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Efficacy and Safety of Tratinterol Hydrochloride Tablets in Bronchial Asthma: A Randomized Double-blind and Multicenter Clinical Trial

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ABSTRACT

Purpose: The aim of this study was to investigate the efficacy and safety of tratinterol hydrochloride in bronchial asthma(BA) treatment.

Methods: Patients enrolled in this study were distributed randomly into a treatment group (tratinterol hydrochloride) and an active control group (procaterol hydrochloride) and were treated for 2 weeks after running-in. The end points were changes in pulmonary function and clinical symptoms after administration. Safety indices were physical examinations, laboratory testing and spontaneous reporting.

Findings: We enrolled 732 subjects,- 365 in the treatment group and 367 in the activecontrol group. Forced expiratory volume(FEV₁), significantly increased in both group after treatment(P<0.05). Least-squares (LS)means were -0.03/in the full-analysis set(FAS)and -0.02 in the per-protocol set(PPS) set, and 95% confidence intervals(CIs) for these sets were-0.09 to 0.03 and -0.08 to 0.04, respectively. Forced expiratory volume (FVC), morning peak expiratory flow(PEF) and asthma scores were significantly different with pretreatment(P<0.05). There was no difference in asymptomatic days or frequency of relief medicine use(P>0.05). No serious adverse events occurred.

Implications: Tratinterol hydrochloride was effective, safe and not inferior to procaterol hydrochloride in treating BA.

Keywords: Tratinterol hydrochloride; β_2 adrenergic receptor agonist; bronchial asthma; multicenter clinical study

INTRODUCTION

Tratinterol hydrochloride [chemical name: 2 - (3-chloro-4- amino-5-threefluorine methyl phenyl)-2-tert-butyl alcohol hydrochloride] is a new,highly selective and long-acting β_2 adrenergic

receptor agonist. A phase I clinical study on the tolerability of trantinterol hydrochloride tablets in healthy Chinese volunteers indicated that the drug was well tolerated at single doses of 25 - 100 µg. To sum up the pharmacodynamic and pharmacokinetic properties and tolerability of trantinterol hydrochloride: clinical trials had recommended its use in the treatment of BA^[1-4]. A dose-finding phase IIa study^[5] showed that the optimal, safest dosage for treating BA was 50µg. Trantinterol hydrochloride tablets (50µg) taken orally twice a day proved to be a small dosage that was convenient, effective and safe. To confirm the drug's efficacy and safety in the treatment of BA, we performed a phase III clinical study with an expanded sample capacity.

PATIENTS AND METHODS

Inclusion Criteria

Our patient selection process included male and female patients age 18 -70 years with mild-moderate, chronic, persistent BA^[6,7] and with $FEV_1 \geq 40\%$ of predicted normal (pretreatment). Medical history of all selected patients was consistent with diagnostic and disease classification criteria set forth in the Chinese Medical Association's 2008 BA treatment guidelines^[6], and by the Global Initiative for Asthma in 2006^[7]. Patients with $30\% \leq FEV_1 < 40\%$ of predicted normal entered the washout period; if at the end of this period, their $FEV_1\%$ was predicted to be $\geq 40\%$, they could either enter or opt out of random selection. We included all selected patients who had positive bronchial dilation test results (20 minutes after inhaling salbutamol 400ug, FEV_1 improvement rate $\geq 12\%$; absolute increase ≥ 200 ml) or positive bronchial provocation test results within 1 year before the study began. Patients whose disease was uncontrolled despite 4 weeks of regular treatment with a stable dose of inhaled corticosteroid were also allowed to participate in the study.

Exclusion Criteria

Patients who had been given medication for bronchiectasis (a long acting β_2 -agonist, theophylline, or unknown composition drugs) within 1 week prior to the study were excluded. (during the study, use of albuterol aerosol (100ug each time) was allowed for temporary relief of asthma symptoms.) Also excluded were pregnant or lactating women; patients with an acute respiratory infection within the 4 weeks before the study; patients with severe hypertension poorly controlled by medication; patients with coronary insufficiency, angina, heart failure, arrhythmias, or other serious cardiovascular diseases; hypertensive patients using β_2 receptor blocker antihypertensive therapy; patients with severe diabetes poorly controlled by medication; patients with hyperthyroidism or epilepsy; patients with serious liver, kidney or blood system diseases; patients taking monoamine oxidase inhibitors and/or tricyclic antidepressants; patients who had taken a long acting β -receptor agonists (LABA) within 1 week prior to the study; patients who were stably taking asthma medication that had an obvious curative effect, or those with unstable drug treatment for asthma within 1 week prior to the study; patients who had taken part in other clinical drug trials within 3 months prior to the study; patients who were mentally ill and/or incapable of cooperation; patients who were allergic to β_2 adrenergic receptor stimulants; patients with drug or alcohol addictions; patients who did not take effective contraception; and patients with other conditions that we considered to make them ineligible for inclusion.

In addition, we excluded the following groups of patients from the analysis: those who failed to take the drugs as planned, those in whom the drugs' therapeutic effects could not be evaluated, those who took antiasthmatic drugs forbidden by the research plan, and those who stopped taking the medicine due to adverse drug events.

Study Design

This was a double-blind clinical study involving a randomized trial, completed at 17 centers in China. The study protocol was approved by the ethics committees of all participating centers (Reg.No [2010]099, http://www.gov.cn/gzdt/2010-11/08/content_1740976.htm), and all patients provided signed informed consent. After 1 week running-in, we randomly distributed patients into either the treatment group or the active-control group using a block randomization schedule created by SAS software (SAS Institute, Cary, North Carolina, USA) to generate random numbers at a ratio of 1:1. Patients were assigned numbers when they entered the study. The treatment group received terbutaline hydrochloride tablets (50µg/d, Jinzhou Jiutai Pharmaceutical Co. Ltd, Jinzhou, China). While the active-control group received procaterol hydrochloride tablets (50µg/d, produced by the Otsuka Pharmaceutical Co., Ltd.) Doses were administered orally twice a day for 2 weeks. Over the entire study, each patient received albuterol aerosol to relieve temporary symptoms.

Drugs for both groups were distributed in uniform packaging and numbered according to the randomization schedule. There were two points of unblinding: first, we followed statistical analyses of both groups after the database was closed; second, we identified the drugs for both groups after completing our statistical analyses. At both the beginning and the end of the 2-week treatment period, all enrolled patients underwent follow-up laboratory testing and lung function assessment. During the treatment period, we distributed peak flow meters (all the same brand and from the same manufacturer) to all patients. We instructed patients to measure PEF each morning and evening, three times at each time point, and to record the best measurement on a diary card. They were also asked to record expectoration, gasp, cough, chest tightness, times they used salbutamol aerosol, medication, and any adverse events during treatment on the card at the same time.

End Points

Efficacy Assessments

The end points of the study included primary and secondary outcomes. The primary outcome was FEV₁; secondary outcomes included FVC, morning PEF, asthma symptom scores (table I), asymptomatic days, and the number of times they used fast rescue medication.

Safety Assessment

All patients underwent routine blood and urine testing, renal and liver function testing, blood glucose assessment, blood plasma testing, blood lipids testing, electrocardiogram (ECG), and chest radiography before selection; they were rechecked after treatment. In addition, at each visit during

the treatment period, we recorded patients' clinical symptoms, signs, use of medication- and adverse events.

Statistical Analysis

Statistical analyses were performed with SAS statistical software version 8.0 (SAS Institute, Cary, North Carolina) for all statistical analyses. We analyzed data from all patients who underwent randomization according to the intention-to-treat principle. Continuous variables were presented as the mean $\pm$ standard deviation (SD), maximums, minimums, and interquartile range. Comparability of characteristics between the 2 study groups was assessed using a 2-sample t test for continuous variables (which satisfied the normal distribution) and the chi-square-test or Wilcoxon test (when appropriate for categorical variables). We used an analysis of covariance (ANCOVA) model to compare differences between main indices, adopting two ANCOVA models into our main index analysis. In Model 1, we used the main index baseline as the covariate, corrected center factors, and compared the difference between the two groups. Then, in Model 2, we incorporated treatment interactions and center factors from Model 1. In both models, the center was entirely corrected as an influencing factor and was statistically significant ($P < 0.001$). Model 2 showed no statistical significance ($P > 0.10$) between centers and treatment interaction effect. Therefore, we chose Model 1 as the model for comparison of the 2 groups. Model 1 showed that a 95% confidence interval (CI) of least-squares (LS) mean difference for the curative effect of treatment factors between the two groups could meet the requirements for non-inferiority of trinitol hydrochloride to procaterol hydrochloride after correction of the central factors.

RESULTS

Patient Population (Table II)

A total of 699 subjects were enrolled in the full analysis set (FAS); 351 in the treatment group and 348 in the active-control. In total, 619 subjects were enrolled in the per-protocol set (PPS), 316 in the treatment group and 303 in the active-control group. A total of 707 subjects were enrolled in the safety set (SS), 356 in the test group and 348 in the active-control group. There were no significant differences in age, gender, height, weight, history of disease, severity of asthma, treatment history or basic lung function (Table II) between the 2 groups – in any set.

Efficacy

Primary End Points

Statistics showed that for patients in both the FAS and PPS, lung function improved in both groups after 2 weeks, compared with baseline. The increases in FEV₁ in the treatment and active-control groups were $(0.26 \pm 0.51)L / (0.29 \pm 0.48)L$ for the FAS and $(0.28 \pm 0.50)L / (0.31 \pm 0.49)L$ for the PPS. In the FAS, the LS Mean of FEV₁ value change between the 2 groups was -0.03 with a 95% CI of

-0.09 to 0.03. In the PPS, the LS Mean of FEV₁ value change between the 2 groups was -0.02 with a 95% CI of -0.08 to 0.04. However, there were no significant differences between the two groups (FAS: p=0.3002; PPS: p=0.4472) (Table III, IV and Figure 1).

Secondary Outcomes

The increases in FVC in the treatment and active-control groups were (0.19±0.46)L/(0.20±0.49)L for the FAS and (0.21±0.44)L/(0.20±0.50)L for the PPS, but there were no significant differences between the two groups (FAS: p=0.9754; PPS: p=0.7341) (Table III, IV and Figure 1). The increases in early morning PEF of the treatment and active-control groups were (31.78±59.01)L·MIN⁻¹/(38.87±59.46)L·MIN⁻¹ for the FAS and (33.32±58.76)L·MIN⁻¹/(39.17±59.94)L·MIN⁻¹ for the PPS, but there were no significant differences between the two groups (FAS: p=0.1186; PPS: p=0.2225) (Table III, IV and Figure 1). The decrease in asthma symptom scores of the treatment and active control groups were (-2.85±2.42)/(-3.01±2.47) for the FAS and (-3.01±2.41)/(-3.15±2.48) for the PPS, in comparison with baselines, but there were no statistically differences between the two groups (FAS: p=0.4141; PPS: p=0.4999) (Table III, IV and Figure 1). The asymptomatic days of the treatment and active-control group during the treatment period were (1.19±2.82)/(1.28±2.95) for the FAS and (1.19±2.79)/(1.33±3.00) for the PPS. However, there were no statistical differences between the two groups (FAS: p=0.5893; PPS: p=0.4831) (Table III, IV and Figure 2). The times of using rescue medication in the two groups during the treatment period were (17.30±26.46)/(17.06±25.61) for the FAS and (17.77±26.66)/(18.19±26.50) for the PPS. However, there was no significant differences between the two groups (FAS: p=0.8609; PPS: p=0.6597) (Table III, IV and Figure 2).

Tolerability Assessment

Neither of the 2 drugs had clinically significant effects on vital signs, including blood pressure, heart rate, body temperature, or pulse rate (Table V).

From Table VI, we could see that no serious adverse events occurred in either group over the entire treatment period. Prevalences of any adverse events in the treatment and active-control groups were 16.29% and 17.09%, respectively, and the extents of these adverse events were mild and acceptable to patients. Adverse effects associated with β₂ receptors selectivity were mainly heart rate increase and muscle tremors, incidences of treatment for these events were respectively 1.97% and 1.40% in the treatment group, which were lower than 3.42% and 2.56% respectively, for the active control group (Table VI).

Findings with Unblinding

Secondary-unblinding results showed that the treatment group received trantinterol hydrochloride tablets, and the active-control group received procaterol hydrochloride tablets. Our statistical analysis found that efficacy in the treatment group was not inferior to that in the active-control group and both groups were safely treated.

DISCUSSION

Asthma is a chronic inflammatory disease of the airways, which involves many cells and cellular elements. The chronic inflammation is associated with airway hyperresponsiveness and is affected by heredity and environment. Symptoms include recurrent episodes of breathlessness, chest tightness, wheezing, and coughing, especially at night or in the early morning. Most patients can alleviate symptoms by themselves or control them with medication. By inducing strong and effective relaxation of bronchial smooth muscle, which is an antiasthmatic effect, β_2 -agonists agents play an important role in the treatment of BA and have become the first choice for an acute attack of asthma^[8-9]. β_2 -agonists are divided into two types, long and short acting.

Salbutamol sulfate and terbutaline sulfate, which are commonly used short-acting β_2 -agonists (SABAs), can be used for temporary relief of asthma symptoms, but are not conducive to long-term asthma control because their half-life is 4 -6 hours^[10-13]. LABAs are available as inhalants and oral preparations. There are many kinds of inhaled β_2 -agonists, such as formoterol and salmeterol, which are widely used in clinical applications. However, there are few oral LABAs. A number of clinical studies have shown the efficacy of procaterol hydrochloride tablets, made by Japanese Otsuka Pharmaceutical Co., Ltd.^[14-15]. But side effects such as palpitations and tremor- limit their further clinical application.

Tratinterol hydrochloride is a third generation LABA and was developed as the first class of new drugs in China, which are not listed -in foreign and domestic markets. Tratinterol hydrochloride tablets are a new formulation that have the advantages of small-dosage, long duration, low toxicity and high specificity (acting only on the β_2 receptor-but not the β_1 receptor) compared with traditional β_2 agonists^[16-18]. A randomized, double-blind, multiple center phase IIb trial showed that tratinterol hydrochloride was similar to the congeneric product procaterol hydrochloride, and was suitable for treating mild to moderate BA. To further evaluate the efficacy and safety of tratinterol hydrochloride tablets in the treatment of BA, we conducted a randomized, double-blind, multicenter phase III clinical trial at 17 centers in the People's Republic of China from May 2009 to March 2011. For the control drug, We chose procaterol hydrochloride, which has been available in China's market for many years and is widely used to control asthma symptoms; this allowed us to evaluate the efficacy and tolerability of the tratinterol hydrochloride more objectively. Over the two weeks of treatment, we found that tratinterol hydrochloride tablets could stably treat BA. Lung function outcomes, such as the primary outcome FEV₁ and the secondary outcomes of FVC and early morning PEF, had clearly improved. We analyzed the primary outcome (FEV₁) in a parallel-control clinical trial: The LS Mean of FEV₁ difference (95% CI) between the two groups was -0.03(-0.09,0.03) in the FAS and -0.02(-0.08,0.04) in the PPS. Whether in the FAS or the PPS, the 95% CI length was no more than -0.10, and we considered outcomes in the treatment group non-inferior to those in the active-control group. The asthma symptom scores of both groups were significantly reduced after 2 weeks of treatment. Neither did the procaterol and tratinterol groups significantly differ in how frequently they used relief drugs or the number of asymptomatic days they experienced, whether they use the drugs by day or at night. Over the entire treatment period, no serious adverse event occurred in either group. The prevalences of all adverse events in the treatment and control groups were 16.29% and 17.09%, respectively, and the extents of these adverse events were mild and acceptable to patients. Heart rate increase and muscle tremors were the main adverse effects associated with selectivity of β_2 receptors, and the incidences of treatment for such events were 1.97%

and 1.40%, respectively, in the treatment group, which were lower than 3.42% and 2.56% in the control group. This might have been related to the higher selectivity of the β_2 agonist receptor.

However, it should be noted that this study reported on only the pharmacodynamic and pharmacokinetic properties of tratinterol hydrochloride and clinically evaluated its efficacy and safety in treating BA. More research on a cytological level needs to be conducted.

STUDY HIGHLIGHTS

1. Only a few types of oral LABAs are used in clinical practice, and their side effects, such as palpitations and tremor, limit further clinical applications.
2. Tratinterol hydrochloride is the third generation of LABAs and was developed as the first class of new drugs in China with the advantages of small dosage, long duration, low toxicity and high specificity (acting only on the β_2 receptor, not β_1 receptor) over traditional alternatives.
3. This randomized, double-blind, multicenter clinical trial with an expanded sample showed that for the treatment of BA, tratinterol hydrochloride was effective, safe, and not inferior to procaterol hydrochloride which has been available in China's market for many years and is widely used to control asthmatic symptoms.
4. THIS research into tratinterol hydrochloride provides a option for treating BA.

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The investigators contributed to study supervision, review of the data, writing of the clinical study report, and patient recruitment. We would also like to thank the study leaders of each site who organized the trial, made decisions during the study and allowed it to proceed well. Additionally, we thank the Department of Health Statistics of Peking University, Beijing, China, for processing the clinical data statistics; Jinzhou Jiutai Pharmaceutical Co., Ltd for providing all study drugs and for their financial support in the treatment. and Shenyang Pharmaceutical University, Shenyang, China, for developing the drug for clinical study. All authors contributed equally to the study, had unlimited access to the clinical study report and statistical analysis, contributed to interpretation of the data and were involved in every stage of manuscript preparation. In addition, all authors made final decisions on all aspects of the article, and hence, are in agreement with, and approve, the final version of the submitted article.

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CONFLICTS OF INTEREST

The study drugs were provided by Jinzhou Jiutai Pharmaceutical Company, Ltd. The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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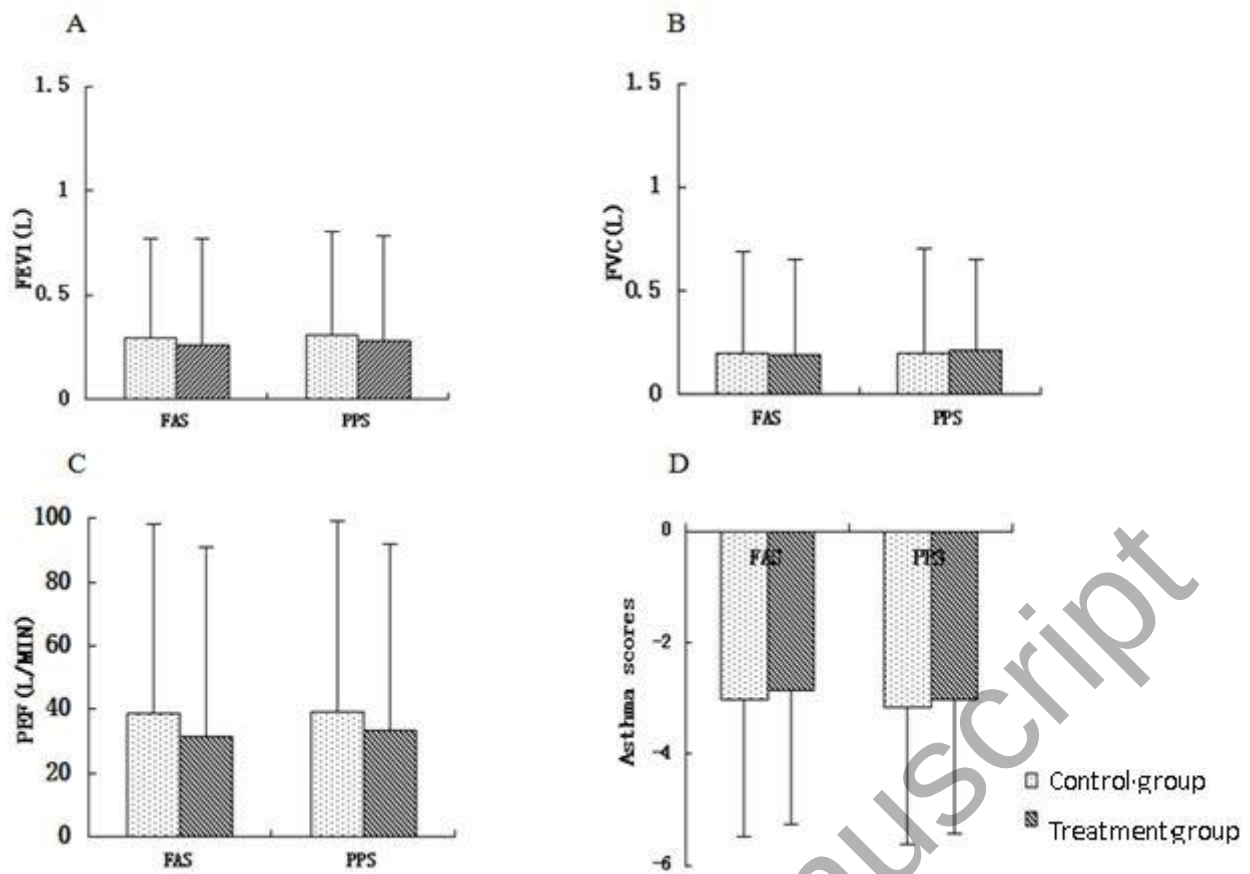


Figure 1. Changes from baseline in lung function and the asthma symptom score with 2 weeks treatment. A, forced expiratory volume in 1 second (FEV₁); B, forced vital capacity (FVC); C, peak expiratory flow (PEF); D, asthma symptom score.

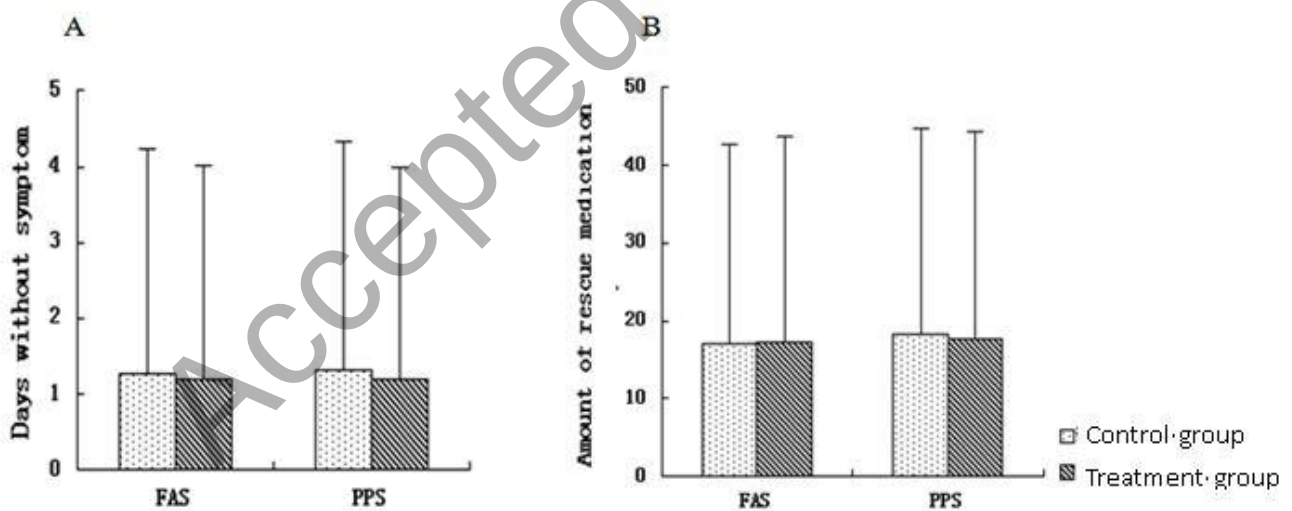


Figure 2. During the treatment period, the asymptomatic days (A) and the times using rescue medication (B) of the 2 groups.

Table I:Symptoms and signs scoring methods.

Gasp	None	0 points	Cough	None	0 points
	Mild:Occasional attack, to a slight degree;that does not affect rest or activity.	1 points		Mild:Intermittent cough in the daytime but only to a slight degree.	1 points
	Moderate:Frequent attacks during any light activity but that do not affect sleep.	2 points		Moderate:Cough that is frequent but that does not affect sleep.	2 points
	Severe: Obvious gasp, even when sitting quietly, cannot lie in bed.	3 points		Severe:Frequent cough day and night or paroxysmal cough that affects work and sleep.	3 points
Expectoration	None	0 points	Chest tightness	None	0 points
	Mild: A small amount of phlegm, about 10–50ml/d or 5–25 ml in the late evening and early morning.	1 points		Mild:Occasional attack to aslight degree thatdoes not affect rest or activity.	1 points
	Moderate:A small amount of phlegm, 51-100ml/d or 26 - 50 ml in the late evening and early morning.	2 points		Moderate:Attacks are frequent, during even light activity, but do not affect sleep.	2 points
	Severe:More than 100 ml/d or more than 50ml in the late evening and early morning.	3 points		Severe:Obvious chest tightness, even when sitting quietly, cannot lie in bed.	3 points

Table II. Demographic and clinical characteristics of the patients in this study (treatment group n=351, control group n=348) .Data are given as mean (SD) unless otherwise noted.

Characteristic	Control group	Treatment group	p
Demographics			
Age (years)	47.66±11.84	47.12±12.33	0.5561
Sex (male/female)	162/186	145/206	0.1627
Height (cm)	164.48±7.48	163.94±7.75	0.3467

Risk factors			
Smoking history	64(18.39%)	53(15.10%)	0.2439
Course disease (years)	6.47±8.61	6.41±9.04	0.8455
Allergy history	35(10.06%)	27(7.69%)	0.2715
Lung function			
FEV ₁ (L)	1.87±0.64	1.86±0.69	0.7624
% of predicted normal	64.66±16.97	63.88±16.31	0.5355
FVC (L)	2.72±0.86	2.70±0.90	0.7729
FEV ₁ /FVC	0.70±0.15	0.70±0.15	0.7895
PEF (L· MIN ⁻¹)	274.26±87.61	274.65±87.61	0.9526
Asthma symptom scores	5.23±2.33	5.31±2.38	0.6506
Vital signs			
SBP (mm Hg)	120.80±9.61	121.10±10.51	0.6916
DBP (mm Hg)	76.81±6.55	76.78±7.16	0.9556
HR (beats/min)	73.33±9.72	73.39±11.10	0.9352
Body temperature (°C)	36.44±0.27	36.44±0.25	0.7413

DBP=diastolic blood pressure;FEV₁=forced expiratory volume in one second;FVC=forced vital capacity;PEF=peak expiratory flow;HR=heart rate;SBP=systolic blood pressure.

Table III. Changes from baseline in lung function, and symptom control with 2 weeks treatment of the 2 groups Data are given as mean (SD).

Parameter	Control (n=64)	Treatment (n=53)	p
Lung function			
FEV ₁ (L)	0.29(0.48)	0.26(0.51)	0.3002
FVC (L)	0.20(0.49)	0.19(0.46)	0.9754
PEF (L· MIN ⁻¹)	38.87(59.46)	31.78(59.01)	0.1186
Asthma symptom score	-3.01(2.47)	-2.85(2.42)	0.4141
Symptom control			
Days without symptoms	1.28(2.95)	1.19(2.82)	0.5893
Times using rescue medication.	17.06(25.61)	17.30(26.46)	0.8609

FEV₁=forced expiratory volume in one second;FVC=forced vital capacity;PEF=peak expiratory flow

Table IV. Changes from baseline in lung function, and symptom control with 2 weeks treatment of the 2 groups Data are given as mean (SD).

Parameter	Control (n=64)	Treatment (n=53)	p
Lung function			
FEV ₁ (L)	0.31(0.49)	0.28(0.50)	0.4472

FVC (L)	0.20(0.50)	0.21(0.44)	0.7341
PEF (L·MIN ⁻¹)	39.17(59.94)	33.32(58.76)	0.2225
Asthma symptom score	-3.15(2.48)	-3.01(2.41)	0.4999
Symptom control			
Days without symptoms	1.33(3.00)	1.19(2.79)	0.4831
Times using rescue medication.	18.19(26.50)	17.77(26.66)	0.6597

FEV₁=forced expiratory volume in one second;FVC=forced vital capacity;PEF=peak expiratory flow.

Table V. Changes from baseline in vital signs, with 2 weeks treatment of the 2 groups. Data are given as mean (SD).

Parameter	Control group(SS)	Treatment group(SS)	p
Vital signs			
SBP (mm Hg)	-0.05(6.33)	-0.16(5.90)	0.8165
DBP (mm Hg)	-0.01(5.51)	-0.10(5.94)	0.8337
HR (beats/min)	-0.42(8.26)	-0.63(8.83)	0.8246
Body temperature (°C)	-0.04(0.26)	-0.03(0.23)	0.5333

DBP=diastolic blood pressure;HR=heart rat;SBP=systolic blood pressure.

Table VI. Adverse events with 2 weeks treatment of 2 groups.Data are given as number (%) of patients.

Parameter	Control group (SS)	Treatment group (SS)
Patients with any event	60(17.09)	58(16.29)
Adverse event		
Palpitate	12 (3.42)	7 (1.97)
Nausea or Vomit	5 (1.42)	5 (1.40)
Tired	3 (0.85)	2 (0.56)
Anemia	1 (0.28)	0 (0.00)
Granulocytopenia	4 (1.14)	1 (0.28)
Granulocytosis	1 (0.28)	2 (0.56)
Elevated liver enzymes	1 (0.28)	9 (2.53)
Dyslipidemia	13 (3.70)	16 (4.49)
Urine Leukocyte positive	2 (0.57)	0 (0.00)
Elevated blood glucose	2 (0.57)	2 (0.56)

Headache	1 (0.28)	4 (1.12)
Dizziness	4 (1.14)	2 (0.56)
Tremor	9 (2.56)	5 (1.40)
Rash or pruritus	0(0.00)	3 (0.84)
Hypokalemic	2 (0.57)	0 (0.00)

All adverse events were considered mild.

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