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R-value comprehensive evaluation method for the effect and long-term influence of Tiaobu Fei-Shen therapies on chronic obstructive pulmonary disease rats

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Abstract

Objective: This study aimed to evaluate the effect and long-term influence of Tiaobu Fei-Shen therapies (Bufei Jianpi, Bufei Yishen, and Yiqi Zishen) on rats with chronic obstructive pulmonary disease (COPD) according to the established R-value comprehensive evaluation method.

Methods: 120 rats were randomly divided into control, model, Bufei Jianpi, Bufei Yishen, Yiqi Zishen, and aminophylline groups. The COPD rat models were established by smoke inhalation and bacterial infection. Rats were gavaged with Bufei Jianpi granule, Bufei Yishen granule, Yiqi Zishen granule, and aminophylline from the 9th week to the 20th week of the experiment. Rats were left for another 12 weeks without treatment to observe the long-term effect. Indicators related to curative effect, including lung function, pathology of lung tissue, inflammation, and right ventricular hypertrophy index were observed. The effect was evaluated with R-value comprehensive evaluation method.

Results: From the 12th to 32nd week, three indicators related to lung function were significantly altered by Tiaobu Fei-Shen therapies and aminophylline, especially Tiaobu Fei-Shen therapies (P<0.05). The relative improvement from high to low was Bufei Yishen, Yiqi Zishen, Bufei Jianpi, and aminophylline. Considering both the 20th and 32nd weeks, five indicators related to pathology of lung tissue were significantly improve by Tiaobu Fei-Shen therapies and aminophylline (P<0.01), especially the Tiaobu Fei-Shen therapies (P<0.05). The relative improvement from high to low was Bufei Yishen, Bufei Jianpi, Yiqi Zishen, and aminophylline. At the 20th, 32nd week, and both 20th and 32nd weeks, all eleven indicators related to curative effect were significantly improved by Tiaobu Fei-Shen therapies and aminophylline (P<0.01), especially Bufei Jianpi granule as compared with aminophylline in the 20th week (P<0.05), and Tiaobu Fei-Shen therapies as compared with aminophylline at both the 20th and 32nd weeks (P<0.01or P<0.05). The relative improvement from high to low was Yiqi Zishen, Bufei Jianpi, Bufei Yishen, and aminophylline at both the 20th and 32nd weeks.

Conclusion: The R-value comprehensive evaluation method can reflect the individual characteristics of three Tiaobu Fei-Shen therapies, which can provide new ideas for comprehensive evaluation of medicines.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases [1]. From a pathological point of view, COPD is characterized by chronic bronchitis, emphysema, emphysematous destruction and small airway inflammation, dynamic hyperinflation, and pulmonary hypertension [2,3]. There are a variety of treatments available for COPD patients, like short-acting and long-acting bronchodilators, anticholinergics, inhaled glucocorticosteroids, and low-dose theophylline [4]. However, it is difficult to improve patient symptoms without side effects or adverse events [5].

Traditional Chinese medicine (TCM) has been used to treat COPD and shows favorable effects [6]. According to TCM theory, COPD is categorized as lung-distention (Fei Zhang Bing). There are three common patterns of stable COPD (pattern of lung-spleen qi deficiency, pattern of lung-kidney qi deficiency, and pattern of lung-kidney qi and yin deficiency), and there is one specific herbal intervention responding to each pattern (Bufei Jianpi granule, Bufei Yishen granule, and Yiqi Zishen granule, respectively), which reflect the individualized therapy of TCM [7,8]. Based on TCM patterns, Tiaobu Fei-Shen therapies

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(Bufei Jianpi, Bufei Yishen, and Yiqi Zishen) have beneficial effects on measured outcomes in stable COPD patients [9].

The mechanism of Tiaobu Fei-Shen therapies may involve alleviating pulmonary tissue injuries, airway limitations and the right ventricular hypertrophy index [10,11]. However, previous studies examined a single indicator at one time point for each mechanistic aspect, and no comprehensive methods were used to reflect the effects of the TCM granules. Therefore, R-value comprehensive evaluation method was established to comprehensively study curative effect.

The R-value comprehensive evaluation method (copyright No: 2013-A-00096833) is based on the theory of "three essential elements" (body status, drug factors and effect factors) for curative effect evaluation in TCM, [12] which unified body status and drug factors into effect factors, then combined with mathematical theoretical analysis models to evaluate the comprehensive efficacy of medicines. The R-value comprehensive evaluation method can evaluate the comprehensive effect of treatments and obtain optimal and lower order treatments [13]. In this study, the R-value comprehensive evaluation method was used to evaluate the treatment effect and long-term effect of Tiaobu Fei-Shen therapies.

Methods

Sources of data

The data devised from our previous study [10,11]. The methods of the previous study is introduced briefly as follows: Sixty male and 60 female Sprague Dawley rats, specific pathogen-free, weighing (200 ± 20) g, 2-month-old, were purchased from Laboratory Animal Center of Henan Province (SCXK [Henan] 2005–0001). A total of 120 rats were randomly divided into control, model, Bufei Jianpi, Bufei Yishen, Yiqi Zishen, and aminophylline groups, with 20 rats in each group. Repeated smoke inhalations and bacterial infections were used to duplicate the stable COPD rat model [14]. The methods were carried out in accordance with the approved guidelines of the Experimental Animal Care and Ethics Committee of the First Affiliated Hospital, Henan University of Chinese Medicine (2012HLD-0001). From the 9th through 20th weeks, the control group and model group were treated with normal saline (2 ml per animal) by intragastric administration. Other groups were treated with Bufei Jianpi granule (4.84 g/kg/d, in Bufei Jianpi group), Bufei Yishen granule (4.44 g/kg/d, in Bufei Yishen group), Yiqi Zishen granule (4.84 g/kg/d, in Yiqi Zishen group), and aminophylline (2.3 mg/kg/d, in aminophylline group) by intragastric administration. Half of rats were sacrificed at the end of week 20. The rest of rats were kept for another 12 weeks without treatment to observe the long-term effects. The nine indicators related to curative effect were detected as follows: ①Lung function (V_T, PEF, EF50) of each group were detected on the 12th, 16th, 20th, 24th, 28th, and 32nd weeks [10]. ② Pathology of lung tissue, [10] bronchial wall thickness, degree of bronchial stenosis, alveolar count, alveolar diameter, and the thickness of pulmonary small vessels were observed at the 20th and 32nd week. ③Right ventricular hypertrophy index was also observed [11].

Establishment of R-value comprehensive evaluation method

Changes in biological indicators depend on the combined action from disease (*dM*) and medicine (*dMe*), so biological indicators can reflect the biological effects of a disease state and treatment methods on a disease state. The R-value comprehensive evaluation method was established to examine changes in biological indicators. In this study, R-value comprehensive evaluation method was used to study effect of different treatments on multiple indicators in COPD model mice to evaluate the effect of Tiaobu Fei-Shen therapies.

Calculation method of R-value

Standardizing the collection of data can help compare different dimensional indicators and reflect the amount of variability between groups [15].

$\bar{X}$ and S represent the mean value and standard deviation of an indicator, respectively. The groups are represented as: control group $\bar{X}_1 \pm S_1$, model group $\bar{X}_2 \pm S_2$, aminophylline group $\bar{X}_3 \pm S_3$, Bufei Jianpi group $\bar{X}_4 \pm S_4$, Bufei Yishen group $\bar{X}_5 \pm S_5$, and Yiqi Zishen group $\bar{X}_6 \pm S_6$.

The R-value is calculated according to formulas (1)–(5)

Formula of model effect:

$$dM = \frac{\bar{x}_2 - \bar{x}_1}{s},\ s = \frac{s_2 + s_1}{2}; \tag{1}$$

Formula of treatment effects:

Aminophylline effect $$dMe_1 = \frac{\bar{x}_3 - \bar{x}_2}{z_1},\ z_1 = \frac{s_2 + s_3}{2}; \tag{2}$$

Bufei Jianpi effect $$dMe_2 = \frac{\bar{x}_4 - \bar{x}_2}{z_2},\ z_2 = \frac{s_2 + s_4}{2}; \tag{3}$$

Bufei Yishen effect $$dMe_3 = \frac{\bar{x}_5 - \bar{x}_2}{z_3},\ z_3 = \frac{s_2 + s_5}{2}; \tag{4}$$

Yiqi Zishen effect $$dMe_4 = \frac{\bar{x}_6 - \bar{x}_2}{z_4},\ z_4 = \frac{s_2 + s_6}{2}; \tag{5}$$

R-value $$R_i = \frac{dMe_i}{dM}, \qquad i = 1,...,4. \tag{6}$$

R-value is unitless and a relative deviation measurement, which can reflect differences between groups, especially between the treatment and model groups.

1) $R < -1$ indicates that the treatments had a powerful influence on this indicator, which can make it better than normal group.

2) $R = -1$ indicates that the treatments improved the indicator in the model state recover to the normal state.

3) $-1 < R < 0$ indicates that the treatments recovered the indicator gradually from the model state, but it did not reach the normal state.

4) $R = 0$ indicates that the treatments had no rectifying effect on this indicator.

5) $R > 0$ indicates that the treatments changed the indicator to higher or lower than model group.

In brief, $R < 0$ indicates that the treatment improved the indicator, and the closer to −1, the stronger the effect. $R \geq 0$ indicates that the treatment did not improve the indicator and could even worsen the indicator compared with the model group.

Establishment of D-value data sets and statistical treatment

For convenience of calculations, we transformed the R-values to D-values.

$$D = R - (-1) \tag{7}$$

In this study, the D-values are transformed by the R-values. The D-values are more convenient to calculate, and can satisfy statistical treatment.

SPSS16.0 statistical analysis software was used for data analysis. The data sets underwent test of normality and homogeneity of variances. Least significant deviation (LSD) of one-way analysis of variance (ANOVA) was used in the data meeting normal distributions, while Kruskal–Wallis H-test was used in other data. The α level of significance was set at 0.05. Paired-samples *t*-test was used to analyze the difference between the 20th and 32nd weeks.

Calculation of comprehensive corrective effect (*Rcom*)

The best effect possible for a treatment is to recover a disease status to the normal state. Complicated reactions of treatments *in vivo* can improve some indicators but change others very little or cause them to become worse. Consequently, only a comprehensive evaluation of all indicators can reflect a treatment effect.

Comprehensive rectifying effect

$$Rcom = \frac{\sum_{i=1}^{n}(D_i)}{n}, \quad (8)$$

where "n" indicates the number of D values.

The D-value and *Rcom* have the same significance. For convenience, we use *Rcom* (D) to represent "D-value or *Rcom*." The meaning of *Rcom* (D) is based on the meaning of the R-value.

1) *Rcom* (D) < 0 indicates that the treatments had a powerful influence on indicators, which can make them better than the normal group.

2) *Rcom* (D) = 0 indicates that the treatments recover the indicators to the normal state from the model state.

3) 0 < *Rcom* (D) < 1 indicates that the treatments could improve the indicators from the model state, but not to the normal state.

4) *Rcom* (D)=1 indicates that the treatments had no rectifying effect on the indicators.

5) *Rcom* (D)>1 indicates that the treatments can worsen the indicators relative to the model group.

The closer the *Rcom* (D) is to 0, the better the improvement effect. The optimal and worst treatments were obtained according to *Rcom* (D). The model group was not influenced by treatment, so in the model group *Rcom* (D)=1.

Results

D-value collection

In our study, there were nine indicators and 120 D-values in the Bufei Jianpi, Bufei Yishen, Yiqi Zishen, and aminophylline groups. At the 20th week, 36 D-values ranged from 0–1, which indicates that the treatment had a good curative effect on all the indicators. At the 32nd week, 36 D-values ranged from 0–1, which indicates that the treatment had a positive long-term effect on these indicators.

Comprehensive evaluation of lung function

From the 12th to 32nd week, including the 12th, 16th, 20th, 24th, 28th, and 32nd week, three indicators (V_T, PEF, EF50) related to lung function were significantly improved by Tiaobu Fei-Shen therapies and aminophylline (P<0.01). The relative improvement on V_T from high to low was Bufei Yishen, Yiqi Zishen, Bufei Jianpi, and aminophylline, among which Bufei Jianpi and Bufei Yishen were significantly better than aminophylline (P<0.01, P<0.05). The relative improvement on the three indicators from high to low was Bufei Yishen, Yiqi Zishen, Bufei Jianpi, and aminophylline, among which the Tiaobu Fei-Shen therapies were significantly better than aminophylline (P<0.05) (Table 1).

Comprehensive evaluation of pathology of lung tissue

At the 20th, 32nd week, and both 20th and 32nd week, five indicators related to lung pathology were significantly improved by Tiaobu Fei-Shen therapies and aminophylline (P<0.01). At the 20th week, the relative improvement from high to low was Bufei Jianpi, Bufei Yishen, Yiqi Zishen, and aminophylline, among which Bufei Jianpi and Bufei Yishen were significantly better than aminophylline (P<0.05). At the 32nd week, the relative improvement from high to low was Bufei Yishen, Bufei Jianpi, Yiqi Zishen, and aminophylline, among which Bufei Yishen was significantly better than aminophylline (P<0.05). Considering both the 20th and 32nd week, the relative improvement from high to low was Bufei Yishen, Bufei Jianpi, Yiqi Zishen, and aminophylline, among which the Tiaobu Fei-Shen therapies were better than aminophylline (P<0.01) (Table 2).

Comprehensive evaluation of curative effect

At the 20th, 32nd week, and both 20th and 32nd weeks, nine indicators related to curative effect (three indicators of lung function, five indicators of lung pathology and right ventricular hypertrophy index) were significantly improved by Tiaobu Fei-Shen therapies and aminophylline (P<0.01). At the 20th week, the relative improvement from high to low was Bufei Jianpi, Bufei Yishen, Yiqi Zishen and aminophylline, among which Bufei Jianpi and Bufei Yishen was significantly better than aminophylline (P<0.05). At the 32nd week and both 20th and 32nd weeks, the relative improvement from high to low was Bufei Yishen, Bufei Jianpi, Yiqi Zishen and aminophylline, among which the Tiaobu Fei-Shen therapies were significantly better than aminophylline (P<0.01) (Table 3).

Discussion

Method selection

R-value comprehensive evaluation is a relative deviation variable found by calculating the different amounts deviations from multiple variables. This method can obtain optimal and lower order treatments and draw statistical conclusions. Comprehensive evaluation of an organism cannot use conventional methods of integrated weighting with weighting coefficients, analytic hierarchy process methods, TOPSIS methods, BP artificial neural network methods, efficacy coefficient methods, data envelopment analysis methods, gray comprehensive evaluation methods, osculating value methods, or fuzzy comprehensive evaluation methods. These methods cannot be used because they require particular values and membership functions in the computation procedure, as well as RSR methods of contingency tables. Although weighting coefficients, special values, and subordinate functions are not used in the comprehensive index method, the principle "homogeneous values multiplication" can be used in this method. If this principle is used in the method of R-value comprehensive evaluation, *Rcom* = 0 even if only one indicator of D-value is 0, which means the best comprehensive effect does not conform to the actual situation. In our study, we used "homogeneous values superposition," which accurately reflects the comprehensive effect of treatment, and obtains optimal treatments.

Table 1. Comprehensive evaluation of lung function from the 12th to 32nd week in each group (*Rcom*, $\bar{D}$±*SD*)

Group	Indicators			
	V_T	PEF	EF50	V_T, PEF, EF50
Model	1.0000±0.0000	1.0000±0.0000	1.0000±0.0000	1.0000±0.0000
Aminophylline	0.8201±0.0331^{aa}	0.6666±0.1143^{aa}	0.8210±0.0566^{aa}	0.7692±0.1034^{aa}
Bufei Jianpi	0.7288±0.0816^{aab}	0.6299±0.1043^{aa}	0.7561±0.0465^{aa}	0.7049±0.0944^{aab}
Bufei Yishen	0.7168±0.0425^{aabb}	0.5849±0.1560^{aa}	0.7690±0.0687^{aa}	0.6902±0.1242 ^{aab}
Yiqi Zishen	0.7271±0.0688^{aa}	0.5941±0.1349^{aa}	0.7802±0.0740^{aa}	0.7005±0.1218 ^{aab}

^{a}P<0.05, ^{aa}P<0.01 vs. model group; ^{b}P<0.05, ^{bb}P<0.01 vs. aminophylline group. $\bar{D}$: mean value of D values. In this table, $\bar{D}$ is the mean of six D values (six time points) for each indicator. SD**:** standard deviation.

Table 2. Comprehensive evaluation of pathology of lung tissue in each group (*Rcom,* $\bar{D}$±*SD*)

Group	Week 20	Week 32	Week 20 and 32
Model	1.0000±0.0000	1.0000±0.0000	1.0000±0.0000
Aminophylline	0.6361 ±0.1308^{aa}	0.6544±0.1128^{aa}	0.6452±0.1155^{aa}
Bufei Jianpi	0.4677 ±0.1077^{aab}	0.4497±0.2017^{aa}	0.4587±0.1528^{aabb}
Bufei Yishen	0.4698±0.0594^{aab}	0.4181±0.1306^{aab}	0.4439±0.0995^{aabb}
Yiqi Zishen	0.4950±0.1412^{aa}	0.4756±0.1650^{aa}	0.4853±0.1451^{aabb}

^{a}P<0.05, ^{aa}P<0.01 vs. model group; ^{b}P<0.05, ^{bb}P<0.01 vs. aminophylline group. $\bar{D}$: mean value of D values. In this table, $\bar{D}$ is the mean of five D values (five indicators) at each time point. SD**:** standard deviation.

Table 3. Comprehensive evaluation of overall curative effect *Rcom,* $\bar{D}$±*SD*

Group	Week 20	Week 32	Week 20 and 32
Model	1.0000±0.0000	1.0000±0.0000	1.0000±0.0000
Aminophylline	0.6985±0.1350^{aa}	0.6842±0.0371^{aa}	0.6913±0.1203^{aa}
Bufei Jianpi	0.5566±0.0559^{aab}	0.4853±0.1913^{aabb}	0.5209±0.1782^{aabb}
Bufei Yishen	0.5614±0.0469^{aab}	0.4670±0.0516^{aabb}	0.5142±0.1515^{aabb}
Yiqi Zishen	0.5748±0.0550^{aa}	0.4906±0.0611^{aabb}	0.5327±0.1747^{aabb}

^{a}P<0.05, ^{aa}P<0.01 vs. model group; ^{b}P<0.05, ^{bb}P<0.01 vs. aminophylline group. $\bar{D}$: mean value of D values. In this table, $\bar{D}$ is the mean of nine D values (nine indicators) at each time point. SD: standard deviation.

Effects of Tiaobu Fei-Shen therapies and their characteristics

According to TCM theory, accumulation of pathogens and damage from deficiency of vital qi is the main pathogenesis of COPD. Therefore, strengthening vital qi and dispelling stasis is the main therapeutic strategy for treatment [16]. The syndromes of lung-spleen qi deficiency, lung-kidney qi deficiency, and lung-kidney qi-yin deficiency are the most common syndromes in stable COPD, and Tiaobu Fei-Shen therapies (Bufei Jianpi, Bufei Yishen, Yiqi Zishen, respectively) are used to treat these syndromes. Our previous multi-center clinical trial demonstrated that Tiaobu Fei-Shen therapies can reduce acute exacerbations, slow down the rate of lung function decline, and improve the quality of life of patients [9]. Our previous animal experiment also indicated that Tiaobu Fei-Shen therapies can improve lung function, alleviate lung pathology injury, and reduce lung proinflammatory cytokine production in COPD rats [10,11]. However, our previous study only reflects changes in a single index at a single time point rather than comprehensive evaluation of the treatment. The R-value comprehensive evaluation method was established to compensate for this shortage.

The principal feature of COPD is progressive airway limitation, and it is one of the main factors limiting physical activity in patients with COPD. The tidal volume (V_T) is lower and the breathing frequency (f) higher in patients with COPD compared with healthy subjects [17]. The mechanism for the ventilatory limitation in COPD is related to expiratory flow limitation and lung hyperinflation [18]. Forced expired volume in 1 sec (FEV1) is a major indicator related to airway limitation in clinical diagnosis, but it is difficult to measure in animals. Therefore, we measured V_T, EF50, and PEF in our experiment using whole body plethysmography. In our previous study, traditional statistical analysis methods showed that Tiaobu Fei-Shen therapies can improve V_T, PEF, and EF50 at the 20th and 32nd week, aminophylline improved PEF at the 20th week, and there were no statistical differences among these groups. In this study, the R-value comprehensive evaluation method showed that Tiaobu Fei-Shen therapies and aminophylline can obviously improve indicators related to lung function in COPD rats from the 12th to 32nd week. Further, Bufei Jianpi and Bufei Yishen were better than aminophylline in improving V_T and the overall improvement effect on three indicators from high to low was Bufei Yishen, Yiqi Zishen, Bufei Jianpi, and aminophylline, among which Tiaobu Fei-Shen therapies were significantly better than aminophylline.

Chronic bronchitis, emphysema, pulmonary hypertension, and small airway remodeling are cardinal pathological features of COPD. In our previous study, traditional statistical analysis methods showed that Tiaobu Fei-Shen therapies and aminophylline can alleviate bronchial wall thickening, bronchial stenosis, alveolar rupture and fusion, and pulmonary artery wall thickening. Bufei Jianpi is better in alleviating pulmonary artery wall thickening at the 20th week. Tiaobu Fei-Shen therapies are better than aminophylline in alleviating bronchial wall thickening, bronchial stenosis, and alveolar rupture. In this paper, the R-value comprehensive evaluation method showed that Tiaobu Fei-Shen therapies and aminophylline can obviously rectify the five indicators related to the lung tissue injury at both the 20th and 32nd weeks. Bufei Jianpi and Bufei Yishen had a better improvement effect than the other treatments. Considering both the 20th and 32nd weeks, the improvement effect from high to low was Bufei Yishen, Bufei Jianpi, Yiqi Zishen, and aminophylline, among which the Tiaobu Fei-Shen therapies were better than aminophylline.

Traditional statistical analysis methods cannot evaluate the comprehensive effect of Tiaobu Fei-Shen therapies and aminophylline

on all nine indicators related to curative effect. R-value comprehensive evaluation method indicates that Tiaobu Fei-Shen therapies and aminophylline have positive and long-term effects on curative effect. The improvement effect of Tiaobu Fei-Shen therapies was better than aminophylline. The improvement effect from high to low is Bufei Jianpi, Bufei Yishen, Yiqi Zishen and aminophylline at the 20th week; Bufei Yishen, Bufei Jianpi, Yiqi Zishen and aminophylline at the 32nd week and both 20th and 32nd weeks. The results indicate that Bufei Jianpi has positive treatment effects, while Bufei Yishen has positive long-term effects.

Conclusions

Traditional statistical analysis methods and R-value comprehensive evaluation methods have advantages, but the R-value comprehensive evaluation method can reflect characteristics of the three Tiaobu Fei-Shen therapies at multiple time points and with multiple indicators. According to the R-value comprehensive evaluation method, Tiaobu Fei-Shen therapies have a positive treatment effect and long-term effect on lung function, pulmonary tissue injury in model COPD rats. Bufei Yishen granule shows positive treatment effects in improving lung function and alleviating pulmonary tissue injury, while Bufei Jianpi granule shows positive curative effects, and Bufei Yishen granule has a positive long-term influence on the comprehensive curative effect.

Authors' contributions

LJS, CHX and XY contributed to the methods establishment. CHX and LY contributed to data analysis and calculation. TYG and BYP contributed to previous animal experiments and manuscript drafting. All authors read and approved the final manuscript.

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