinic research on 111 cases asthma patients showed that Chinese medicine can significantly low the IgE[8]. The herbs are used for bronchodilator medicine that can treat acute asthma and anti- airway allergic inflammation to cease the attack of asthma. At the same time prevent asthma attack . T lymphocyte play an important regulative role in homoral immunity .in recent years , in the regulation of formation of IgE, T_H clone that prompt B cell to secret more IgE was found when lymphocytes were cultured . some patients belong to the type of IgE dependence. these patients have a higher level of IgE in blood serum , IgE results in releasing of medium after mastocyte cross linking , so that it brings about bronchospasm and asthma attack . In the meantime .it was found that patients of asthma that was induce by sensitinogen have lower T_H in peripheral blood and higher T_H in the lung tissue . and it lasts a long time . The suggested that T_H migrates to lung and has an important role in bring about type 1 allergic reaction . PCCJ regulate T cell subgroup and prevent asthma attack , and increase CAMP in plasma and lung cells type 2 , return the lung volume to normal , the herbs exert protective effect on the adrenocortical cells of the steroid dependent asthmatic patients by suppressing the exogenous steroids

regulate the disorder in different level on hypothalamus-pituitary-adrenocotical axis in the patients. Ma huang or Ephedra sinica contain in PCCJ is well-known traditional Chinese medicine . This herb has been well studied in the Chinese literature. Its uses include the treatment of asthma , high fever , nasal congestion , tracheitis ,cough, hemorrhage , circulatory collapse , and shock[9] . Ma huang is claimed to open pores ,facilitate the movement of lung-qi(or energy), and control wheezing . A classical formula combines Ma Huang with apricot , gypsum , and licorice. Active constituents of Ma Huang include L- ephedrine (80-90%), L-methylephedrine , D-pseudoephedrine , D-N-methylpseudoephedrine , D-norpseudoephedrine , and 0.3-1.5 alkaloid . Ephedrine is an adrenergic agonist , acting on both α -and β-receptors causing vasoconstriction and mydriasis . L-ephedrine has a β-adrenergic agonistic action that relaxes of bronchial muscle [10]. Licorice is a root used as expectorant in cough ,bronchitis and asthma [11]. Active chemicals include glycyrrhizin, a glycone glycyrrhetinic acid, 2-β-glucoronosyl glucoronic acid, isoliquiritigenin-4-glucoside liquintigenin, medicarpin , licorice, licoflavone, saponin and tannic acids [12]. Meckenzie et al study that healthy human were given glycyrrhetinic acid and plasma contisone and cortisol levels were measured .Results showed increased urinary free cortisol and unchanged plasma cortisol with decrease urinary and plasma cortisone [13]. As per materia medica , licorice also an antiallergic effect by inhibiting histamine-induced increased permeability of capillaries[14]. Licorice contains triterpenes , which have a similar structure to adrenal cortex hormones and might be a possible basis for anti-inflammatory action [15]. Koda et al . discovered that licorice reduced immunoglobulin E (IgE) serum by inhibiting PCA in rats [16]. Other antiasthmatic effects include inhibition of PAF. Huang also states that licorice has active antitussive chemicals, 18-β-glycyrrhetic acid and terpnoids, and is an expectorant . It can reduce inflammation of laryngeal mucosa and exhibits protective action to reduce irritation[17]. Some licorice derivatives have shown potency equal to codeine in suppressing cough [18]. Gypsum is described by traditional medicine as an herb that clears heat from the lungs and treats cough and wheezing with fever and thick sputum[19]. It has been reported that Radix Codonopsis Pilosulae , Radix Ophiopogon , Gypsum can improve the immune function and increase cAMP in plasma[20] . The dried kernel of apricot (Prunus armeniaca) is used in the formula . It contains the glucosides amygdalin and amygdalase , Amygdalase and pepsin in the stomach hydrolyzes amygdalin to make cyanic acid that stimulates the respiration center , producing antitussive and antiasthmatic effects . As materia mdica , research has shown a paste made of the dried kernel improves cough , wheezing, and phlegm production in chronic brochitis [21]. Scutellaria baicalensis is a Chinese medicine used for allergies , upper respiratory infections (URIs), and inflammation Its claimed effects include aphrodisiac, antispasmodic ,stringent, antiallrgic, antibiotic , diaphoretic ,febrifuge and tonic [22]. Scutellaria is claimed to inhibit phosphodisterase . It contains wogonin ,baicalein ,oroxylinyl ,volatile oil, scutellarin , scutellarein , and β-sitosterol[23]. Baicalein appears to inhibit mast cell degranulation and promote bronchodilation in the guinea pig model of asthma [24]. Koda et al: discovered that Scutellaria inhibited PCA in rats and resulted in reduced serum IgE [16]. Other research has also shown that Scutellaria

inhibits skin reactions of guinea pig to passive allergic and histamine tests[25]. Schisandra Chinensis , which dried fruit from Schisandra Chinensis is used in many antiasthmatic herbal preparations . It contains sesuicarene , β-2-bisabolene , β-chamigrene , α-ylangene, and glycosides . Schisandra stimulates the respiratory center and has antitussive and expectorant effects[26]. It also has anti-inflammatory and antiallrgic actions. Koda et al. observed that Schisandra inhibits PCA in rats reduced IgE in serum [16]. Ohkura concluded that gomisin a from Schisandra inhibits leucotriene synthesis by preventing arachidonic acid release[27]. Perilla Frutescens (soshi) has multiple effects, including antispasmodic diaphoretic, antitussive, expectorant, and sedative and herb for cephalic pulmonary, and uterine problems. It is folk medicine for asthma, bronchitis, cephalgia, chest,cholera, colds,cough, fish poison , flu, mararia, nausea, pregnancy, rheumatism, spasm, sunstroke, and uteritis[28] . It contains alcohol and L-perilla aldehyde , which has antibacterial and antitussive effects[29]. Morus alba contains morin , dihydromorin , dihydrokaempterol , 2,4,4',6-tetrahydroxybenzophenone ,maclurin, muberrin, mulberrochromene , and cyclomulberrochromene. It is recommended in traditional medicine as an 'antirheumatic', antihypertensive, and diuretic. Morus alba is often used with lycii root for cough and wheezing or with licorice for cough with phlegm[30]. Psoralae corylifolia has cardiovascular , antibacterial, and anticancer effects and can relax bronchial smooth muscle in vivo. It is used in traditional medicine to invigorate the kidney -yang and warm the spleen. It is claimed to aid the kidney in grasping lung energy to control wheezing. It often used with Juglandis [31]. Root of Codonopsis corylifolia for cough with watery sputum, decreased appetite, fatigue, and weight loss [32]. Frittillaria Cirrhosa contains alkaloids. This herb causes bronchodilation and inhibits mucosal secretions. Materia medica states that at low concentrations it has bronchodilatory effects in cats and rabbits similar to that of atropine. At high concentrations , it bronchoconstricts . It also has antitussive actions and is used to relive cough and dyspnea[33]. The use of herb -based intervention in treating chronic medical problems has been increasing in western country . PCCJ should be research further not only because of effective in the clinic for treating asthma but also because their effects could be useful in developing new asthma and allergy medications .