Annals of Clinical Case Reports

Research Article
Published: 14 Dec, 2021

Xuefu Zhuyu Decoction: A Safety Tactics to Lessening Cholesterol and Improving the Treatment Effect of the Autoimmune Alveolar Proteinosis

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Abstract

Objective: The aim of this study was to explore the efficacy of Xuefu Zhuyu decoction in treating autoimmune PAP (aPAP) and its underlying mechanism.

Methods: 12 aPAP patients from January 2012 to February 2018 were enrolled. According to the different therapies, they were divided into two groups: Whole Lung Lavage (WLL) group and Xuefu Zhuyu Decoction (XFZYD) group. The results of multiple clinical tests and examination were used as data sources.

Results: Compared with the standard baseline of CT, the percentage of affected lung parenchyma in WLL group and XFZYD group were 69.28 ± 10.25 and 67.55 ± 8.44, respectively. Both groups decreased gradually over time, reaching the lowest at the 24th month, but XFZYD group was significantly lower than the WLL group since the 3rd month after baseline. The improvements of the Partial Alveolar-arterial Oxygen gradient ($P(A\text{-}a)O_2$) and the Partial arterial pressure of Oxygen (PaO_2) were consistent with the reduction of the affected lung on CT images. In XFZYD group, the forced vital capacity (FVC) % and carbon monoxide diffusing capacity (DLCO) % were markedly improved after 3-month treatment. The contents of Lactate Dehydrogenase (LDH), Carcino Embryonic Antigen (CEA) and Neuron Specific Enolase (NSE) in serum were significantly decreasing in the two different treatment groups. Serum Total Cholesterol (TC) in the XFZYD group gradually decreased over time, reaching the lowest value at 24 months, while serum High-Density Lipoprotein Cholesterol (HDL-C) had the opposite trend. There was no difference of Low-Density Lipoprotein Cholesterol (LDL-C) and Triglyceride (TG) between the WLL and XFZYD group, and Alanine Amino Transferase (ALT) and Aspartate Aminotransferase (AST) of XFZYD group maintained at normal levels.

Conclusion: XFZYD might be an effective and safe method for the treatment of aPAP, and it can ameliorate the symptom of aPAP and reduce the level of serum cholesterol.

Keywords: Autoimmune pulmonary alveolar proteinosis; Whole lung lavage; Xuefu Zhuyu decoction; Therapy

Abbreviations

PAP: Pulmonary Alveolar Proteinosis; aPAP: autoimmune PAP; PT: Patients; XFZYD: Xuefu Zhuyu Decoction; TCM: Traditional Chinese Medicine; GM-CSF: Granulocyte Macrophage Colony Stimulating Factor; WLL: Whole Lung Lavage; DSS: Disease Severity Score; PaO_2: Partial Pressure of Oxygen in arterial blood; $P(A\text{-}a)O_2$: Partial Alveolar-arterial Oxygen gradient; ECG: Electrocardiogram; SaO_2: Arterial Oxygen Saturation; ALT: Alanine Amino Transferase; AST: Aspartate Aminotransferase; LDH: Lactate Dehydrogenase; CEA: Carcino Embryonic Antigen; NSE: Neuron Specific Enolase; FVC: Forced Vital Capacity; DLCO: Carbon Monoxide Diffusing Capacity; CT: Computed Tomography; HRCT: High-Resolution Computed Tomography; TG: Total Triglyceride; TC: Total Cholesterol; HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol

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Received Date: *25 Oct 2021*
Accepted Date: *08 Dec 2021*
Published Date: *14 Dec 2021*

Citation:
Wang F, Xiao B, Huang X, Du J, Cheng W, Li J, et al. Xuefu Zhuyu Decoction: A Safety Tactics to Lessening Cholesterol and Improving the Treatment Effect of the Autoimmune Alveolar Proteinosis. Ann Clin Case Rep. 2021; 6: 2056.

ISSN: 2474-1655

Introduction

Pulmonary Alveolar Proteinosis (PAP) is a rare clinical syndrome and enigmatic disorder, which is characterized by abnormal accumulation of surfactant in the alveoli and variable natural history [1]. According to statistics, the annual incidence and prevalence of PAP are 0.36 and 3.70 cases per million populations, respectively. It is difficult for any individual medical clinic or rehabilitation center to accumulate the important experience with this disease; thus, the single cases reports or small case series account for more than 75% of all described PAP cases [2]. The disclosed data shows that autoimmune PAP (aPAP) is the major type and it accounts for over 90 percent of all PAP patients [3]. For aPAP patients, the main clinical manifestations are alveolar proteinosis, alveolar lipoproteinosis and alveolar phospholipidosis. The precipitated surfactants are composed of polar lipids (80%), neutral lipids (10%) and protein composition (10%) [4,5]. In addition, the cholesterol content of macrophages in the alveoli will be significantly increased while the phospholipids be slightly increased, resulting in an increase in the ratio of cholesterol to phospholipids in lung surfactants along with causing the course of the symptom to be more serious [6]. Therefore, reducing the cholesterol level of alveoli might be a useful strategy to improve treatment effect of the autoimmune alveolar proteinosis. Traditional Chinese Medicine (TCM) has a long history and has formed its own unique theoretical system [7]. Within the framework of TCM theory, aPAP is recognized by Qi stagnation and Blood stasis syndrome, and TCM practitioners always prescribe prescriptions using herbal medicines and acupuncture according to its specific syndromes. Xuefu Zhuyu Decoction (XFZYD) belongs to the Chinese Herbal Medicine (CHM) drugs and it has the function of promoting Qi and Blood circulation and relieving the symptoms of Qi stagnation and Blood stasis [7,8], which has obtained the certification approved by the China Food and Drug Administration in 2002. The components of XFZYD include 11 kinds of plant-extracts, as follows: Peach kernel (Taoren), *Angelica sinensis* (Oliv.), Diels (Danggui), *Ligusticumi chuanxiong* Hort. (Chuanxiong), *Carthamus tinctorius* L. (Honghua), *Paeonia lactiflora* Pall. (Chishao), *Rehmannia glutinosa* Libosch. (Di huang), *Citrus aurantium* L. (Zhiqiao), *Bupleurum chinense* DC. (Chaihu), *Platycodon grandiflorum* (Jacq.) A. DC. (Jiegeng), *Achyranthes bidentata* Bl. (Niuxi), and *Glycyrrhiza uralensis* Fisch. (Gancao).The modern pharmacological study indicates XFZYD can lower blood lipid [9,10] and improve hemorheology and microcirculation [11]. Besides, XFZYD also can be used in the treatment of cardiovascular diseases [7,12]. According to our clinical experience, we found that aPAP patients reflected an alleviated dyspnea and a better lung characteristic in CT images after taking XFZYD for one month. Herein, we followed up the patients' condition, conducted the observation for one year in this study, and compared the clinical indexes of these patients that adopted the Whole Lung Lavage (WLL) treatment and XFZYD treatment.

Methods

Patient selection

This study involved 12 aPAP patients that were collected from the inpatient of the Department of Respiratory and Critical Care Medicine of the Affiliated Hospital of Qingdao University, from January 2012 to February 2018. All patients were diagnosed by transbronchial lung biopsy and had positive results for GM-CSF auto antibodies (>5 μg/mL). According to the different treatment, the 12 patients were randomly divided into two groups: Whole Lung Lavage group (WLL) group and Xuefu Zhuyu Decoction (XFZYD) group. Patients would get a mark based on the Disease Severity Score (DSS) for PAP definition by Inoue et al. [13] and were divided into different grades, details were shown in Table 1. The grades were as follows: Grade 1, $PaO_2 \geq 70$ mmHg without respiratory symptoms; Grade 2, $PaO_2 \geq 70$ mmHg with respiratory symptoms; Grade 3, 60 mmHg ≤ PaO_2<70 mmHg; Grade 4, 50 mmHg ≤ PaO_2<60 mmHg; and Grade 5, PaO_2<50 mmHg.

Whole lung lavage

WLL was conducted by a double-lumen endobronchial tube under general anesthesia. Lavage was initially performed in the relatively severe lungs. Patients were in a lateral position with ventilated lung up and lavage lung down. Before operation, the ventilated lung underwent a lung ventilation tolerance test, the pure oxygen was ventilated for at least 20 min to wash out nitrogen in lung and raise oxygen storage. Then, 500 mL 37°C saline was injected in lavage lung and drained 200 mL to 250 mL by gravity, and repeated lavage until drainage fluid was clear. The total lavage volume ranged from 9 to 15 liters, with an average of 12.8 ± 0.36 liters/lung. The lavage time maintained between 90 min to 150 min. The blood pressure, pulse, Electrocardiogram (ECG), arterial Oxygen Saturation (SaO_2), peak airway pressure, and artery blood gas analysis were monitored during the entire surgery. If SaO_2 was under 90% during lavage, positive pressure ventilation was given until SaO_2 was higher than 92% and then lavage is continued. Afterwards, according to the range of pulmonary rales, lavage fluid recovery rate, blood oxygen saturation and partial pressure oxygen, the furosemide 20 mg to 40 mg and added dexamethasone 5 mg to 10 mg through vein injection and bilateral lung ventilation giving positive end expiratory pressure (6 cmH_2O) for 20 min to 1 h. Thereafter, the patient was taken off the ventilator, removed the tracheal intubation, and changed to nasal catheter for oxygen. Then we performed lavage again for the next lung with an interval of one week.

Preparation of Xuefu Zhuyu decoction

The TCM doctors designed dialectical treatment to these patients. They added up or wiped out some crude herbs to XFZYD based on each patient's pathogenetic conditions, the patient's prescription is shown in the Table 1. The crude herbs in the decoction were purchased from Tong Ren Tang Pharmacy in Qingdao (Shandong, China). The TCM mixture was heated with 1 liter of water at high temperature until boiling, and then gently heated until there was about 300 mL of the liquid. The patients took it once a day, 30 min before meal.

Laboratory test

The automatic chemical analyzer (HITACHI 7600P, FUJI-FILM Wako Pure Chemical Corporation, Japan) was used to measure the levels of serum Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) and blood lipids, according to the manufacturer's instructions of commercial kits. Lactate Dehydrogenase (LDH) was measured with an automatic chemical analyzer (HITACHI 7600P, Beijing Lead man Biochemical Co., Ltd., China). Carcinoembryonic Antigen (CEA) and Neuron-Specific Enolase (NSE) were detected by an automatic electrochemiluminescence immunoassay analyzer (Roche Cobas E602, Roche Diagnostics, Germany). An automatic analyzer (GEM Premier 4000, Werfen Life Group, Spain) is used to analyze the arterial blood gas of the PAP patients when the patients breathed indoor air. The German Master Screen Body (Jaeger Company, Bad Wildungen, Hessen, Germany) was used to measure the pulmonary

function on PAP patients, including FVC% Pred and Carbon Monoxide Diffusing Capacity (DLCO)% Pred. Philips 40 brilliance Computer Tomography (CT) was used to conduct the conventional chest CT and the chest High-Resolution CT (HRCT).

Statistical analysis

All results were expressed as mean ± SD. Clinical indexes of the 2 groups were analyzed through repeated measurement analysis of variance. The Fisher's exact test or Chi-square test was used to evaluate proportions for variables between the WLL group and XFZYD group. The P value of <0.05 was considered as statistically different. All data analysis was performed using SPSS version 22.0 (SPSS, Inc, Chicago, IL), while figures was made by Graph Pad Prism 7.0.

Results

Clinical characteristics

Clinical characteristics of the aPAP patients are listed in Table 2. The average age of patients in the WLL group was 46.8 ± 8.10 years, while the average age of patients in the XFZYD group was 44.6 ± 6.50 years (t=0.4996, P=0.6308). The proportion of men in the WLL group was 80%, while the proportion of men in the XFZYD group was 75% (P>0.9999). The results of the analysis of the course of disease showed that the WLL group and XFZYD group were 6.2 ± 3.11 months and 5.6 ± 4.18 months, respectively (t=0.08575, P=0.9338). There was no significant difference in DSS scores between the WLL group and the XFZYD group, but there were two smokers and one patient with a history of exposure to pneumoconiosis in the WLL group, one smoker and one patient with a history of exposure to pneumoconiosis in the XFZYD group. All patients in two groups had the main symptoms of breathing difficulties. The histological staining images showed that the alveoli were filled with homogeneous red protein-like substances in both groups (Figure 1a). In the WLL group, milk-like liquid was drained out during operation (Figure 1b). One-third of patients received the second whole lung lavage at the 8 and 12 months. For the XFZYD group, the average medication time of XFZYD group was 9.5 ± 3 months.

CT analysis

We performed CT examinations at 1, 3, 6, 12 and 24 months after lavage or medication (Figure 2a). At baseline examination, both groups showed diffuse ground-glass shadows and thickening of interlobular septa in the CT images. After total lung lavage, four of the six patients gradually improved their CT images over time, and the other 2 patients got worse 6 months after surgery, and finally received a second operation at 8 and 12 months. The percentage of affected lung parenchyma in the upper right lobe bronchial layer was estimated by Image J software (Figure 2b). The results showed that CT percentages of the affected lung parenchyma in the WLL group and XFZYD group were 69.28 ± 10.26% and 67.55 ± 8.44%, respectively. With the time passing, both groups had gradually decreased and reached the lowest values at 24 months: 27.32 ± 13.06% and 7.27 ± 3.04%, respectively. The XFZYD group was significantly lower than the WLL group after 3 months (Table 3, Figure 2c). These data indicate that XFZYD is more effective in improving the symptoms of aPAP patients.

Arterial blood gas analysis and pulmonary function

The results of arterial blood gas showed that PaO_2 of WLL group increased gradually with time and reached 70 ± 7.61 mmHg at 24 months. Interestingly, the XFZYD group was significantly higher than the WLL group after 3 months (Table 3, Figure 3a). The P(A-a)O_2 decreased significantly in the WLL and XFZYD groups during the 24-month follow-up compared to baseline, and the P(A-a)O_2 of XFZYD group was significantly lower than that of WLL group at the 3 months and later (Table 3, Figure 3b). The results of lung function indicated that FVC of WLL group was slightly higher than baseline at each time point after operation, but the difference was not significant. After 3-month treatment, the XFZYD group showed improved effects in FVC% Pred (P=0.0109) and DLCO% Pred (P=0.046) than baseline, especially in 6, 12 and 24 months (P=0.0001, 0.0002) compared with baseline (Table 3, Figure 3c). The change trend of DLCO% Pred was similar to FVC% Pred, and the XFZYD group was markedly higher than the WLL group at the same time point (Table 3, Figure 3d).

Serum markers

There was no significant difference in LDH level between the WLL group and the XFZYD group, which was 366.67 ± 29.68 U/L and 369.33 ± 25.70 U/L, respectively. The LDH was significantly lower than the baseline during follow-up in the WLL group and XFZYD group (Table 3, Figure 4a). Tumor markers were also included in the comparison of the two groups. The results indicated that CEA and NSE was significantly decreased in WLL groups during the 24 months (P<0.0001), and the XFZYD group was markedly better than the WLL group (Table 3, Figure 4b, 4c).

The content of ALT and AST and serum lipids

The ALT, AST and serum lipids were monitored to evaluate the side effects of XFZYD and the results of ALT or AST were shown in Table 3 and Figure 4d, 4e. The results showed that there was no increase in ALT or AST in patients in the both groups. In our previous study, we found that patients with PAP have elevated blood lipids by the statin therapy. The serum Total Cholesterol (TC) of the WLL group and the XFZYD group were increased to 5.85 ± 0.50 mmol/L and 5.99 ± 0.60 mmol/L in the level of baseline, respectively.

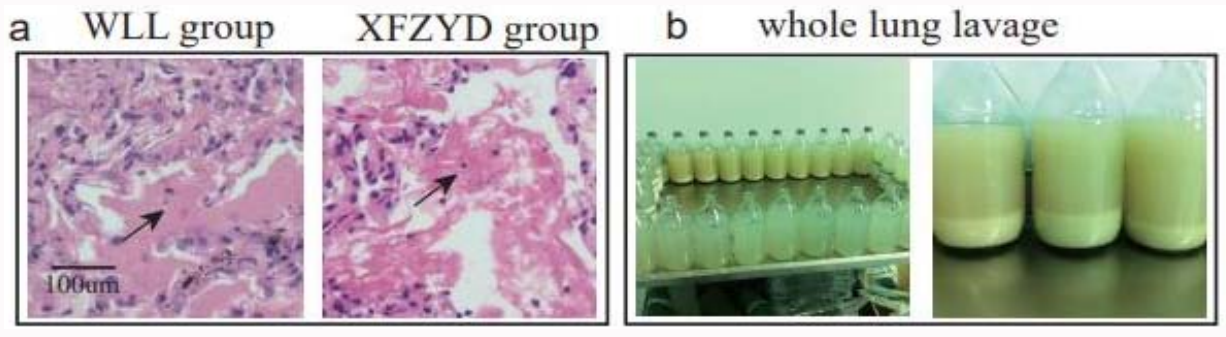

Figure 1: (a) The alveolar space was filled with lipoprotein rich material (as shown by the arrow), bar 100 μm (200x); (b) Milk like liquid was drained out during whole lung lavage.

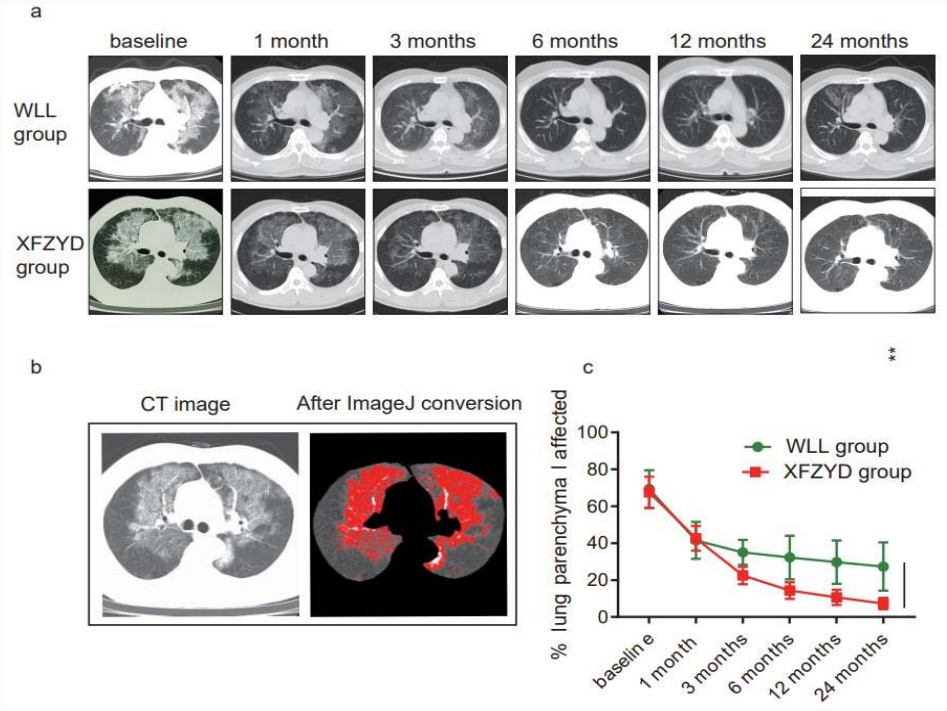

Figure 2: (a) CT showed diffuse ground-glass opacity and interlobular septal thickening in the WLL group and XFZYD group, and they relieved gradually with time after therapy, (b) Using image J software to estimate the percentage of affected lung parenchyma, (c) Percentage of lung involvement during follow-up in the WLL group and XFZYD group.

Table 1: The prescription of aPAP patients in XFZYD group.

		Dosage (g)	PT1	PT2	PT3	PT4	PT5	PT6
Xuefu Zhuyu Decoction	*Prunus persica* (L.) Batsch (Taoren)	12		√	√	√	√	√
	Angelicae sinensis (Oliv.) Diels (Danggui)	20	√	√	√	√	√	√
	Ligusticumi chuanxiong Hort. (Chuanxiong)	12		√	√	√	√	√
	Carthamus tinctorius L. (Honghua)	12	√	√	√	√	√	√
	Paeonia lactiflora Pall. (Chishao)	12	√		√	√	√	√
	Rehmannia glutinosa Libosch. (Dihuang)	15	√	√	√	√	√	√
	Citrus aurantium L. (Zhiqiao)	12		√	√	√	√	√
	Bupleurum chinense DC. (Chaihu)	12	√	√	√	√	√	√
	Platycodon grandiflorum (Jacq.) A. DC. (Jiegeng)	12	√	√	√		√	√
	Achyranthes bidentata Bl. (Niuxi)	15	√	√	√		√	√
	Glycyrrhiza uralensis Fisch. (Gancao)	6	√	√	√	√	√	√
Combined Chinese Herbal Medicine	*Astragalus membranaceus* (Fisch.) Bge.(Huangqi)	20	√	√	√	√	√	√
	Hirudo nipponica Whitman. (Shuizhi)	12	√	√	√	√	√	√
	Ophiopogon japonicus (L.f) Ker-Gawl. (Maidong)	12	√	√		√		
	Schisandra chinensis (Turcz.) Baill.(Wuweizi)	12	√	√		√		
	Adenophora tetraphylla (Thunb.) Fisch. (Shashen)	12	√	√				
	Atractylodes lancea (Thunb.) DC. (Cangzhu)	15			√	√	√	
	Houttuynia cordata Thunb. (Yuxingcao)	15			√	√	√	√
	Fritillaria thunbergii Mig. (Zhebei)	12	√			√		√
	Atractylodes macrocephala Koidz. (Baizhu)	20	√					
	Scutellaria baicalensis Georgi (Huangqin)	12	√		√			

Abbreviation: PT: Patient

In the WLL group, serum TC was lower than baseline at 1, 3, 6, and 24 months, while the serum TC of the XFZYD group was significantly lower than that of the WLL group after 3 months (Table 3, Figure 5a). After WLL or drug treatment, serum TG was significantly reduced, but the difference between the two groups was not significant (Table 3, Figure 5b). The concentration of High-Density Lipoprotein

Table 2: Clinical characteristics.

Characteristic	WLL group	XFZYD group	P
Gender▽			
Male	4	5	>0.9999
Female	2	1	
Average age (years)△	46.8 ± 8.10	44.6 ± 6.50	0.632
Course of disease (months)△	6.2 ± 3.11	5.6 ± 4.18	0.9338
DSS◇			
Grade 3	1	1	0.7881
Grade 4	4	3	
Grade 5	1	2	
Smoking history▽	2	1	>0.9999
Dust exposure history▽	1	1	>0.9999

▽data was analyzed by Fisher's exact test
△data was analyzed by t test
◇data was analyzed by Chi-square test

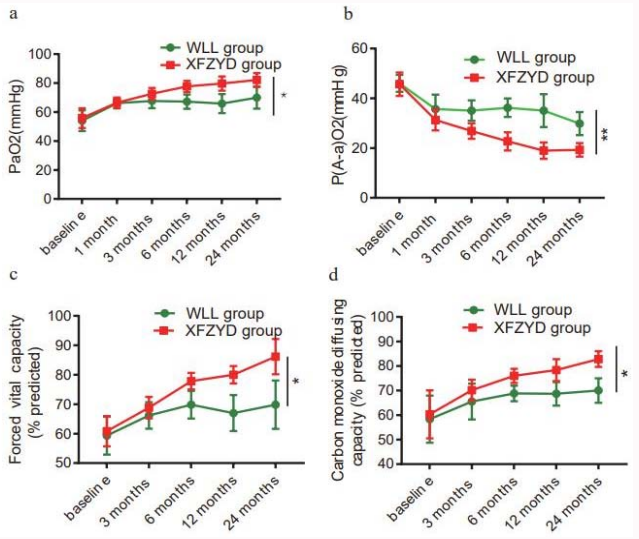

Figure 3: (a) PaO_2 was gradually increased in XFZYD group and it was much better than that of the WLL group, (b) P(A–a) O_2 had a marked decrease in the XFZYD group, (c) FVC was elevated gradually in the XFZYD group since the third months, it was much higher than the WLL group, (d) The change of DLCO in XFZYD was similar to that of FVC.

Cholesterol (HDL-C) was significantly increased during the whole treatment compared with the baseline level. After treatment for 3 months, the High-Density Lipoprotein Cholesterol (HDL-C) in the XFZYD group was higher than the WLL group (Table 3, Figure 5c), but there was no difference between the two groups regarding the LDL-C concentration (Table 3, Figure 5c).

Discussion

The Whole Lung Lavage (WLL) has always been considered the standard of treatment of PAP over the past decades, but it also has many adverse reactions such as infection, maturation, pleural cavity, pleural effusion, hypoxic discharge and even death [14]. Recently, Ilaria Campo completed a global survey of pearl total lung lavage and found that among approximately 368 PAP patients, PAP patients received 2.5 ± 1.5 WLL surgeries within five years, of which 10% required more than 5 surgeries [14]. In our study, 2 of 6 patients received the second full course of lavage at the 8 and 12 months because of the worsening course. But the patients in XFZYD group

Table 3: Comparison of clinical indexes between the two groups.

Type	Time		Group		Time * Group	
	F	P	F	P	F	P
Affected lung (%)	136.63	0	18.28	0.008	6.49	0.001
PaO_2	57.92	0	7.64	0.04	4.08	0.008
P(A-a)O_2	63.34	0	131.81	0	4.35	0.005
FVC	9.61	0.008	12.51	0.017	23.64	0
DLCO	52.25	0	7.29	0.043	2.79	0.054
LDH	53.91	0	114.7	0	8.42	0.006
NSE	127.01	0	48.3	0.001	1.31	0.299
CEA	130.79	0	22.89	0.005	3.76	0.019
ALT	1.87	0.155	0.21	0.663	1.92	0.147
AST	1.46	0.25	0.12	0.743	0.5	0.737
TC	58.02	0	43.38	0.001	7.18	0.014
TG	61.42	0	2.586	0.169	0.9	0.497
HDL	21.52	0	14.447	0.013	3.55	0.015
LDL	3.6	0.014	2.664	0.164	2.36	0.07

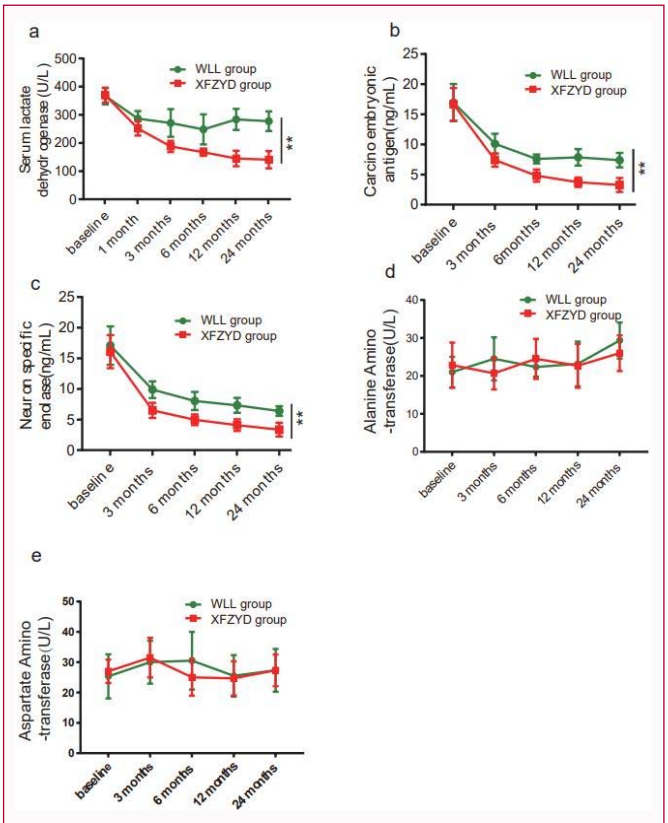

Figure 4: In the WLL group and XFZYD group, (a) LDH, (b) CEA and (c) NSE were all decreased during follow up, especially in XFZYD group. (d) ALT and (e) AST remained in normal range after medication.

showed good symptoms. In general, the level of P(A-a)O_2 decreasing at least 10 mmHg was defined that the treatment would be clinically effective [15]. In this study, the level of P(A-a)O_2 in the WLL group decreased 16.15 mmHg, while P(A-a)O_2 was decreased 26.36 mmHg in the XFZYD group. Interestingly, P(A-a)O_2 in the XFZYD group eventually returned to normal levels. Similarly, PaO_2, FVC% Pred and DLCO% Pred in the XFZYD group were tightly higher than that in the WLL group. In this study, we also used Image J software to estimate the effectiveness of the lungs and found that the XFZYD group is also

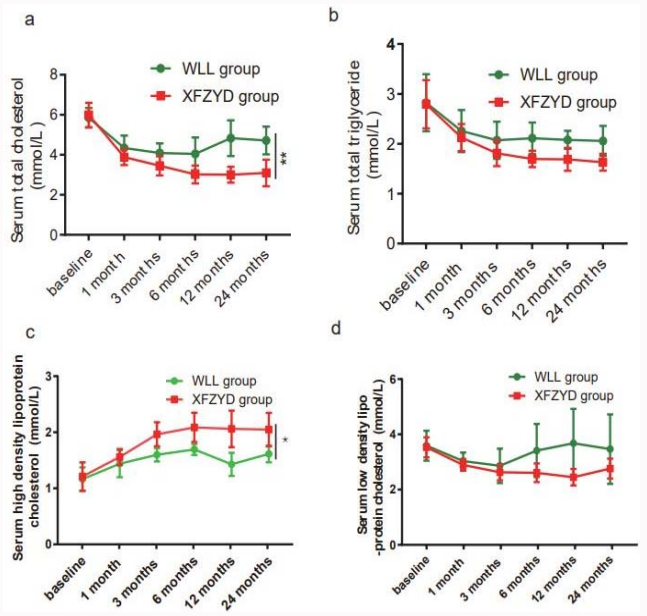

Figure 5: (a) Serum TC was decreased significantly in the XFZYD group, (b) TG and (c) (LDL-C) There was no difference in TG and LDL-C level between the two groups, (d) HDL-C was elevated after therapy in XFZYD group.

more useful than the WLL group. All these data verify that XFZYD is more effective than WLL in the treatment of aPAP. LDH is a specific-marker for the evaluation of the PAP severity. According to previous reports, elevated LDH levels are associated with P(A-a)O_2, DLCO% Pred and FVC% Pred [16,17]. In our study, the LDH concentration dropped significantly after WLL operation and had continuously maintained at a low level for 24 months. Study showed that CEA is negatively correlated with DLCO% Pred [18,19]. Our study also measured the changing concentrations of CEA and NSE; the results indicated that both of CEA and NSF were apparently decreased after WLL or XFZYD treatment. In addition, the reduction of CEA and NSE in the XFZYD group was more pronounced than that in the WLL group from the third month. Therefore, we concluded that the XFZYD group can eliminate markers, including tumor markers and LDH, better than the WLL group. Study showed that the free cholesterol in fluid of bronchoalveolar lavage of aPAP would increase about 60-fold and cholesterol esters also improve 24-fold [2]. It is generally believed that the change of cholesterol is connected to the HDL-C concentration in blood [6]. According to our present study, the XFZYD could reduce cholesterol levels (especially TC), which could act the same treatment effect with the baking simvastatin [9]. Corresponding, the level of HDL had increased significantly, which was the product of cholesterol decomposition. Therefore, we assumed that XFZYD could improve the therapeutic effect by promoting the degradation of alveolar cholesterol into HDL. Bedsides, other biochemical indexes including ALT level and AST level would maintain at a normal level, suggesting XFZYD with the favorable bio safety. In summary, XFZYD might be an effective strategy for the treatment of aPAP patients based on existing clinical data. But it requires more samples and more detailed pathological studies to explain the possible mechanism of XFZYD that was involved in this recovery process.

Acknowledgement

We really thank Dr. Zengguang Li form the Traditional Chinese Medicine Clinic of Pingdu People's Hospital for helping us treat PAP patients.

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