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Original Article

The effect of Zinc on immune function, length of hospital stay and pain relief in the adjuvant treatment for asthmatic bronchitis

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Abstract: Aim: This study aimed to investigate the role of zinc in the treatment of asthmatic bronchitis and its effect on immune function and length of hospital stay. Methods: Ninety-three adult patients with asthmatic bronchitis admitted to our hospital from June 2016 to May 2019 were enrolled and retrospectively analyzed. They were randomly divided into a control group (CG, n=46), which received routine treatment and an observation group (OG, n=47), which underwent routine treatment + zinc. The time it took to achieve pain relief, the immune function, and the length of hospital stay were compared between the two groups. Results: The time it took to eliminate gasping, wheezing sounds, and coughing and the length of the hospital stay in the OG were shorter than they were in the CG after the treatment (P<0.05). The OG showed higher levels of indicators such as FVC, PEF, and FEV 1% as well as serum zinc concentration, and higher IgA, IgG, and IgM immunoglobulin levels than the CG after 2 weeks of treatment (P<0.05). Also the OG exhibited higher CD3+, CD4+, and CD4+/CD8+ levels than the CG (P<0.05). However, the groups did not differ in their CD8+ levels (P>0.05). The IL-8 and TNF-α levels in the OG after 2 weeks of treatment were lower than those in the CG (P<0.05). The effective rates in the OG and CG were 91.49% and 76.09%, respectively (P<0.05). Conclusion: Zinc helps to relieve symptoms quickly, improve the immune function, and shorten the hospital stay.

Keywords: Zinc, asthmatic bronchitis, pain relief, immune function, length of stay

Introduction

Asthmatic bronchitis is a common respiratory disease in children over 3 years old, but now urban industrialization and serious environmental pollution also trigger asthmatic bronchitis in adults, who suffer a long course of the disease and recurrent symptoms [1]. Desai et al. [2] found that recurrent episodes of asthmatic bronchitis may be caused by allergens, infections, and climate change, etc., episodes which are more likely to occur in the colder months of winter and spring.

Brightling et al. [3] demonstrated that recurrent episodes of asthmatic bronchitis are associated with respiratory virus infections, including human rhinovirus (HRV) and respiratory syncytial virus (RSV) infection. Recurrent wheezing is a risk factor for asthma attacks. Asthmatic bronchitis significantly increases the risk of asthma. Therefore, for patients diagnosed with asthmatic bronchitis, it is necessary to choose the appropriate treatment options and drugs to effectively control their symptoms.

It was found that routine treatment cannot completely cure asthmatic bronchitis, and that it especially does not improve patients' immune function [4]. Kim et al. [5] showed that the occurrence of asthmatic bronchitis is also related to zinc deficiency. Zinc plays an important role in the mechanism of immune functions. Therefore, this study included 93 patients with asthmatic bronchitis admitted in our hospital from June 2016 to May 2019 to seek more safe and effective methods for the treatment of asthmatic bronchitis.

Materials and methods

Baseline data

Ninety-three adult patients with asthmatic bronchitis admitted to our hospital from June

2016 to May 2019 were enrolled and retrospectively analyzed, including 50 cases of mild wheezing, 33 cases of moderate wheezing, and 10 cases of severe wheezing. They were divided randomly into the observation group (OG, n=47) and the control group (CG, n=46) according to their order of admission. The patients in the CG ranged in age from 19-42 years, and their course of disease ranged from 0.3-2 years; The patients in the OG ranged in age from 20-45 years, and their course of disease ranged from 0.3-2 years.

Inclusion criteria: Patients who met the diagnostic criteria for asthmatic bronchitis in adults [6]; and patients with complete medical records. Exclusion criteria: Patients who were lost to follow-up; patients under 18 years of age; patients who also had cardiogenic asthma, bronchial foreign bodies, gastroesophageal reflux; patients who underwent treatment affecting their immune function. This study was approved by the Ethics Committee of the People's Hospital of Pengzhou. All study participants provided a written informed consent before participating in the study.

Methods

The CG received routine treatment, including eliminating phlegm to smooth wheezing, antiallergic therapy, antispasmodic treatment, etc. In addition, antiviral treatment or anti-infective treatment was reasonably implemented according to each patient's situation.

The OG received licorzinic capsules in additional to the routine treatment, 2-3 times a day, 0.5-1.0 mg/kg/day for 2 weeks (specifications: 5 g * 15 packs, Nanjing Ruinian Best Pharmaceutical Co., Ltd.).

Outcome measurement

Symptom improvement. The time it took to be free from gasping, making wheezing sounds, and coughing, and the length of hospital stay were recorded.

Pulmonary function. Forced vital capacity (FVC), peak expiratory flow (PEF), and forced expiratory volume in one second % (FEV1%) before and 2 weeks after the treatment were measured using a pulmonary function tester (FGC-A+).

Immune function. The serum zinc concentration, and the IgA, IgM, and IgG levels were measured before and 2 weeks after the treatment. Before and after treatment, 3 ml of fasting peripheral blood was taken from each patient in the morning, and centrifuged at 3000 r/min for 5 min. The supernatant was collected and measured using an enzyme-linked immunosorbent assay (ELISA) in strict accordance with the instructions. The kit was provided by Oumeng Medical Laboratory Diagnostics Co., Ltd.

T lymphocyte levels. T lymphocyte subsets such as the CD3+, CD4+, CD8+, and CD4+/CD8+ levels were determined before and 2 weeks after the treatment. Before and after the treatment, 5 ml of fasting venous blood was taken from the patients in the morning and measured using a FACSCanto flow cytometer (Manufacturer: Becton, Dickinson and Company, Franklin Lakes, NJ).

Inflammation levels. Interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α) were measured before and 2 weeks after the treatment. Before and after the treatment, 5 ml of fasting peripheral blood from each patient was taken in the morning, and centrifuged at 3000 r/min for 5 min. The supernatant was collected, stored at -20°C and measured using ELISA. The measurement and operation were performed strictly according to the instructions of the kit (Abcam, USA).

Effective criteria [7]. Cure: all symptoms such as wheezing sounds, coughing, and gasping were eliminated after the treatment; pulmonary function was recovered, and there was no recurrence after the drug withdrawal. Improvement: all the symptoms mentioned above were significantly relieved after the treatment; pulmonary function was close to the normal range. Ineffective: all the symptoms remained or became even more serious after the treatment; pulmonary function was abnormal, or relapse occurred after treatment.

Response rate = (cure + improvement)/total number of patients × 100%.

Statistical analysis

The statistical analysis was performed using SPSS 22.0. The measurement data were ex-

Table 1. Baseline data ($\bar{x}$ ± s)/[n (%)]

Data		Observation (n=47)	Control (n=46)	t/X^2	*P*
Gender	Male	25 (53.19)	26 (56.52)	0.104	0.747
	Female	22 (46.81)	20 (43.48)		
Age (year)		30.52 ± 8.46	31.59 ± 8.62	0.604	0.547
Course of disease (year)		1.02 ± 0.38	1.04 ± 0.39	0.250	0.803
BMI (kg/m^2)		23.16 ± 1.32	24.01 ± 1.39	0.849	0.163
Weight (kg)		65.28 ± 11.19	66.85 ± 11.42	0.670	0.505
Severity of wheezing	Mild	26 (55.32)	24 (52.17)	1.153	0.187
	Moderate	17 (36.17)	16 (34.78)		
	Severe	4 (8.51)	6 (13.04)		
Underlying diseases	Diabetes	18 (38.30)	16 (34.78)	1.527	0.192
	CAD	14 (29.79)	15 (32.61)		
	Hypertension	11 (23.40)	10 (21.74)		
	Others	4 (8.51)	5 (10.87)		

CAD: coronary artery disease.

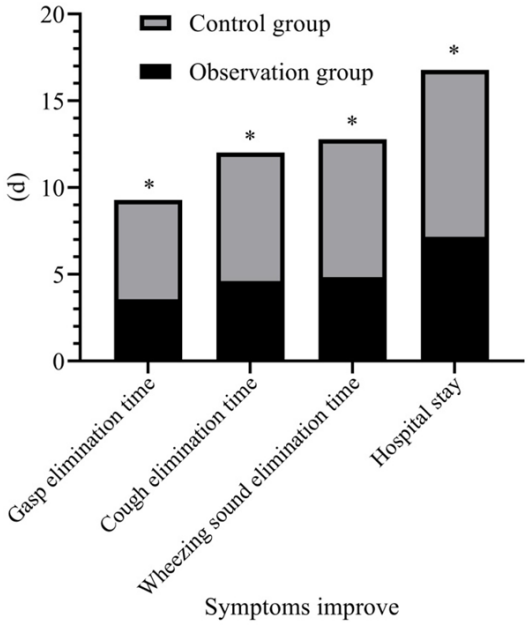

Figure 1. Comparison of the improvement of symptoms between the two groups. Compared with the control group, the wheezing sound elimination time, the cough elimination time, and the gasp elimination time and length of stay in the observation group was significantly shorter (P<0.05). * indicates P<0.05.

pressed as the mean ± standard deviation. Comparisons between the two groups were performed using independent sample t tests. The count data were expressed as [n (%)]. Comparisons between the two groups were performed using X^2 tests. The multi-point comparisons were analyzed using ANVOA. P<0.05 indicated that the difference was statistically significant.

Results

Baseline data

There was no significant difference in the proportions of gender, average age, weight, course of the disease, BMI, severity of wheezing, or underlying diseases in the two groups (P>0.05) (**Table 1**).

Comparison of the improvement of the symptoms in the two groups

The time it took to become free of gasping, coughing, and making wheezing sounds and the length of hospital stay in the OG after treatment were (3.56 ± 1.18) days, (4.61 ± 1.33) days, (7.16 ± 1.85) days, and (7.16 ± 1.85) days, while in the CG, the times were (5.72 ± 1.54) days, (7.41 ± 1.49) days, (7.94 ± 1.57) days, and (9.62 ± 2.02) days respectively, which were significantly longer than those in the OG (P<0.05) (**Figure 1**).

Comparison of the pulmonary function in the two groups

After 2 weeks of treatment, the levels of FVC, PEF, and FEV 1% in the OG were significantly higher than the corresponding levels in the CG (P<0.05) (**Table 2**).

Comparison of the immune function in the two groups

After 2 weeks of treatment, the serum zinc concentration and the levels of immunoglobulin

Table 2. Comparison of the pulmonary function in the OG and the CG ($\bar{x} \pm s$)

Group	Time	FVC (L)	PEF (L/min)	FEV1%
Observation (n=47)	Before treatment	1.85 ± 0.56	192.72 ± 18.52	59.43 ± 5.61
	Two weeks after treatment	2.56 ± 0.23	249.86 ± 15.28	69.34 ± 5.32
Control (n=46)	Before treatment	1.83 ± 0.55	193.34 ± 19.41	58.91 ± 5.43
	Two weeks after treatment	2.20 ± 0.21	213.34 ± 15.49	61.28 ± 5.17
t		7.878	11.446	7.407
P		0.000	0.000	0.000

Note: t and *P* are the statistical values after 2 weeks of treatment between the observation group and the control group.

Table 3. Comparison of the immune function in the OG and the CG ($\bar{x} \pm s$)

Group	Time	Serum zinc (μmol/L)	IgA (g/L)	IgM (g/L)	IgG (g/L)
Observation (n=47)	Before treatment	9.32 ± 0.27	0.35 ± 0.12	0.63 ± 0.13	5.70 ± 0.43
	Two weeks after treatment	10.45 ± 0.36	0.68 ± 0.14	1.16 ± 0.23	6.75 ± 0.53
Group (n=46)	Before treatment	9.30 ± 0.28	0.34 ± 0.11	0.65 ± 0.14	5.72 ± 0.45
	Two weeks after treatment	9.95 ± 0.31	0.42 ± 0.15	0.86 ± 0.15	6.01 ± 0.42
t		7.171	8.644	7.433	7.452
P		0.000	0.000	0.000	0.000

Note: t and *P* are the statistical values after 2 weeks of treatment between the observation group and the control group.

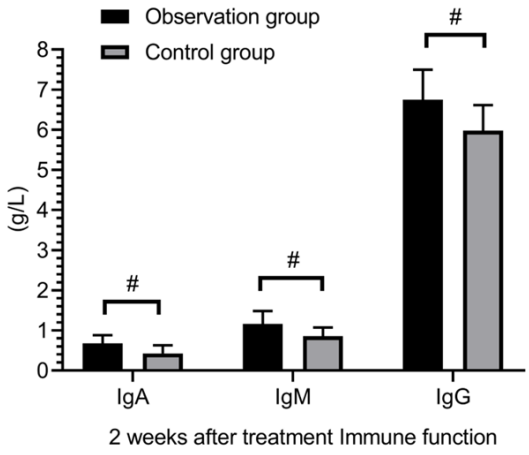

Figure 2. Comparison of the immune function in the two groups after treatment. After 2 weeks of treatment, the IgA, IgM, and IgG levels were significantly higher in the observation group than they were in the control group (P<0.05). # indicates P<0.05.

IgA, IgM, and IgG in the two groups significantly improved and were significantly higher in the OG compared with the corresponding values in the CG (P<0.05) (**Table 3**; **Figure 2**).

Comparison of the T lymphocytes in the two groups

The CD3+, CD4+, CD8+, and CD4+/CD8+ levels in the OG were not significantly different from the corresponding levels in the CG before treatment (P>0.05). They all increased after 2 weeks of treatment and were significantly higher in the OG than in the CG (P<0.05). However, the two groups showed no differences in their CD8+ levels (P>0.05) (**Table 4**; **Figure 3**).

Comparison of the inflammation levels in the two groups

The levels of IL-8 and TNF-α in the OG before the treatment were not statistically different from those in the CG (P>0.05), but after 2 weeks of treatment, they were significantly lower in the OG than they were in the CG (P<0.05) (**Figure 4**).

Comparison of the effective rates in the two groups

There were 20 cured cases, 23 improved cases and 4 ineffective cases in the OG. In the CG, there were 16 cured cases, 19 improved cases, and 11 ineffective cases. The effective rates were significantly different in the two groups (X^2=4.077, P=0.043) (**Figure 5**).

Discussion

Asthmatic bronchitis has a variety of clinical manifestations. The onset time, frequency of the symptoms, and duration of wheezing will affect the prognosis. At present, studies on the

Table 4. Comparison of the T lymphocytes in the OG and the CG ($\bar{x} \pm s$)

Group	time	CD3+ (%)	CD4+ (%)	CD8+ (%)	CD4+/CD8+
Observation (n=47)	Before treatment	58.86 ± 5.13	35.42 ± 6.28	23.51 ± 8.34	1.43 ± 0.59
	Two weeks after treatment	66.89 ± 5.83	43.12 ± 7.14	23.61 ± 6.98	1.89 ± 0.53
Control (n=46)	Before treatment	57.29 ± 5.30	35.19 ± 6.15	22.84 ± 8.43	1.44 ± 0.58
	Two weeks after treatment	60.35 ± 5.39	38.45 ± 6.49	23.03 ± 7.51	1.61 ± 0.54
t		5.614	3.299	0.386	2.524
P		0.000	0.001	0.701	0.013

Note: t and *P* are the statistical values after 2 weeks of treatment between the observation group and the control group.

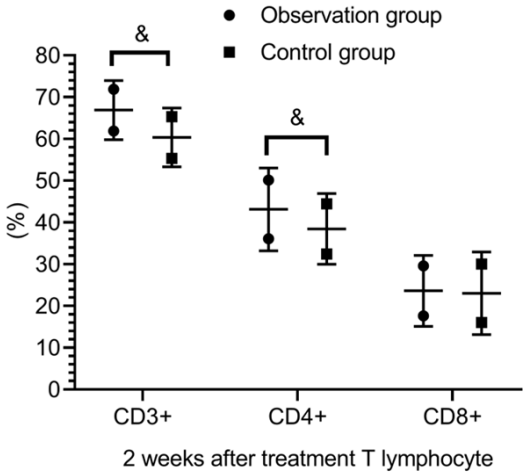

Figure 3. Comparison of the T lymphocytes in the two groups. The observation showed higher CD3+ and CD4+ levels after 2 weeks of treatment, and the difference in the CD8+ levels was not significant between the two groups (P>0.05). & indicates P<0.05.

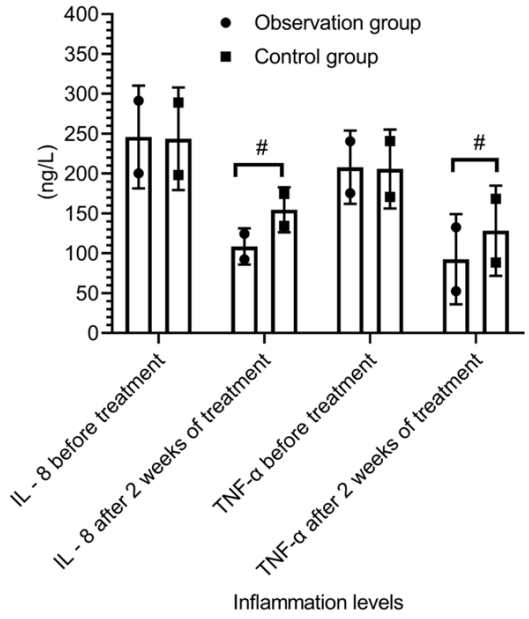

Figure 4. Comparison of the inflammation levels in the two groups. Compared with the control group, the observation group showed the same IL-8 and TNF-α levels before the treatment, but it showed lower IL-8 and TNF-α levels after two weeks of treatment. # indicates P<0.05.

pathogenesis of asthmatic bronchitis mainly focus on two theories: airway immune inflammation and airway remodeling. Both theories tell us that different inflammatory mediators, inflammatory cells, and cytokines are involved in the development and pathogenesis of asthmatic bronchi [8, 9].

Örtqvist et al. [10] showed that immune function is affected during the occurrence of asthmatic bronchitis and can be observed in the change of CD4+ and CD8+ cell levels. In addition, Pawar et al. [11] found that the progression of asthmatic bronchitis is not only related to the immune system, but also to zinc deficiency. Zinc is present in many organs such as the skin, liver, muscles, bones, and hair. An essential trace element, it is also an important component of various catalytic enzymes and plays an important role in the synthesis of proteins, DNA and RNA [12].

When zinc levels are low, the body weight will consistently decrease, and the immune function will be dysfunctional, which will show stronger oxidative stress and inflammatory immune responses, increasing the risk of infections [13]. Therefore, zinc supplements can help improve immunity. Choi et al. [14] found that zinc affects the differentiation and proliferation of T lymphocytes, and zinc deficiency can damage T cell function and affect the regulation of the immune system.

After treatment with zinc in the OG, the T lymphocyte subsets such as CD3+, CD4+, and CD4+/CD8+ were higher than they were in the CG (P<0.05), suggesting that zinc supplemen-

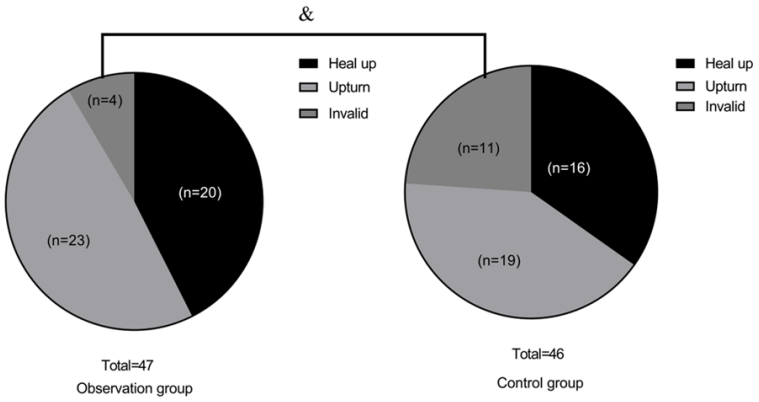

Figure 5. Comparison of effective rates in the two groups. The two groups showed no difference in the numbers of cured and improved patients. However, the observation group showed fewer ineffective cases than the control group. $^{\&}P<0.05$.

tation can significantly improve T lymphocyte levels. T lymphocytes are the executors of cellular immunity and can differentiate into various subgroups and affect the occurrence and progression of asthmatic bronchitis [15]. They are usually divided into two major subgroups according to the surface markers CD8 and CD4, and the CD4/CD8 ratio is the key to maintaining immune balance. Once the body is stimulated by allergens, T lymphocytes in the peripheral blood will change significantly [16].

Guillou et al. [17] found that, compared with healthy people, an increase in the proportion of CD8+ cells and a decrease in the CD4/CD8 ratio are observed in the peripheral blood of patients with asthmatic bronchitis. However, the proportion of CD3+ and CD4+ cells does not remain the same. It was also found that different types of asthma may result in differences in T lymphocyte levels. Therefore, it is recommended that the T cell subsets of patients with asthmatic bronchitis be dynamically monitored. In addition, Hoekstra et al. [18] showed that the CD4+ as well as the CD4/CD8 cells will increase in patients with acute asthma attacks, but the number of CD3+ and CD8+ cells will not change significantly. Therefore, patients with asthmatic bronchitis show differences in the function and number of T lymphocyte subsets.

In addition, the results also showed that the gasping, coughing, and the wheezing sound elimination time and the hospital length of stay in the OG were shorter than they were in the CG after the administration of the zinc treatment ($P<0.05$), and the OG showed better pulmonary function, higher immunoglobulin levels, a better effective rate, and lower inflammatory factors than the CG, suggesting that the treatment of asthmatic bronchitis with zinc can reduce clinical symptoms more rapidly, accelerate the recovery, reduce the inflammation level and improve the pulmonary function. Specifically, zinc can help increase the concentration of immunoglobulin IgG, improve the stability of mast cell membranes, and reduce airway inflammation and avoid the recurrence of asthmatic bronchitis [19, 20].

Zinc can accelerate the repair of mucosal epithelial cells in the digestive and respiratory tracts, keep the immune system strong and healthy, and effectively control asthmatic bronchitis [21]. Zinc can regulate the immune function, promote the secretion of Th1 type cytokines, inhibit the formation of Th2 cytokines, and maintain the dynamic balance of Th1/Th2 [22]. Second, zinc supplementation can enhance NK cell function and prevent the recurrence of respiratory infections from causing wheezing and other symptoms [23]. In addition, zinc is an anti-oxidant, which can regulate the airway inflammatory response and improve symptoms [24, 25].

In summary, zinc helps to relieve symptoms quickly, improves the immune function, and shortens the hospital stay.

However, the small sample size and short follow-up time in this study may lead to biased results. In our future research, we will also explore this topic in a prospective way and provide more guidance for the treatment of patients with asthmatic bronchitis.

Disclosure of conflict of interest

None.

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