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Original Article

The efficacy of Qi-Wei-Bai-Zhu-San as an adjuvant therapy for treating senile, community-acquired pneumonia with lung-spleen Qi deficiency syndrome and the effect of this medicine on the Th17/Treg levels in patients' peripheral blood

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Abstract: Objective: We aimed to investigate the clinical efficacy of Qi-Wei-Bai-Zhu-San (QWBZS) in treating senile community-acquired pneumonia (CAP) with lung-spleen Qi deficiency syndrome. Methods: Sixty patients with senile CAP due to lung-spleen Qi deficiency were randomized to a study group and a control group of 30 patients each. The patients in the control group received conventional treatment (antibiotic therapy and symptomatic treatment), while the patients in the study group took QWBZS orally as an adjuvant therapy in addition to the conventional treatment. After one week, the treatment effect and levels of immunity markers were compared between the two groups. Results: Compared with the control group, the study group had a higher total effective rate and more significant improvement in pulmonary function and arterial blood gas marker and serum inflammatory factor levels (all $P<0.05$). Also, the study group had a higher percentage of Treg cells in their peripheral blood mononuclear cells (PBMC) and a lower percentage of Th17 cells in their PBMC and Th17/Treg values (all $P<0.05$). Conclusion: QWBZS can significantly improve the clinical outcome in treating senile CAP with lung-spleen Qi deficiency syndrome, lower the Th17/Treg ratio in the peripheral blood, and improve the serum inflammatory marker levels.

Keywords: Senile pneumonia with lung-spleen Qi deficiency syndrome, Qi-Wei-Bai-Zhu-San, inflammatory factors, Th17 cells, Treg cells, Th17/Treg

Introduction

Community-acquired pneumonia (CAP) is a respiratory infection contracted outside of the healthcare system, and patients with severe CAP can have a high mortality rate [1, 2]. In China, the incidence of this disease is high [3]. Some studies have reported an average medical cost of 16,000 RMB per person each year for CAP patients in China; and in the USA, about 5.6 million people are affected by CAP every year, which incurs a medical expense of around 10 billion US dollars [4, 5]. Since elderly people have weaker immunity and tolerance to diseases, they are the major population to suffer from this disease [6, 7]. Therefore, research on how to improve the clinical outcome in treating senile CAP has become an essential topic in world public health.

In Western medicine, antibiotic therapy and symptomatic treatment are common ways of treating CAP. However, drug resistance is likely to occur when antibiotics are administered for a long period of time, and the treatment can be even harder in elderly patients due to their weakened body functions [8]. According to the traditional Chinese medicine (TCM), CAP belongs to the category of "cough", and lung-spleen Qi deficiency syndrome is most commonly found in CAP, with the major symptoms including loss of appetite, slight wheezing, copious thin phlegm, and persistent cough [9, 10]. Qi-Wei-Bai-Zhu-San (QWBZS) is an herbal prescription which was first introduced for the treatment of gastrointestinal diseases [11]. It has been found that the application of this medicine with formula modification based on pattern differentiation can also alleviate lung-

spleen Qi deficiency, but the effectiveness of QWBZS for treating CAP remains unclear.

In this study, we innovatively used QWBZS with formula modification based on pattern differentiation in addition to Western medicine and compared the efficacy of this method with that of the conventional method in order to validate the effectiveness and safety of this TCM in treating senile CAP with lung-spleen Qi deficiency syndrome.

Materials and methods

Baseline data

A total of 60 elderly patients treated in Beijing Luhe Hospital, Capital Medical University between January 2019 and October 2019 for CAP of lung-spleen Qi deficiency were selected as subjects. The study was approved by the Ethics Committee of Beijing Luhe Hospital, Capital Medical University, and informed consent was obtained from the patients and their families.

Inclusion criteria: 1) Patients who met the diagnostic criteria of Western medicine as defined in *Guidelines for the diagnosis and treatment of community-acquired pneumonia* and the diagnostic criteria of TCM as defined in *Guidelines for TCM diagnosis and treatment of community-acquired pneumonia, 2011 edition* [12, 13]; 2) Patients aged no less than 60 years according to the latest WHO definition of elderly people; 3) Patients who were willing to take part in this study and who signed the informed consent.

Exclusion criteria: 1) Patients who had other respiratory diseases that would affect the results of the study; 2) Patients with severe dysfunction in their parenchymal organs such as the liver and kidneys; 3) Patients with severe systemic diseases; 4) Patients who had mental illness and could not cooperate with the treatment; 5) Patients who had received treatment for CAP before; 6) Patients who needed to take other medicine for treating CAP.

Sixty patients were enrolled in this study (male 39, female 21, age range 60-68 years) and who were randomly assigned to a study group or a control group (both n=30).

Treatment methods

After their hospital admission, both groups received chest X-rays and biochemical blood tests. Blood cultures drawn from two different sites were carried out to detect the pathogens, and the treatment began when the pathogen was still being identified. Antibiotics were given to the patients within 8 hours after hospital admission, and other measures were taken based on the patients' symptoms for intervention. The patients received intravenous infusions of moxifloxacin (400 mg) for 3 days and oral administrations of moxifloxacin (400 mg) once a day. Apart from this, the patients in the control group received no other treatment, but the patients in the study group also took QWBZS orally. The medicine was prepared by immersing the solution in cold water for 30 min, boiling it on high-heat, and then heating it on low-heat for about 20 min. Afterward, the medicine was divided into two portions for the patients to take twice a day (morning and evening). The major ingredients in QWBZS are *Atractylodes macrocephala* (10 g), *Codonopsis pilosula* (5 g), licorice (5 g), *Poria cocos* (12 g), *Agastache rugosa* (12 g), *Radix aucklandiae* (5 g), and *Pueraria lobata* (12 g), with white hyacinth bean (10 g), Chinese yam (10 g), coix seeds (10 g), *Platycodon grandiflorum* (10 g), orange peel (8 g), lotus seeds (5 g), and bitter almond (5 g) served as minor ingredients. Moreover, 5 g of coltsfoot flower, radix aucklandiae, roasted malt, and ginger were added, respectively, to the prescription of QWBZS if the patients presented noticeable symptoms of coughing, abdominal distension, loss of appetite, or cold and heat syndrome. One week after the treatment, the treatment effects in the patients were evaluated, and the serum inflammatory factor, Th17/Treg, arterial blood gas (ABG) marker, and pulmonary function marker levels were examined in the two groups.

Outcome measures

Treatment effect: The patients were considered to be healed if their symptoms disappeared completely and the results of their biochemical blood tests and x-rays became normal; the patients were considered to have an effective treatment if they experienced evident improvements in their symptoms and results of the biochemical blood tests and x-rays; the patients were considered to have an ineffect-

Table 1. Baseline data in the two groups

Item	Study group (n=30)	Control group (n=30)	χ^2/t	P
Age (years)	68.25±6.75	67.51±6.57	0.430	0.669
Gender (male/female, n)	19/11	20/10	0.073	0.787
BMI (kg/m^2)	22.38±3.27	22.04±3.87	0.368	0.715
Time interval from onset to treatment (d)	5.32±2.36	5.03±2.57	0.455	0.651
Complication (n)				
High blood pressure	10	11	0.387	0.466
Hyperlipidemia	4	2		
Diabetes	8	5		
Others	1	3		
None	7	9		

Note: BMI, body mass index.

ive treatment if there were no significant improvements in their symptoms or the levels of the relevant markers. The calculation of the total effective rate was as follows: total effective rate = (number of cases healed + number of cases that had an effective treatment)/total number of cases * 100% [14].

Clinical signs: The time courses of the disappearances of cough, fever, and rale were measured to evaluate the improvements in the patients' clinical signs [15].

The serum inflammatory factor levels: ELISA was performed to quantify the content of serum interleukin (IL)-6, tumor necrosis factor (TNF)-α, procalcitonin (PCT), and IL-17 using a multimode microplate reader (Varioskan LUX, Thermo Fisher Scientific, USA, kit for IL-6: K4143-100, Biovision, USA; kit for TNF-α: 58-9201-96, Cayman, USA; kit for PCT: H00058-488-AP11, Abnova, Taiwan; kit for IL-17: K47-40-100, Biovision, USA). The serum C-reactive protein (CRP) level was measured using transmission turbidimetry (7180 automated biochemical analyzer, Hitachi, Japan) [16-18].

The levels of Th17, Treg, and Th17/Treg in the peripheral blood: Flow cytometry was performed to examine the percentages of Th17 and Treg cells in the peripheral blood mononuclear cells (PBMC) and to calculate the ratio of Th17/Treg in the two groups [19].

ABG markers: The pH, partial pressure of oxygen (PaO_2), and partial pressure of carbon dioxide ($PaCO_2$) values in the arterial blood were measured with a blood gas analyzer (ABL90 FLEX, Leidumit Medical Equipment, Denmark) [14, 16].

Pulmonary function: The forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and FEV1/FVC were measured with a spirometer (Spirolab III, MIR, Beijing, China) [14-16].

Statistical analysis

SPSS 24.0 (SPSS Inc, Chicago, IL, USA) was used for the statistical analysis. Count data are presented as n, % and examined using χ^2 tests; measurement data are presented as the mean ± standard deviation. Independent samples t-tests were conducted for the comparisons between groups, and paired samples t-tests were used for the comparisons between pre- and post-treatment within a group. The two-tailed tests were performed with a 0.05 significance level.

Results

Baseline data

There were no intergroup differences in the baseline data (all P>0.05, **Table 1**).

QWBZS improved effectiveness

The total effective rate was much higher in the study group than in the control group (96.67% vs. 76.67%, P=0.023, χ^2=5.192, **Table 2**).

QWBZS reduced the time course of the symptom disappearance

The time course of the disappearance of cough, fever, and rale was shorter in the study group than in the control group (6.57±0.93 vs. 7.23±1.14, 2.60±0.71 vs. 3.10±0.89, 4.87±0.72 vs. 5.48±0.97, all P<0.05, **Figure 1**).

Table 2. The total effective rate in the two groups (n, %)

Treatment effect	Study group (n=30)	Control group (n=30)	χ^2	P
Healed	7	18	3.227	0.041
Effective	16	11		
Ineffective	7	1		
Total effective rate	76.67%	96.67%	5.192	0.023

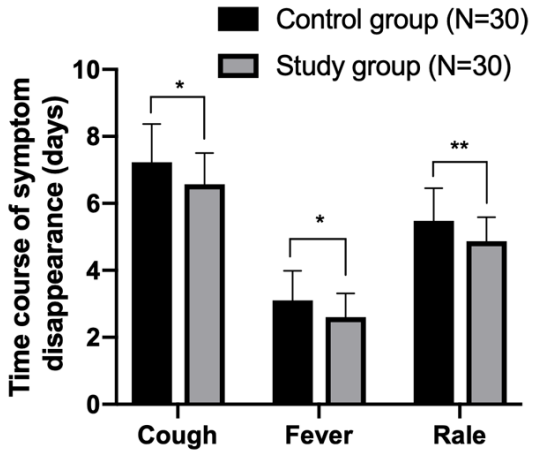

Figure 1. Time course of the symptom disappearance in the two groups. *P<0.05, **P<0.01.

QWBZS improved the serum inflammatory factor levels

After treatment, the level of serum IL-10 increased and the levels of serum IL-6, IL-17, TNF-α, PCT, and CRP were reduced in both groups (all P<0.01). Compared with the control group, the study group had a higher level of IL-10 and lower levels of IL-6, IL-17, TNF-α, PCT, and CRP after the treatment (all P<0.05, **Table 3**).

QWBZS improved the Th17/Treg levels in the peripheral blood

After treatment, the percentage of Th17 in the PBMC and TH17/Treg values decreased and the percentage of Treg in the PBMC increased in both groups (all P<0.001). Compared with the control group, the study group had a lower percentage of Th17 in the PBMC and the Th17/Treg values and a higher percentage of Treg in the PBMC (all P<0.05, **Table 4**).

QWBZS improved the levels of the ABG markers

There were no intergroup differences in the levels of the ABG markers (pH, PaO_2, and $PaCO_2$) before the treatment (all P> 0.05). After the treatment, both groups experienced increased pH values and PaO_2 levels and a reduced level of $PaCO_2$ (all P<0.001), but the study group had higher pH values and PaO_2 levels and a lower level of $PaCO_2$ than the control group (all P<0.05, **Table 5**).

QWBZS improved pulmonary function

There were no intergroup differences in the FEV1, FVC, and FEV1/FVC levels before the treatment (all P>0.05). After the treatment, the levels of these markers increased in both groups (all P<0.001), but the study group had a higher magnitude of increase in these levels than the control group (all P<0.05, **Table 6**).

Discussion

TCM and Western medicine have different interpretations of the mechanisms of CAP based on their unique theoretical systems. In Western medicine, CAP is believed to be a respiratory infection caused by bacteria, including *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus*, and the patients are treated with antibiotic and symptomatic therapies [1, 3]. According to Western medicine, the reason elderly people are more susceptible to CAP is that their lung elasticity, their physical defenses against bacteria in the respiratory tract, and their body function and immunity are weakened. However, drug resistance caused by the irrational use of antibiotics makes the treatment difficult. In TCM, the main causes of CAP is believed to be chronic cough and asthma and lung deficiency involving the spleen, but some CAP can also be induced by fatigue impairing the spleen and spleen disease involving the lungs [9, 10, 20]. According to TCM, the susceptibility to CAP in elderly people is due to fluid retention causing dampness and encumbrance of spleen Qi, chronic cough, and lung deficiency causing the lungs' failure to disperse and descend, and Qi deficiency and the lungs failing to distribute fluid causing dampness retention and sputum. As medical science advances worldwide, the integration of TCM and Western medicine has been more and more recognized and become a new trend in clinical treatment.

In our study, the seven major components in QWBZS were *Atractylodes macrocephala*, *Codonopsis pilosula*, licorice, *Poria cocos*, *Agas-*

Table 3. The serum inflammatory factor levels in the two groups ($\bar{x}$ ± sd)

Inflammatory factor	Control group (n=30)		Study group (n=30)	
	Before treatment	After treatment	Before treatment	After treatment
IL-6 (ng/L)	67.52±9.53	35.72±7.26***	68.33±9.88	26.37±6.58***,#
IL-10 (ng/L)	6.85±1.37	10.30±1.63***	6.71±1.39	14.57±1.98***,#
IL-17 (ng/L)	21.59±4.67	15.07±3.89***	22.46±4.86	10.76±3.99***,#
TNF-α (ng/L)	80.78±12.37	49.28±10.58***	81.25±11.46	40.39±8.98***,#
PCT (μg/L)	1.77±0.68	0.71±0.28***	1.84±0.70	0.46±0.21***,#
CRP (mg/L)	66.48±10.77	17.22±2.88***	67.03±10.85	12.49±1.93***,#

Note: ***P<0.001 vs. before the treatment; #P<0.05 vs. the control group; IL, interleukin; TNF, tumor necrosis factor; PCT, procalcitonin; CRP, C-reactive protein.

Table 4. Percentages of the Th17 and Treg cells in the PBMC in the two groups ($\bar{x}$ ± sd, %)

Item	Control group (n=30)		Study group (n=30)	
	Before treatment	After treatment	Before treatment	After treatment
Th17	1.53±0.41	1.17±0.39***	1.58±0.43	0.93±0.31***,#
Treg	2.76±0.47	3.05±0.57***	2.71±0.53	3.33±0.62***,#
Th17/Treg	0.55±0.15	0.38±0.11***	0.58±0.17	0.30±0.08***,#

Note: ***P<0.001 vs. before the treatment; #P<0.05 vs. the control group; PBMC, peripheral blood mononuclear cell.

Table 5. The ABG marker levels in the two groups ($\bar{x}$ ± sd)

ABG marker	Control group (n=30)		Study group (n=30)	
	Before treatment	After treatment	Before treatment	After treatment
pH	7.03±0.15	7.31±0.21***	7.05±0.13	7.44±0.23***,#
PaO_2 (mmHg)	57.65±10.23	75.43±13.65***	58.32±9.75	84.89±13.27***,#
$PaCO_2$ (mmHg)	59.33±6.25	47.42±7.30***	60.26±6.17	42.14±6.76***,#

Note: ***P<0.001 vs. before the treatment; #P<0.05 vs. the control group; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide.

Table 6. Pulmonary function in the two groups ($\bar{x}$ ± sd)

Pulmonary function	Control group (n=30)		Study group (n=30)	
	Before treatment	After treatment	Before treatment	After treatment
FEV1 (L)	1.23±0.28	1.51±0.22***	1.31±0.26	1.84±0.31***,#
FVC (L)	2.03±0.35	2.28±0.35***	2.06±0.37	2.52±0.43***,#
FEV1/FVC (%)	58.86±6.49	64.39±6.37***	59.62±8.87	70.62±7.26***,#

Note: ***P<0.001 vs. before the treatment; #P<0.05 vs. the control group.

tache rugosa, *Radix aucklandiae*, and *Pueraria lobata*. The first four ingredients, also known as "decoction of four noble drugs", serve to improve spleen function, and the last three ingredients serve to modulate spleen and lung function. In this prescription, *Atractylodes macrocephala* served as the monarch drug, which mainly alleviates the spleen deficiency and enhances the lung function; *Codonopsis pilosula* and licorice served as the minister drugs, which had a similar function to *Atractylodes macrocephala* and served to assist the monarch drug to enhance the efficacy; *Poria cocos*, *Agastache rugosa*, and *Radix aucklandiae* served as the adjuvant drugs, which worked to reduce the adverse effects of the medicine; *Pueraria lobata* worked to harmonize the ingredients in the prescription and promote the function of the monarch, minister, and adjuvant drugs.

According to the studies by Wang et al. on the active ingredients of *Atractylodes macrocephala*, it was found that *atractylenolide* I is the main component in this herb which plays a crucial role in immunoregulation and antiinflammation [11, 21]. Gao et al. analyzed the *Poria cocos* extracts and found pachymaran to be its major ingredient. It can exert a good antimicrobial effect and increase the benificial flora in the intestines [22, 23]. Zhang et al. reported that *Codonopsis pilosula* can adjust the blood glucose level and enhance immunity in the body [24]. However, the clinical application of QWBZS and its medical value in treating senile CAP remained unclear.

In the present study, we designed a randomized controlled trial and investigated the efficacy of the combined use of Western medicine and QWBZS in treating senile CAP with lung-spleen Qi deficiency syndrome. Compared with Western medicine alone, the patients who received both Western medicine and QWBZS experienced a higher effective rate and shorter time course of the disappearance of cough, fever, and rale. To further explore the reason behind this result, we compared the levels of the relevant markers in the two groups and found that patients who received the combination of Western medicine and QWBZS displayed more improvement in their pulmonary function and ABG marker levels than the control group, which is similar to the results of the study by Handley et al. [25]. However, compared to the glucocorticoid used by Handley et al. in their studies as adjuvant therapy, QWBZS as a Chinese herb prescription produces fewer side effects in the human body [25]. Moreover, we also compared the serum inflammatory factors and the percentage of Th17 and Treg in the PBMC between the two groups and found that the combined use of Western medicine and QWBZS could alleviate inflammation more significantly, which may have a direct impact on the recovery of pulmonary function and symptom disappearance. Th17 is a typical member of the subgroup of T lymphocytes with pro-inflammatory properties, and its major effectors are IL-17 and IL-6, which can promote Th17 cell differentiation synergistically [26]. Thus, a decrease in the percentage of Th17 in PBMC can be associated with a reduction in the IL-17 and IL-6 levels. Treg cells are a subgroup of T lymphocytes which exert the opposite effect of Th17, as its main property is anti-inflammation, with IL-10 working as one of its major effectors [27]. The increases in the percentage of Treg in the PBMC and the serum IL-10 level can indicate an enhancement in the anti-inflammatory effect. In our study, the use of QWBZS as an adjuvant therapy significantly lowered the percentage of Th17 in the PBMC as well as the IL-17 and IL-6 levels and elevated the percentage of Treg in the PBMC and the IL-10 level, suggesting that the combined use of Western medicine and QWBZS could increase the anti-inflammatory effect in patients. Some studies have demonstrated that the imbalance between Th17 and the Treg levels is significantly associated with the occurrence and progression of lung diseases, and the results of our studies suggest that QWBZS can effectively improve this balance in senile CAP patients [19]. This may be because *Atractylodes macrocephala*, *Codonopsis pilosula*, and *Poria cocos* from QWBZS have anti-inflammatory and immunomodulatory effects and pachymaran, a *Poria cocos* extract, can inhibit the growth of gram-negative and positive bacteria, further promoting the recovery of the immune function in the body.

In conclusion, QWBZS can markedly improve clinical outcomes in the treatment of senile CAP with lung-spleen Qi deficiency syndrome, which may be due to the medicine's ability to improve pulmonary function, serum inflammatory factor levels, and the immune function in patients. However, since the QWBZS prescription was applied with a formula modification based on pattern differentiation for each individual, it will be necessary for clinicians to take into account the patients' actual conditions in clinical practice when referencing our report. Meanwhile, the sample size in our study was small, so more studies with a larger sample size need to be carried out in the future for verification.

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Disclosure of conflict of interest

None.

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