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Effect of *Qingfei Huatan Huoxue Decoction* combined with azithromycin on pulmonary function and inflammatory factors in children with *Mycoplasma pneumonia*

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Abstract: To investigate the effect of *Qingfei Huatan Huoxue Decoction* combined with azithromycin on pulmonary function and inflammatory factors in children with *Mycoplasma pneumonia.* A total of 155 children with *Mycoplasma pneumonia* of toxic heat blocking lung syndrome were randomly divided into the control group (n=77) and the observation group (n=78) from March 2020 to March 2021. Both groups of children were given conventional treatment and azithromycin intravenous drip and the observation group was additionally given oral administration of *Qingfei Huatan Huoxue Decoction*, with 7 days as a course of treatment totaling 2 courses. The lung function, inflammatory factor level, immune function and coagulation function were compared between the two groups before and after treatment. After treatment, the symptom integral of fever, cough and pulmonary wet rales in the two groups were reduced, while FEV1, PEF and FEV1/ FVC were significantly increased, serum TNF-α, IFN-γ and IL-6 were significantly reduced, the levels of Immunoglobulin M (IgM), IgG and IgA were significantly reduced and plasma PT and APTT were significantly reduced, with more significant changes observed in the observation group (all $P<0.05$). The disappearance time of fever, cough and pulmonary moist rales in the observation group was significantly shorter than that in the control group ($P<0.05$). The recovery rate of the observation group was significantly higher than that of the control group ($P<0.05$). *Qingfei Huatan Huoxue Decoction* combined with azithromycin exhibit a promising efficacy in the treatment of *Mycoplasma pneumonia* in children.

Keywords: *Mycoplasma pneumonia,* children, Qingfei Huatan Huoxue recipe, azithromycin, lung function, inflammatory factors.

INTRODUCTION

Mycoplasma pneumonia is the pathogen of human *Mycoplasma pneumonia*. The pathological changes in *Mycoplasma pneumonia* are mainly interstitial pneumonia accompanied by bronchopneumonia in some cases, which is called primary atypical pneumonia (Kumar *et al.*, 2019; Tsai *et al.*, 2021). The main infection is through droplets, with an incubation period of 2 to 3 weeks and mild or rather hidden clinical symptoms. Its symptoms resemble general respiratory symptoms such as headache, sore throat, fever, and cough; however, deaths have also been reported (He *et al.*, 2016; Kumar, 2018). Its onset is mainly concentrated in autumn and winter. *Mycoplasma pneumonia* is a common pathogen that causes pneumonia in children (Krafft and Christy, 2020). Azithromycin is the preferred macrolide antibiotic for the treatment of *Mycoplasma pneumonia* in children (Qiu *et al.*, 2020). Nonetheless, its efficacy is undermined by its slow onset of action and increased drug resistance (Alishlash *et al.*, 2019). Traditional Chinese medicine (TCM) syndrome differentiation believes that pneumonia belongs to the category of febrile fever, and its pathogenesis is mainly phlegm-heat obstruction and lung-qi stagnation (Sun *et al.*, 2020). The syndrome of toxic heat blocking the lung is one of the main syndromes of *Mycoplasma pneumonia*, and three methods of "clearing, releasing and reducing" are mainly adopted in TCM for treatment (Lee *et al.*, 2021). Moreover, TCM proposes that blood stasis persists during pulmonary infection (Fan *et al.*, 2020). Recent research has shown that the use of drugs for blood circulation promotion and blood stasis removal contributes to facilitating the mitigation of *Mycoplasma pneumonia* inflammation and ameliorating blood coagulation function (He *et al.*, 2020). *Qingfei Huatan Huoxue Decoction* clears away heat and removes phlegm, promotes blood circulation and disperses blood stasis. It has been found that *Qingfei Huatan Decoction* combined with the blood circulation promotion and blood stasis removal treatment can significantly alleviate the level of serum inflammatory factors in patients with pneumonia and restore lung function (Xue and Da, 2021). Accordingly, this study evaluated the clinical effect of *Qingfei Huatan Huoxue Decoction* combined with azithromycin on the clinical symptoms, lung function, blood coagulation indicators, inflammation indicators, and immune indicators.

MATERIALS AND METHODS

Clinical data

A total of 155 children with *Mycoplasma pneumonia* who were hospitalized in the pediatric department of our hospital from March 2020 to March 2021 were identified

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as research subjects. Inclusion criteria: (1) Patients aged 3-16 years old; (2) Patients who met the diagnostic criteria of traditional Chinese and Western medicine (Rogozinski *et al.*, 2017) and the syndrome of TCM was toxic heat blocking the lung syndrome; (3) The children and their legal guardians signed informed consent. Exclusion criteria: (1) Patients with cardiovascular disease, nervous system disease, coagulation dysfunction, liver and kidney insufficiency, and malignant tumor; (2) Patients with other diseases affecting lung function; (3) Patients with relevant treatment before enrollment; (4) Patients with an allergic constitution, previous history of allergies or those who were allergic to the drugs used in this study; (5) Patients with use of drugs that affect the blood coagulation function in the past one month; (6) Patients with prior severe pneumonia that has not been cured. Elimination criteria: (1) Patients with serious adverse drug reactions and deterioration of the condition during treatment that are not suitable for follow-up trials; (2) The children and their legal guardians voluntarily withdrew from the trial. The children were assigned to the control group (n=77) and the observation group (n=78) by the random number table method. This study was conducted in strict accordance with the protocol of the medical ethics committee of our hospital. This paper was ethically approved by the ethics committee of Xi'an Children's Hospital (Approved No. of ethics committee: CLI2019-12-229).

Treatment methods

Both groups of children were given conventional treatment including anti-infection, antipyretic, oxygen inhalation, nebulization, and fluid rehydration. The control group was given azithromycin (Azithromycin Injection Company; SFDA approval number: H20040654) intravenously, 10mg/kg, once a day, and the treatment course spanned 5-7 days. In addition to the treatment given to the control group, the observation group was additionally given oral administration of *Qingfei Huatan Huoxue Decoction*. The component includes ephedra 4g, bitter almond 9g, roasted licorice 5g, raw plaster 30g and salvia 10g, Curcuma 6 g, Panzanosaurus 10g, red peony 10g and it was made into decoctions by the *Department of Traditional Chinese Medicine* of our hospital, 100mL/bag; 3 to 5 years old, 2/3 bags once, 2 times a day; >5 years old, 1 bag once, 2 times a day. A treatment course spanned 7 days and a total of 2 courses were given to all patients.

Observation indicators

(1) Baseline data: The sex, age, course of disease, and axillary temperature of the children were recorded upon enrollment. (2) Main TCM symptom integral: with reference to *Guiding Principles for Clinical Research of New Chinese Medicines,* symptom integral was established (Lian *et al.*, 2020; Sucher, 2013). 1) Fever: <37.4^{o}C is counted as 0 point, 37.4^{o}C ~38.0^{o}C as 2 points, 38.1℃~39.0^{o}C as 4 points, >39.0^{o}C as 6 points. 2) Cough: 0 points for no cough, 2 points for occasional cough, 4 points for intermittent cough that does not affect sleep, and 6 points for frequent coughing that affects sleep. 3) Lung wet rales: 0 points for clear breathing, 2 points for rough breathing, 4 points for occasional dry or wet rales, and 6 points for apparent dry or wet rales or weakened breath sounds. (3) Disappearance time of clinical symptoms: The disappearance time of fever, cough, and pulmonary rales in the two groups were recorded. (4) Pulmonary function: Before treatment and after treatment, the FEV1 and FVC and PEF were recorded, and the FEV1/FVC ratio was calculated. (5) Inflammatory factors: Before and after treatment, peripheral venous blood of children was collected and centrifuged to isolate the serum, and serum tumor necrosis factor-α (TNF-α), interferon -γ (IFN-γ) and interleukin-6 (IL-6) levels were determined using the ELISA kits. The kits were purchased from Jiangxi Aiboin Biotechnology Co., Ltd. (No. IB-E10269, IB-E10033, IB-E10049). (6) Immune function: the immunoturbidimetric method was used to determine the levels of immunoglobulin M (IgM), IgG, and IgA. The kits were purchased from Shanghai Yaji Biotechnology Co., Ltd. (No. E025), Beijing Biolab Technology Co., Ltd. Company (No. ARB14270), Beijing Biolab Technology Co., Ltd. (No. SNM258). (7) Blood coagulation function: the first-phase method was used to determine the plasma prothrombin time (PT), and the kit was purchased from Beijing Biolab Technology Co., Ltd. (No. GL1846). ELISA method was used to determine the activated partial thromboplastin time (APTT) and the kit was purchased from Jiangxi Aiboin Biotechnology Co., Ltd. (No. IB-E20817). (8) Efficacy: The treatment efficacy was graded as follows. If breathing is normal, X-rays show completely absorbed lung inflammation shadows, lung signs disappear and TCM symptom scores reduce by ≥90%, the treatment efficacy is considered cured. Markedly effective: If breathing is normal, X-rays show partially absorbed lung inflammation shadows, and TCM symptom scores reduce by 67% to 90%, the treatment efficacy is considered markedly effective. If respiratory frequency does not exceed the upper limit of normal value at peerage by 10 times per minute, and the main TCM symptom score reduces by 33% to 67%, the treatment efficacy is considered effective. If the main TCM symptom score reduces by less than 33%, the treatment efficacy is considered ineffective. The effective rate (%) = (cured + markedly effective) / total number of cases × 100%. (9) Adverse reactions: During the treatment period, the occurrence of nausea and vomiting, abdominal pain, flatulence, headache, and other adverse drug reactions of the two groups of children was recorded.

STATISTICAL ANALYSIS

All the data analysis was conducted by SPSS20.0 software. The measurement data conforming to the normal distribution were expressed as (x±s) and examined

using the independent sample *t*-test for inter-group comparison and the paired sample *t*-test for intra-group comparison. Counting data were expressed as frequency or composition ratio. The chi-square exact probability method was used for the analysis of the counting data when the total number of cases was less than 40 or the minimum theoretical frequency was less than 1. The chi-square correction method was used for the analysis of the counting data when the total number of cases was greater than or equal to 40 and the minimum theoretical frequency was 1 to 5. The chi-square non-correction method was used for the analysis of the counting data when the number of the total cases was greater than or equal to 40 and the minimum theoretical frequency was greater than 5. A *P* value less than 0.05 was considered statistically significant.

RESULTS

Baseline data

The two groups did not differ in terms of the baseline data including gender, age, course of disease, axillary temperature and other baseline data (P>0.05). See table 1.

Main TCM symptoms integral

There was no statistically significant difference in the scores of fever, cough, and pulmonary rales before treatment between the two groups (P>0.05). After treatment, the scores of fever, cough and pulmonary rales in the two groups were all significantly reduced as compared to those before treatment, with a greater decrease observed in the observation group (P<0.05, table 2).

Symptoms disappearance time

A significantly shorter disappearance time of fever, cough and pulmonary rales in the observation group than in the control group was observed (P<0.05, table 3).

Lung function

No significant difference was witnessed in FEV1, FEV1/FVC, and PEF between the two groups before treatment (P>0.05). After treatment, FEV1, FEV1/FVC, and PEF were significantly increased in the two groups, in which the increase in the observation group was more significant (P<0.05). See table 4.

Serum inflammatory factors

Before treatment, no significant difference in serum TNF-α, IFN-γ and IL-6 between the two groups was identified (P>0.05). After treatment, the serum TNF-α, IFN-γ and IL-6 of the two groups were all significantly decreased, with more substantial changes in the observation group (P<0.05), as displayed in fig. 1.

Immune function

The two groups had no significant difference in IgM, IgG, and IgA levels before treatment (P>0.05). The levels of IgM, IgG, and IgA in the two groups were significantly dropped after treatment, with a greater decrease in the observation group (P<0.05), as presented in table 5.

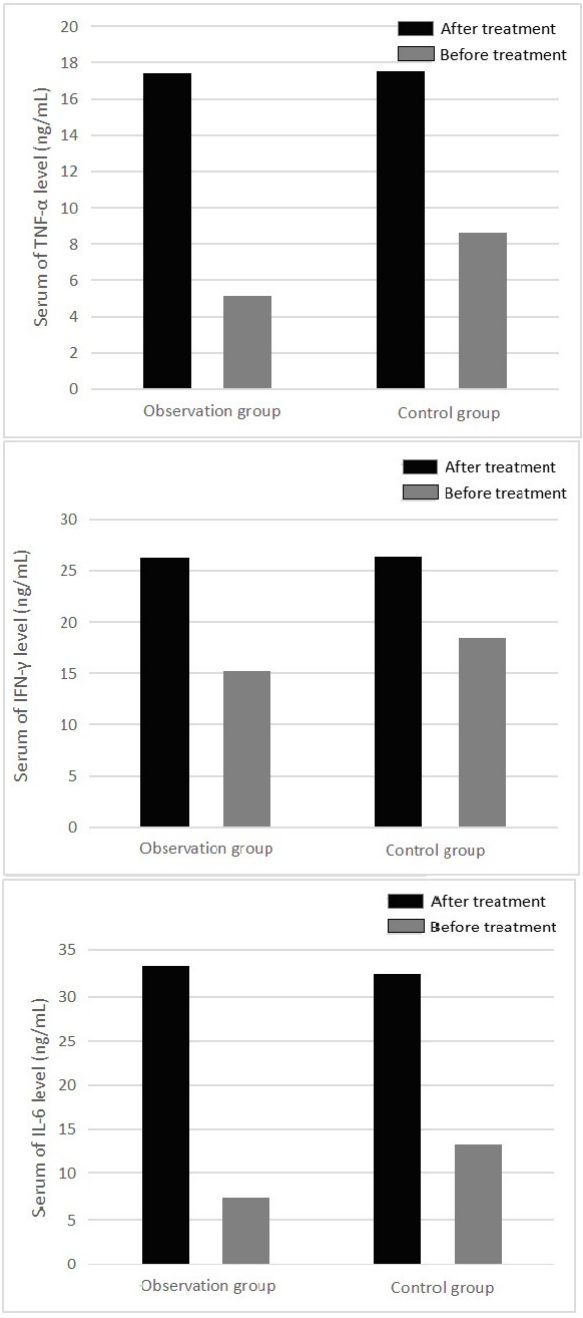

Fig. 1: Comparison of serum inflammatory factors before and after treatment in the two groups of children (ng/mL, $\bar{x}\pm s$)

Coagulation function

Prior to treatment, there was no significant difference in PT and APTT between the two groups (P>0.05). After treatment, PT and APTT of the two groups were significantly lower than before treatment and the changes in the observation group were more obvious (P<0.05, table 6).

Table 1: Comparison of baseline data between the two groups of children

Groups	N	Sex (male/female)	Age (years)	Course of disease (days)	Axillary temperature (℃)
Observation group	78	40/38	5.32±1.28	4.29±1.12	39.12±1.14
Control group	77	42/35	5.38±1.24	4.34±1.15	39.16±1.17
t/χ^2		12.241	0.296	0.274	0.216
P		0.847	0.767	0.784	0.830

Table 2: Changes of main TCM symptom integral of the two groups of children before and after treatment (point, $\bar{x}\pm s$)

Groups	N	Time	Fever	Cough	Pulmonary rales
Observation group	78	Before treatment	2.16±0.32	2.66±0.18	2.28±0.25
		After treatment	0.31±0.11#	0.58±0.13#	0.47±0.16#
		t	48.006	82.383	53.609
		P	≤0.001	≤0.001	≤0.001
Control group	77	Before treatment	2.13±0.28	2.63±0.21	2.31±0.27
		After treatment	0.78±0.12	1.03±0.15	0.98±0.14
		t	38.925	54.521	38.424
		P	≤0.001	≤0.001	≤0.001

Table 3: Comparison of the disappearance time of symptoms between the two groups of children after treatment (day, $\bar{x}\pm s$)

Groups	N	Fever	Cough	Pulmonary rales
Observation group	78	4.46±0.35	7.98±1.34	8.22±1.19
Control group	77	7.65±0.37	12.47±1.42	13.27±1.23
t		55.148	20.249	25.979
P		≤0.001	≤0.001	≤0.001

Table 4: Comparison of lung function between the two groups of children before and after treatment ($\bar{x}\pm s$)

Groups	N	Time	FEV1 (L)	FEV1/FVC (%)	PEF (%)
Observation group	78	Before treatment	1.38±0.09	53.12±9.86	75.12±3.39
		After treatment	1.97±0.07#	64.79±9.77#	94.32±2.41#
		t	45.517	7.401	40.593
		P	≤0.001	≤0.001	≤0.001
Control group	77	Before treatment	1.36±0.12	53.15±9.84	75.14±3.36
		After treatment	1.51±0.06	57.11±9.68	89.52±2.38
		t	9.823	2.525	30.711
		P	≤0.001	≤0.001	≤0.001

Table 5: Comparison of the immune function of the two groups of children before and after treatment (g/L, $\bar{x}\pm s$)

Groups	n	Time	IgM	IgG	IgA
Observation group	78	Before treatment	1.86±0.41	6.96±2.11	1.09±0.43
		After treatment	0.93±0.21#	10.27±1.74#	0.48±0.12#
		t	7.830	10.689	12.068
		P	≤0.001	≤0.001	≤0.001
Control group	77	Before treatment	1.84±0.38	6.93±2.13	1.15±0.39
		After treatment	1.39±0.23	8.73±1.79	0.67±0.09
		t	8.890	5.677	10.523
		P	≤0.001	≤0.001	≤0.001

Note: Compared with the control group after treatment, #P<0.05

Table 6: Comparison of coagulation function between the two groups of children before and after treatment（$\bar{x}\pm s$）

Groups	N	Time	PT (s)	APTT (s)
Observation group	78	Before treatment	12.58±0.96	28.96±7.65
		After treatment	10.39±0.64#	23.11±6.23#
		t	16.764	5.237
		P	≤0.001	≤0.001
Control group	77	Before treatment	12.59±0.94	29.23±7.84
		After treatment	11.12±0.58	25.67±6.18
		t	11.678	3.129
		P	≤0.001	0.002

Note: Compared with the control group after treatment, #P<0.05

Table 7: Comparison of recovery rate between the two groups after treatment [n(%)]

Groups	N	Cured	Markedly effective	Effective	Ineffective	Effective rate
Observation group	78	20	39	18	1	59/75.64
Control group	77	13	26	32	6	39/50.65
χ^2						14.247
P						≤0.001

Table 8: The occurrence of adverse reactions during the treatment of the two groups of children [n(%)]

Groups	N	Nausea and vomiting	Abdominal pain	Flatulence	Headache	Total incidence
Observation group	78	1	0	1	0	2/2.56
Control group	77	2	1	1	1	5/6.49
χ^2						8.731
P						0.653

Recovery rates

The observation group outperformed the control group in terms of the recovery rate (P<0.05).

The occurrence of adverse reactions during the treatment

The two groups showed no significant difference in the total incidence of adverse reactions (P>0.05), as presented in table 8.

DISCUSSION

Currently, *Mycoplasma pneumonia* remains highly prevalent in children and typically strikes on a seasonal basis. Fever, cough, and shortness of breath are typical manifestations of *Mycoplasma pneumonia* in children (Søndergaard *et al.*, 2018). Disease progression may result in coughing accompanied by dry and wet rales in the lungs. Therefore, conventional treatment mainly centers on anti-infection, antipyretic, oxygen inhalation, nebulization and fluid rehydration (Dai *et al.*, 2021). Azithromycin is a commonly used sensitive drug against *Mycoplasma pneumonia* infection (Han *et al.*, 2020). Previous research has found that azithromycin could reduce the level of C-reactive protein in children with *Mycoplasma pneumonia* and diminish the content of myocardial enzymes to ensure a robust treatment efficacy (Shan *et al.*, 2017). Clinical practice has found a rising trend of the resistance of *Mycoplasma pneumonia* to azithromycin and other macrolide drugs (Duan *et al.*, 2019), which consequently, gives rise to an escalating incidence of refractory *Mycoplasma pneumonia* year by year. Currently, drugs for *Mycoplasma pneumonia* with symptomatic efficacy are absent in Chinese medicine. However, research has shown that the disease can be relieved by improving the body's immunity, regulating lung function, and increasing lung *yang qi* (Yin *et al.*, 2021). The *Qingfei Huatan Huoxue Decoction* is composed of ephedra, bitter almonds, roasted licorice, raw gypsum, salvia, turmeric, pangasius and red peony root. Ephedra facilitates sweat, dispels cold and relieves asthma. Bitter almonds function well in reducing phlegm, relieving cough, and alleviating asthma. Modern pharmacology points out that both are effective in anti-inflammation (Yaseen *et al.*, 2020). Roasted licorice can relieve cough and asthma, invigorate *qi* and rejuvenate the pulse, and has the effect of reconciling medicine. Raw gypsum can clear heat and relieve fire, remove irritability and quench thirst, which is mostly used to treat febrile fever, damp-heat syndrome and lung fever, cough and asthma. Salvia, turmeric and red peony, the three

complementing and reinforcing each other as a whole, promote blood circulation and dispel blood stasis to resolve stagnation, eliminate stasis, tonify both *qi* and blood, and enhance the efficiency of the medicine. Dioscorea lanceolate dispels wind and dampness, relaxes muscles and muscles and activates collaterals. the above-mentioned medicines serve as an interplay to clear the lungs and resolve phlegm, promote blood circulation and remove blood stasis.

Encouragingly, the findings of this study revealed that *Qingfei Huatan Huoxue Decoction* combined with azithromycin in the treatment of *Mycoplasma pneumonia* in children garnered a satisfying outcome compared to the monotherapy of azithromycin, wherein children's fever, cough, and pulmonary rales were substantially alleviated after treatment, and the symptoms disappearance time was markedly shortened. Previous research has shown that the activation of blood and removal of blood stasis drugs can restore the activity of alveolar surfactants and promote the recovery of lung function. Furthermore, it improves pulmonary capillary perfusion, maintains its wall integrity, and prevents diffuse intravascular coagulation (Liu *et al.*, 2019). Remarkably, the results of this study show that the two treatment options can effectively ameliorate the lung function of children, with superior lung functions observed after combined treatment, which is in line with the results of the previous study, indicating that the addition of *Qingfei Huatan Huoxue Decoction* boosts the recovery of lung function. Inflammation is a major cause of *Mycoplasma pneumonia*. The present study found that combined treatment yields a promising efficacy in the mitigation of lung inflammation in children, which is consistent with the results of previous studies. It is presumably related to the improvement of the blood hypercoagulability state of children and absorption of inflammation. A prior study has revealed that cellular immunity and humoral immunity are closely related to refractory *Mycoplasma pneumonia* in children (Sehatzadeh, 2012). The current study added *Qingfei Huatan Huoxue Decoction* and yielded a favorable effect on improving the immunity of children, which can further minimize the damage of infection to the body. Moreover, the safety evaluation showed that the overall incidence of adverse reactions of the combined treatment plan was lower than that of the monotherapy of azithromycin, yet the difference was not statistically significant, indicating a high safety profile of *Qingfei Huatan Huoxue Decoction*.

CONCLUSION

Qingfei Huatan Huoxue Decoction combined with azithromycin exhibits a promising effect in the treatment of *Mycoplasma pneumonia* in children. It alleviates the clinical symptoms of children, improves lung function and immune function, boosts blood coagulation function, and reduces inflammation.

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