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Original Research Article

Effect of tetrandrine tablets on cytokines, immune function, blood gas and respiratory function in patients with stage II pneumoconiosis

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Abstract

Purpose: *To investigate the impact of tetrandrine tablets on cytokines, immune function, blood gas and respiratory function in patients with stage II pneumoconiosis.*
Methods: *136 subjects with stage II pneumoconiosis diagnosed and treated in People's Hospital of Linyi City, Linyi City, China were divided into control and study cohorts, each with 68 individuals. Patients in control cohort received conventional symptomatic treatment, while study cohort additionally received tetrandrine tablets orally 3 times per day, for 4 weeks. Lung function, serum indicators and blood gas indicators were determined before and after treatment.*
Results: *After treatment, the levels of forced expiratory volume in one second (FEV1) and FEV1/FVC in both groups were significantly increased in both cohorts, with significantly higher values in study cohort. In both cohorts, there were higher post-treatment numbers of $CD4^+$ and $CD8^+$ cells and $CD4^+/CD8^+$ ratio than before treatment, but with significantly higher values in study cohort ($p < 0.05$). After treatment, there were significantly raised levels of peripheral capillary oxygen saturation (SpO_2), minute ventilation (VE) and tidal volume (VT) in the two cohorts, with higher values in the study group cohort ($p < 0.05$). Moreover, treatment resulted in a significant reduction in partial pressure of end-tidal carbon dioxide ($PETCO_2$), with significantly lower levels in study cohort ($p < 0.05$). After treatment, concentrations of interleukin-1 beta (IL-1β), matrix metalloproteinase-7 (MMP-7), and tumor necrosis factor beta-1 (TNF-β1) in study cohort were significantly reduced, relative to pre-treatment.*
Conclusion: *Tetrandrine tablets are efficacious in stage II pneumoconiosis patients. The drug is beneficial in improving immune function, reducing levels of inflammatory mediators, and improving lung function and blood gas indicators in patients. Future studies incorporating additional parameters and a larger number of patients will be required to provide a more comprehensive understanding of the efficacy and safety of this treatment protocol.*

Keywords: *Tetrandrine tablets, Stage II pneumoconiosis, Cytokines, Immune function, Blood gas indicators*

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INTRODUCTION

Pneumoconiosis refers to a class of occupational diseases with diffuse fibrosis of lung tissue caused by long-term inhalation and retention of pathogenic dust in the lungs, and it comprises graphite pneumoconiosis, coal workers pneumoconiosis, silicosis and other types [1]. Most pneumoconiosis patients are workers in quarries, coal mines, and glass and ceramic factories. Dust inhalation through the breath inflames the lungs, and in turn, leads to fibrotic lesions which negatively impact lung function in patients [2].

Patients with pneumoconiosis usually have no obvious clinical symptoms at the early stage, but they often have advanced pneumoconiosis in stage II when diagnosed. Pneumoconiosis is associated with heavy medical bills, severe morbidity, high death rates, unbearable financial burdens on patients' families, and high psychological pressure. Presently, no specific medication has been developed for curing pneumoconiosis. Therefore, pneumoconiosis treatment is based only on managing and slowing down disease progression, with the major goal of enhancing the immune function of patients while improving their quality of life [3].

Tetrandrine is a bisbenzylisoquinoline alkaloid isolated from the root of *Stephania tetrandra* (Fangji, Menispermaceae, S. Moore). It is a natural calcium channel blocker which reduces the levels of type I and type III collagen mRNA in lung tissue and the deposition of collagen in the lungs, thereby effectively alleviating pulmonary fibrosis and inflammatory responses [4]. Meanwhile, in clinics, the major index of stage II pneumoconiosis is lung tissue fibrosis. Thus, this study was carried out to determine the impact of tetrandrine tablets in patients with stage II pneumoconiosis *via* its effect on the cytokines, immune function, blood gas indices, and respiratory function parameters in these patients.

METHODS

General information on patients

A total of 136 patients with stage II pneumoconiosis who were treated in People's Hospital of Linyi City from February 2021 to March 2023, were divided into control and study cohorts, each with 68 patients. This study protocol was reviewed and approved by the ethics committee of People's Hospital of Linyi City (approval no. PHLYC2023004), and complied with the guidelines of Declaration of Helsinki. All the subjects signed informed consent.

Inclusion criteria

Patients in the following categories were included in the study: patients diagnosed with stage II pneumoconiosis based on clinical symptoms, signs, and examinations [5]; patients who did not receive cardiopulmonary function diagnosis and treatment in the previous 3 months, and those with complete clinical medical records.

Exclusion criteria

The excluded patients were those with other pulmonary diseases; patients with serious complications; those with history of drug allergy; patients with severe heart, liver, and renal insufficiency, and those with hypotension and shock.

Treatments

The control group was given conventional symptomatic treatments such as conventional oxygen inhalation, expectorant, asthmatic therapy, and pulmonary function rehabilitation therapy. In addition, the patients were advised to reduce their exercise regimen. The study group was treated with oral tetrandrine tablets (Zhejiang Zhongyi Pharm. Co. Ltd, packaged in 20 mg tablets) at an oral level of 60 mg thrice daily for 6 days, in addition to the treatment in the control group. Both groups of patients were treated continuously for 3 months with a gap of one day allowed after each 6-day tetrandrine treatment.

Evaluation of parameters/indices

Treatment effectiveness

At the end of treatment, clinical efficacy was evaluated [6]. The therapeutic outcome was classified as significant, effective, or ineffective. Treatment effect was significant (S) if systolic pulmonary artery pressure (PAPs) decreased by > 15 %, with complete disappearance of clinical symptoms or decrease in score of > 50 %, when compared to the score before treatment. Treatment was deemed effective (E) if PAPs decreased by 5 – 15 %, with complete disappearance of clinical symptoms or 20 – 50 % decreases in score, when compared to scores before treatment. However, treatment was seen as ineffective if PAPs decreased by < 5 % or increased, without a reduction in clinical symptoms. Therapeutic efficacy (T) was calculated using Eq 1.

T (%) = {(S+E)/N}100 …… (1)

where N is the total number of cases

Pulmonary function

Lung function parameters were measured using a pulmonary function testing system (Jaeger, Germany) [7]. The parameters measured were forced expiratory volume in one second (FEV1), forced expiratory volume in one second as a % of the predicted value (FEV1%pred) and the ratio between FEV1 and forced vital capacity (FVC). Each patient was tested three times before treatment and after treatment, and the highest value was subjected to analysis.

Serum indices

Pre- and post-therapy blood sample (4 mL) was obtained from the peripheral vein of each subject in the fasted state. The blood samples were centrifuged at 3500 rpm for 10 min to separate sera, and the serum samples were preserved frozen [8]. Serum concentrations of TNF-β1, MMP-7 and IL-1β were determined with ELISA. The instrument used was a Bio-Tek fully automatic enzyme microplate reader. The DxFLEX flow cytometer (Beckman, USA) was used to measure serum levels of $CD4^+$ and $CD8^+$ cells in both groups of patients, and the $CD4^+/CD8^+$ value was calculated.

Blood gas indices

The arterial blood gas parameters were measured before and after treatment using a pulmonary function testing system (Jaeger, Germany). The parameters measured were blood oxygen saturation (SpO_2), end-tidal partial pressure of carbon dioxide ($PETCO_2$), tidal volume (VT), and resting minute ventilation (VE).

Statistical analysis

Statistical analysis was performed using SPSS version 20.0. Comparison of count data was done with Chi-squared test. Measured data are expressed as mean ± standard deviation (SD). Comparisons were made using Student's *t*-test, with $p < 0.05$ indicating statistical significance.

RESULTS

General data

Basic data were comparable in the two groups. Table 1 shows the general information on the two groups.

Clinical efficacy

Table 2 indicates that therapeutic effectiveness was significantly higher in the study cohort.

Lung function indices

Pre-therapy pulmonary function indices were comparable in the two cohorts. However, after treatment, the levels of FEV1, FEV1%pred and FEV1/FVC in both groups were significantly higher than the pre-treatment values, with the study group having significantly higher values than control cohort. These results are presented in Table 3.

Table 1: Basic data of subjects (n=68)

Cohort	Course of illness (years)	Age (years)	Gender	
			Male	Female
Study	4.62±1.62	51.52±8.56	37	31
Control	4.23±1.82	50.46±7.64	36	32
χ^2/t	1.320	0.762	0.030	
P-value	0.189	0.448	0.863	

Table 2: Therapeutic effectiveness in the 2 cohorts (n = 68)

Cohort	Significantly efficacious	Efficacious	Ineffective	Overall efficacy
Study	44 (64.71)	21 (30.88)	3 (4.41)	65 (95.59)*
Control	32 (47.06)	22 (32.35)	14 (20.59)	54 (79.41)
χ^2				32.924
P-value				0.000

***P* < 0.05, vs. control group

Table 3: Lung function index levels (n = 68)

Group	FEV1 (L)		FEV1/FVC (%)		FEV1%pred (%)	
	Pre-therapy	Post-therapy	Pre-therapy	Post-therapy	Pre-therapy	Post-therapy
Study	1.42±0.45	2.13±0.60*,a	54.63±8.62	68.65±7.35*,a	48.62±7.33	63.26±7.66*,a
Control	1.37±0.57	1.84±0.55*	53.74±7.85	62.35±9.54*	47.26±8.28	56.34±8.59*
t	0.542	2.805	0.601	4.119	0.968	4.734
P-value	0.589	0.006	0.549	0.000	0.335	0.000

Note: #,a*P* < 0.05, #vs. pre-treatment; avs. control

Table 4: Immune function index levels (n = 68)

Cohort	$CD8^+$ (%)		$CD4^+$ (%)		$CD4^+/CD8^+$	
	Pre-treatment	*Post-treatment*	*Pre-treatment*	*Post-treatment*	*Pre-treatment*	*Post-treatment*
Study	31.24±4.72	24.34±3.29*,a	34.65±5.62	45.32±6.27*,a	1.12±0.25	1.74±0.30*,a
Control	30.84±4.26	27.62±4.33*	35.70±6.41	40.38±5.90*	1.16±0.27	1.43±0.33*
t	0.495	-7.749	-0.970	4.518	-0.856	5.473
P-value	0.621	0.000	0.334	0.000	0.394	0.000

Note: *,a*P* < 0.05, *vs. pre-treatment; avs. control

Immune function index

Before treatment, the levels of immune function indices were comparable in both cohorts. After treatment, $CD4^+$ level and $CD4^+/CD8^+$ ratio in both groups were significantly increased, with higher values in the study cohort ($p < 0.05$). However, post-treatment $CD8^+$ level was significantly decreased, although the control cohort had higher $CD8^+$ value (Table 4).

Arterial blood gas indicator values

Before treatment, there were no significant differences in the levels of arterial blood gas parameters between the two groups. However, in both cohorts, treatment raised the levels of SpO_2, VE and VT, with significantly higher values in study cohort. In contrast, levels of $PETCO_2$ in both cohorts were significantly decreased after treatment, but $PETCO_2$ level was significantly lower in the study cohort ($p < 0.05$; Table 5).

Inflammatory factor levels

Inflammatory factor levels in both cohorts were comparable before treatment. However, post-treatment levels of IL-1β, MMP-7 and TNF-β1 in the observation and control groups were significantly lower than the corresponding pre-treatment levels, with higher levels in control cohort (Table 6).

DISCUSSION

Pneumoconiosis, an interstitial pulmonary illness due to inhaled dust, presents with chronic and acute lung inflammatory lesions which result in generalized fibrosis which leads eventually to respiratory insufficiency [9]. Pneumoconiosis currently ranks amongst the most life-threatening occupation-based pathologies in the world, with an estimated annual death toll running into tens of thousands, and more new cases diagnosed annually [9]. Although dust prevention and use of respirators and other protective measures have resulted in reduction in the incidence of pneumoconiosis, new cases still occur in places where silica materials are widely used in mining and industry [10].

The main pathology in pneumoconiosis is due to the outbreak of humoral immunity caused by macrophages, lymphocytes, and cytokines, as well as cellular immune suppression, leading to immune dysfunction or imbalance [11]. In addition, inflammatory response and pulmonary fibrosis are important pathological changes in pneumoconiosis, and they lead to functional respiratory disorders in patients [12]. At present, there are no specific methods for curing pneumoconiosis in clinical practice. Therefore, it is of great clinical significance to find new drugs or treatment regimens for improving the effectiveness of treatment of pneumoconiosis. This study used tetrandrine tablets to treat patients with stage II pneumoconiosis and investigated the effect of the drug on levels of cytokines, immune function indices, blood gas parameters, and respiratory function indices. The results showed that this treatment method had good clinical efficacy. Pneumoconiosis presents mainly as lung tissue fibrosis, and with the prolongation of the disease, the degree of pulmonary fibrosis in patients increases. Firstly, pulmonary fibrosis causes obstruction of blood circulation in the lungs, damages the respiratory defense system, leads to decreased immune function in patients, and causes repeated infections.

Table 5: Arterial blood gas index levels (n=68)

Group	SpO_2 (%)		$PETCO_2$ (kPa)		VE (L/min)		VT (mL)	
	Before treatment	***After treatment***	***Before treatment***	***After treatment***	***Before treatment***	***After treatment***	***Before treatment***	***After treatment***
Observation	80.65±9.58	96.65±14.75*,a	6.52±1.45	4.60±0.37*,a	5.68±0.62	7.75±0.75*,a	355.65±55.65	483.25±78.95*,a
Control	80.45±9.75	90.75±12.35*	6.60±1.50	5.48±0.72*	5.95±0.55	6.75±0.72*	354.36±55.25	410.65±65.68*
t	0.121	2.529	-0.316	-8.964	-2.686	6.403	0.136	5.829
P-value	0.904	0.013	0.752	0.000	0.008	0.000	0.892	0.000

*$P < 0.05$, vs. pre-treatment; $^a p < 0.05$, vs. control

Table 6: Inflammatory factor levels in both cohorts (n = 68)

Group	IL-1β (pg/mL)		MMP-7 (ng/mL)		TNF-β1 (ng/mL)	
	Before treatment	***After treatment***	***Before treatment***	***After treatment***	***Before treatment***	***After treatment***
Study	42.56±8.23	23.42±4.37*,a	113.30±21.12	77.52±11.82*,a	22.41±3.58	11.38±3.14*,a
Control	43.21±7.25	30.37±5.42*	114.53±20.24	96.13±16.73*	21.82±4.10	15.42±2.85*
t	-0.489	-8.232	-0.347	-7.492	0.894	-7.856
P-value	0.626	0.000	0.729	0.000	0.373	0.000

*$P < 0.05$, vs. pre-treatment; $^a p < 0.05$, vs. control

In severe cases, patients may develop irreversible failure of pulmonary function. Arising from the absence of clinical signs and specific drug treatment in the early stage of pneumoconiosis, by the time severe signs like cough, chest congestion and phlegm occur, the disease is already at a serious stage. The present research revealed significantly higher therapeutic effectiveness in the study cohort.

Treatment raised values of FEV1, FEV1%pred and FEV1/FVC in both cohorts, with higher study cohort values. Moreover, in the two cohorts, $CD4^+$ and $CD4^+/CD8^+$ values were significantly raised by treatment, while the level of CD8+ was significantly lowered, with smaller levels in the study cohort than in the control group. After treatment, the levels of SpO_2, VE and VT in both groups were significantly higher than those before treatment, with significantly higher levels in the study group than in the control group. The levels of $PETCO_2$ in both groups were significantly lowered after treatment, but $PETCO_2$ level in the study group was significantly lower than that in the control group. These results suggest that the use of tetrandrine tablets in stage II pneumoconiosis patients produces good clinical efficacy which is beneficial for improving immune function, lung function and blood gas indices of patients.

Tetrandrine, an alkaloid, not only exerts major analgesic and anti-inflammatory effects but also effectively reduces spasms in lung vascular smooth muscle in patients, resulting in enhanced lung tissue microcirculation and alleviating pneumoconiosis symptoms [13]. In addition, tetrandrine inhibits calcium channels in fibroblasts and blocks their capacity to proliferate [13]. Additionally, tetrandrine inhibits the biosynthesis of collagen in the lungs of patients with pneumoconiosis, and it acts on cellular microtubules such that collagen only forms fibrous structures outside the cell, thereby reducing collagen levels in pneumoconiosis tissues, and loosening or even degrading nodules in pneumoconiosis patients [14]. Studies have revealed that tetrandrine suppresses several cardiovascular and pulmonary illnesses, is hepatoprotective and cancer cell apoptosis-inducing, and reverses multi-drug insensitivity [15,16]. The occurrence and development of pneumoconiosis are intertwined processes of inflammatory and fibrotic lesions involving crucial cytokine roles. Clinical research has shown that inflammatory response is one of the important mechanisms that cause lung tissue damage in patients with pneumoconiosis in the early stage [17]. The pulmonary fibrosis-induced arterial obstruction in pneumoconiosis causes changes in blood flow dynamics, leading to ischemia and hypoxia in the lung tissue of patients. These changes lead to the release of inflammatory mediators, induction of expression of adhesion molecules on vascular endothelial cells, activation and initiation of the coagulation process, and aggravation of lung tissue injury [18].

The pro-inflammatory factor IL-1β exacerbates local inflammation in the lung tissue, while TGF-β1 is the most potent promoter of collagen deposition and lung tissue fibrosis which ultimately results in pulmonary fibrosis in pneumoconiosis [19]. Studies have revealed that an increase in serum MMP-7 activity is an index of the extent of pneumoconiosis and poor prognosis in subjects with lung fibrosis [20]. In the study cohort, the concentrations of IL-1β, MMP-7, and TNF-β1 were significantly lower than the pre-treatment and control cohort values. This suggests that the use of tetrandrine tablets in stage II pneumoconiosis patients produces good clinical efficacy and is beneficial for reducing the levels of inflammatory mediators. It has been reported that tetrandrine inhibits the uptake of deoxy-glucose by neutrophils and monocytes, and also inhibits the adhesion of inflammatory cells. In addition, tetrandrine inhibits the random movement, chemotaxis, and phagocytosis of human neutrophils *in vitro* [21]. Tetrandrine inhibits the activity of hexose monophosphate shunt and the production of hydrogen peroxide and superoxide anion, thereby exerting anti-phagocytic, antioxidant, and other anti-inflammatory effects [22].

Limitations of this study

The limitations of the study include lack of blinding, small sample size (136 patients), short treatment duration (4 weeks), and absence of long-term follow-up. The single-center design and lack of a placebo control group further restrict the generalizability of the findings. Future research addressing these limitations and incorporating additional outcome measures could provide a more comprehensive understanding of the efficacy and safety of tetrandrine tablets in the treatment of pneumoconiosis patients.

CONCLUSION

The use of tetrandrine tablets in stage II pneumoconiosis patients produces good clinical efficacy which is beneficial for improving immune function, reducing the levels of inflammatory mediators, and improving lung function and blood

gas indicators in the patients. Future studies incorporating additional parameters will be required to provide a more comprehensive understanding of the efficacy and safety of this treatment protocol.

DECLARATIONS

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Ethical approval

This study received approval from the ethics committee of People's Hospital of Linyi City (approval no. PHLYC2023004),

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was performed by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Zhongmin Deng and Guijun Wei designed the study, supervised the data collection, and analyzed the data. Lei Qiu interpreted the data and prepared the manuscript for publication. Huifei Lu supervised the data collection, analyzed the data and reviewed the draft of the manuscript.

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