

Traditional Chinese medicine as an adjunctive therapy to oral montelukast for treating patients with chronic asthma

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Abstract

Background: This study aimed to explore the efficacy and safety of Ping Chuan Ke Li (PCKL) as an adjunctive therapy to oral montelukast compared with placebo plus montelukast for treating patients with chronic asthma (CAS).

Methods: This randomized controlled trial involved 72 patients with CAS. They were randomly allocated to an intervention group or a control group, 36 subjects per group. Participants in the intervention group received PCKL and oral montelukast, while those in the control group received placebo and oral montelukast. The primary outcome was lung function, measured by forced expiratory volume in 1 second (FEV₁). The secondary outcomes included quality of life, measured by St. George's Respiratory Questionnaire (SGRQ), and adverse events (AEs).

Results: Compared to placebo plus montelukast, PCKL and montelukast revealed greater efficacy in lung function, measured by FEV₁ ($P < .05$), and quality of life, measured by the SGRQ scale ($P < .05$). Additionally, no significant differences were found in AEs between the 2 groups.

Conclusion: Traditional Chinese medicine PCKL as an adjunctive therapy to oral montelukast alleviated the symptoms of CAS. Future studies with larger sample sizes are still needed to verify the efficacy and safety of PCKL plus montelukast in patients with CAS.

Abbreviations: AEs = adverse events, CAM = Complementary and alternative medicine, CAS = chronic asthma, FEV₁ = forced expiratory volume in 1 second, LTRA = leukotriene receptor antagonist, MMDT = modified Mai-Men-Dong-Tang, PCKL = Ping Chuan Ke Li, SAS = Statistics Analysis System, SGRQ = St. George's Respiratory Questionnaire, SPSS = Statistical Package for the Social Sciences, TCM = traditional Chinese medicine.

Keywords: asthma, clinical trial, Ping Chuan Ke Li, traditional Chinese medicine

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1. Introduction

Asthma is a very common chronic condition among the respiratory diseases. It involves airways narrowing, swelling, and production of extra mucus in patients. It manifests with difficulties in breathing, and triggers coughing, wheezing, and shortness of breath. Its prevalence rate is reportedly 4.3% worldwide,^[1] ranging from 0.7% to 21.0%.^[1–2] It has been estimated that around 300 million people worldwide have asthma, and this number will increase to 400 million by 2025.^[3] Thus, it accounts for significant healthcare costs and also loss in work productivity.^[3]

Its treatment focuses on maintaining near-normal lung function in patients, as well as minimizing activity limitations, and episodes of asthma worsening. Unfortunately, in many patients, chronic asthma (CAS) cannot be controlled with a single type of medicine, and most of them still present with poorly controlled asthma and poor quality of life.^[4–5] It has been reported that montelukast, a leukotriene receptor antagonist (LTRA), can effectively control such condition. However, it still has limited efficacy.^[6]

Complementary and alternative medicine (CAM), especially traditional Chinese medicine (TCM), including acupuncture^[7] and Chinese herbal medicine,^[8] is an effective alternative therapy for patients with asthma and its usage for asthma control from 14% to 60%.^[9–11] Despite its common use worldwide, the

evidence for its efficacy is still limited. Therefore, the lack of evidence for CAM in treating CAS in adults warrants strictly designed randomized clinical trials.

Ping Chuan Ke Li (PCKL) has been used to treat patients with asthma in China with no significant adverse events.^[12–16] It has been reported that PCKL can effectively inhibit airway inflammation and remodeling in experimental asthma animals.^[17–20] It can not only reduce inflammatory cell infiltration in the lung tissue of asthmatic rats, but can also decrease bronchial mucosa and airway wall thickening, blood vessel wall thickening, and vascular proliferation.^[17–20] A previous pilot clinical trial also explored the effect of PCKL in patients with CAS.^[14] However, there is no scientific evidence to evaluate its efficacy in patients with CAS from a more convincingly designed randomized controlled trial. In the present study, we conducted the first randomized controlled trial to explore the efficacy of PCKL as an adjunctive therapy to oral montelukast compared with placebo combined with montelukast in patients with CAS. The dose of PCKL administered in this study is consistent with that in the previous pilot study.^[14] We hypothesized that for treatment of CAS, the efficacy of PCKL as an adjunctive therapy to oral montelukast would be superior to the efficacy of placebo combined with montelukast.

2. Methods and materials

2.1. Study design

The present study was approved by the ethics committee of The First Affiliated Hospital of Heilongjiang University of Chinese Medicine and was conducted at the same hospital from January 2013 to December 2016. Seventy-two eligible patients with CAS were randomly allocated to an intervention group or a control group at a ratio of 1:1. Patients in the intervention group received PCKL as an adjunctive therapy to oral montelukast, while those in the control group were given placebo with oral montelukast.

2.2. Patients

All patients in this study were diagnosed with mild to moderate CAS and aged between 18 and 60 years. In addition, all patients manifested >12% enhancement in forced expiratory volume in 1 second (FEV₁) after bronchodilator inhalation. Furthermore, all included patients provided written informed consent before enrollment in the present study. Patients were excluded if they had severe organ diseases, such as respiratory, cardiac, or hepatic diseases; cancer; were pregnant or breastfeeding; underwent surgery; were allergic to the study medications; or received steroid medicine within 1 month before the study.

2.3. Randomization and blinding

Stratified randomization was done by a computerized generation random number list generated using Statistics Analysis System (SAS) package (Version 8.1; SAS Institute Inc, Cary, NC) after the run-in period. All patients were randomly allocated to the intervention group or control group at a 1:1 ratio. The randomization assignments were concealed in sequentially numbered, opaque, sealed envelopes. PCKL and placebo were distributed by a dispenser, who did not involve the process of treatment and efficacy evaluation or data

analysis. Attending doctors and practitioner, patients, the outcome assessors, and data analysts were blinded to the treatment allocation information.

2.4. Intervention

All patients in both groups were administered montelukast orally every night, 10 mg/day for 3 months. In addition, patients in the intervention group received PCKL (10 g/sachet, 2 sachets 3 times daily).^[14] Patients in the control group were given a placebo (the same dose as the PCKL in the intervention group). Patients in both groups were treated at 3 months. To ensure the safety and availability of the medication, the herbal medicine was administered in a condensed granular form, and was packed in sachets. Each sachet contained 10 g of medicine, and was provided by a licensed manufacturer of TCM. The placebo was also provided by the same manufacturer, with a similar appearance, packaging, and similar bitter taste as the PCKL.

2.5. Outcome measurements

The primary outcome of the lung function was measured by FEV₁. The secondary outcomes included quality of life, measured by St. George's Respiratory Questionnaire (SGRQ),^[21] and any adverse events (AEs) were recorded to evaluate the safety of PCKL.

2.6. Statistical analysis

All data in the present study was analyzed by the Statistical Package for the Social Sciences (SPSS) software (version 17.0). Sample size was calculated based on the difference in change of FEV₁ of 12% between the intervention group and control group with $\alpha=0.5$, $\beta=0.8$, and assuming a 20% drop-out rate.^[22] Thus, the required sample size of the present study was estimated to be 72 patients, with 36 assigned to each group. Continuous data was analyzed by the *t*-test or Mann-Whitney rank sum test. Categorical data was analyzed by the χ^2 test or Fisher's exact test. All data were analyzed by intention-to-treat. A value of $P<.05$ was considered as statistically significant.

3. Results

One hundred eight patients were initially assessed by practitioners in the present study (Fig. 1). Of these 108 patients, 36 were excluded because they did not meet the inclusion criteria, met the exclusion criteria, and declined to participate the study. Thus, 72 patients with CAS were randomly divided the intervention group or the placebo group in a ratio of 1:1. Of the 72 included patients, 7 subjects withdrew from the study, because of the consent withdrawal ($n=2$), lost to follow-up ($n=3$), and adverse events ($n=2$) (Fig. 1).

The demographics and baseline characteristics of all included patients are showed in Table 1. No significant differences were found in age, race, duration of asthma, body mass index, smoking status, and lung function between both groups at baseline (Table 1).

The outcome measurements are shown in Table 2. The mean change from baseline (with a 95% confidence interval) was assessed between the intervention and control groups in order to evaluate the efficacy of PCKL as an adjunctive therapy to oral montelukast for the treatment of CAS. When compared to placebo and montelukast, PCKL plus montelukast improved lung

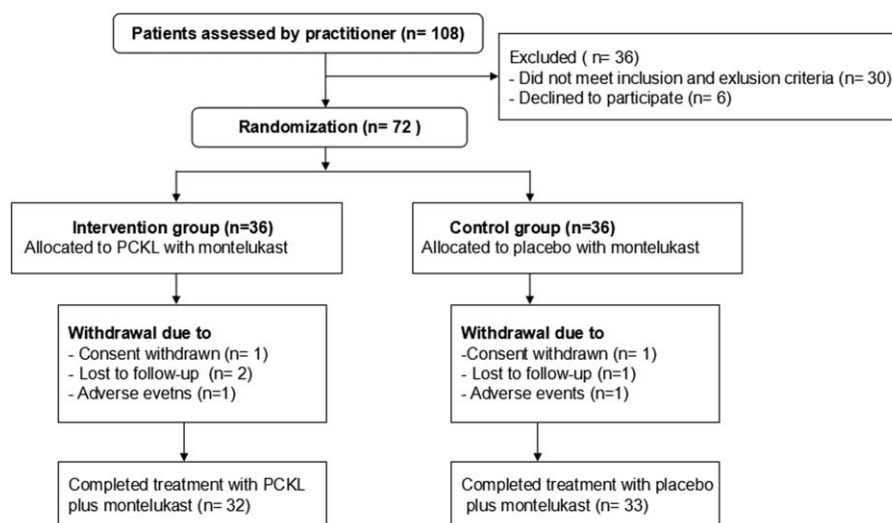


Figure 1. Flowchart of patient's selection. PCKL = Ping Chuan Ke Li.

function, as measured by FEV₁ ($P < .05$); and enhanced the quality of life, as measured by the SGRQ scale ($P < .05$).

All AEs that occurred in the intervention and control groups are listed in Table 3. There were no significant differences in AEs between the 2 groups. The most frequent AEs were nausea

(intervention group, 13.8% vs control group, 8.3%), and upset stomach (intervention group, 8.3% vs intervention group, 11.1%).

4. Discussion

The results of the present study confirmed our hypothesis that PCKL with montelukast was superior at 3 months compared with placebo with montelukast for treating CAS. Previous studies have evaluated the efficacy of TCM for treating asthma.^[22–23] One study investigated the efficacy of augmented Yu Ping Feng San (aYPFS) as an adjunctive therapy to oral montelukast compared with placebo and montelukasta for treating children with mild persistent asthma.^[2,3] This study demonstrated that aYPFS as an add-on to montelukast can alleviate the symptoms of asthma in children. The other study explored the efficacy of modified Mai-Men-Dong-Tang (MMDT).^[22] The results indicated that MMDT can significantly improve FEV₁ in patients with persistent asthmatic symptoms.^[22]

To our best knowledge, this study is the first randomized placebo-controlled double blinded trial with concealed allocation to the practitioners, patients, outcome assessors, and data analyst conducted in China. The results of the present study are consistent with the previous study,^[22] which also found that PCKL can improve lung function after 3 months of treatment

Table 1

Demographics and baseline characteristics of patients at trial entry.

Values	Intervention group (n=36)	Control group (n=36)	P value
Mean age, year	37.8 (15.7)	38.3 (16.1)	.89
Sex			
Male	21 (58.3)	19 (52.7)	.64
Female	15 (41.7)	17 (47.3)	.64
Duration of asthma, year	5.6 (2.5)	5.3 (2.7)	.62
BMI, kg/m ²	25.8 (4.6)	26.1 (4.8)	.79
Smoking status			
Smokers	14 (38.9)	11 (30.6)	.46
Nonsmokers	22 (61.1)	25 (69.4)	.46
Lung function			
FEV ₁ % (predicted)	67.1 (14.3)	66.9 (14.6)	.95

Data are present as mean ± standard deviation or number (%).

BMI=body mass index, FEV₁=forced expiratory volume in 1 second.

Table 2

Primary and secondary outcomes at the end of 3 month (change from baseline).

Outcomes	Intervention group (n=36)	Control group (n=36)	Difference	P value
FEV ₁ , % predicted	6.1 (1.5, 11.6)	0.8 (-3.3, 2.9)	5.3 (1.1, 8.9)	<.05
GRQ score				
Total	-16.1 (-25.6, -8.4)	-5.9 (-9.1, 2.5)	-10.2 (-16.4, -6.8)	<.05
Symptom	-23.1 (-40.4, -10.6)	-14.0 (-22.8, -2.7)	-9.0 (-15.5, -3.8)	<.05
Activity	-12.7 (-19.3, -3.3)	-4.5 (-9.7, -0.8)	-8.1 (-13.6, -4.0)	<.05
Impact	-11.5 (-16.7, -5.8)	-3.2 (-7.1, -0.5)	-8.3 (-14.1, -4.8)	<.05

Data are present as mean change ± standard error.

FEV₁=forced expiratory volume in 1 second, SGRQ score=St. George's Respiratory Questionnaire Scores.

Table 3**Adverse events reported in intervention and control groups.**

Adverse events	Intervention group (n=36)	Control group (n=36)	P value
Nausea	5 (13.8)	3 (8.3)	.46
Vomiting	3 (8.3)	1 (2.8)	.33
Cough	2 (5.6)	1 (2.8)	.56
Runny nose	1 (2.8)	3 (8.3)	.33
Diarrhea	2 (5.6)	1 (2.8)	.56
Mild sore throat	1 (2.8)	1 (2.8)	1.00
Mild stomach pain	2 (5.6)	1 (2.8)	.56
Stomach upset	3 (8.3)	4 (11.1)	.69
Tiredness	1 (2.8)	2 (5.6)	.56

Data are present as number (%).

with PCKL and montelukast. In our study, the difference of mean change of FEV₁% predicted between 2 groups was 5.3, which was considered as the minimal clinical important difference in lung function improvement, according to the previous published study.^[24]

In this study, the results demonstrated that, compared to placebo and montelukast, PCKL plus montelukast can not only improve lung function, measured by FEV₁, but a can also enhance the quality of life, measured by the SGRQ scale. In addition, both groups exhibited similar safety profiles. Thus, PCKL plus montelukast treatment appears to be promising for improving both lung function and quality of life in patients with CAS.

The present study also had several limitations. First, the achieved efficacy was the results of the synergistic efficacy of PCKL with montelukast, and not of montelukast alone, although the baseline medication was similar between both groups. Second, it was difficult to discern whether the AEs were caused by PCKL or montelukast, because all patients in the intervention group received both medications. Third, the present study did not include a follow-up assessment owing to its short duration. Fourth, this study did not include results of asthma control test and major biochemical assays for safety and toxicity parameters as our outcome measurements. Future studies should avoid this limitation. Finally, the sample size in the present study was small. Thus, the issue of larger sample sizes to study the effect of PCKL on persistent asthma still needs to be addressed in the future.

5. Conclusion

The results of the present study suggest that PCKL as an adjunctive therapy to oral montelukast can improve lung function and quality of life in patients with CAS. Long-term randomized controlled trials with follow-up evaluation are still needed to confirm the present results.

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