Effect of Acupoint Liquid Nitrogen Cryotherapy on Neuro - Endocrine - Immune Network System in Patients with Lung Qi Deficiency Syndrome in Remission Stage of Bronchial Asthma

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Abstract [**Objectives**] To observe the effect of acupoint liquid nitrogen cryotherapy on the neuro-endocrine-immune network system of lung qi deficiency syndrome during the remission period of bronchial asthma and explore its possible mechanism. [**Methods**] A total of 100 patients with bronchial asthma were randomly divided into control group and observation group, with 50 cases in each group. The control group was given budesonide spray inhalation treatment, combined with acupoint liquid nitrogen freezing treatment, twice a year for a course of treatment, followed up for 1 year. The other 50 healthy volunteers were included in the healthy group, and no treatment was given in the healthy group. Serum immunoglobulins A, G, E (IgA, IgG, IgE) were detected before and after treatment in each group, serum cytokines [interleukin-4 (IL-4), interleukin-10 (IL-10), tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ)], plasma neurotransmitters [substance P (SP), vasoactive intestinal peptide (VIP)]. [**Results**] Before treatment, compared with healthy group, the contents of IgA, IgG, IL-10, IFN-γ and VIP in observation group and control group were decreased, while the contents of IgE, IL-4, TNF-α and SP were increased, with statistical significance ($P<0.05$). After treatment, compared with before treatment, IgA, IgG, IL-10, IFN-γ and VIP contents in observation group and control group were increased ($P<0.05$), and observation group was higher than control group ($P<0.05$), IgE, IL-4 and SP contents in observation group and control group were decreased ($P<0.05$). The observation group was lower than the control group ($P<0.05$). [**Conclusions**] Acupoint liquid nitrogen cryotherapy may improve the immune function of the body, regulate the release of cytokines and regulate neuromediators, and thus play a role in the prevention and treatment of bronchial asthma.

Key words Acupoint liquid nitrogen cryotherapy, Neuro-endocrine-immune, Bronchial asthma, Remission period, Lung qi deficiency, Treatment of winter diseases in summer

1 Introduction

Bronchial asthma is a chronic recurrent inflammatory disease of the airway, characterized by clinical manifestations such as cough, chest tightness, shortness of breath and asthma, with low control and cure rate and high recurrence rate. Relevant epidemiological surveys show that there are about 30 million asthma patients in China at present, and most of them are not well controlled[1]. With the passage of time and repeated illness, it not only affects the quality of life of patients, but also brings economic burden to society and families. Since Western medicine mainly relies on hormone-containing Western medicine to treat this disease, long-term use will produce adverse reactions. In view of the obvious limitations of the current treatment methods of Western medicine, medical research has turned its attention to traditional Chinese medicine. Early interventional therapy of traditional Chinese medicine has a good effect on it. The acupoint liquid nitrogen cryotherapy for summer treatment of winter disease carried out by the Department of Traditional Chinese Medicine of People's Hospital of Xinjiang Uygur Autonomous Region has achieved good results in the treatment of bronchial asthma[2], but its mechanism of action is still unclear. From the holistic concept, our research group studied the effects of this therapy on some immunoglobulins, cytokines and neuromediators in patients with bronchial asthma in remission, and explored the possible mechanism of acupoint liquid nitrogen cryotherapy from the perspective of neuro-endocrine-immune network system.

2 Materials and methods

2.1 Clinical data 100 patients with bronchial asthma in remission treated at the acupoint liquid nitrogen freezing clinic of the Department of Traditional Chinese Medicine of the People's Hospital of Xinjiang Uygur Autonomous Region during the "dog days of summer" of the lunar calendar from July to August 2021 were randomly divided into an observation group and a control group, with 50 cases in each group. There were 23 males and 27 females in the observation group, aged 18 - 65 years, with an average age of (42.7 ± 19.8) years; the course of disease was 3 to 30 years, with an average age of (13.34 ± 12.45) years. In the control group, there were 22 males and 28 females, aged 20 - 65 years, with an average age of (43.6 ± 18.5) years; the duration of the disease ranged from 3 to 30 years, with an average of (12.76 ± 13.65) years. Fifty healthy volunteers were confirmed to be disease-free by physical examination at the Physical Examination Center of People's Hospital of Xinjiang Uygur Autonomous Region in the same period. As the healthy group, there were 24 males and 26 females, aged 26 - 64 years, with an average of

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(52.23 ± 8.59) years. The differences in gender and age among the three groups were not statistically significant and comparable. This study met the ethical requirements of the Medical Ethics Committee of the People's Hospital of Xinjiang Uygur Autonomous Region (Ethical Approval No.:KY2021052632).

2.2 Diagnostic criteria

2.2.1 Western medicine diagnosis. The diagnostic criteria of Western medicine refer to the diagnostic criteria of bronchial asthma in remission in the *Guidelines for Prevention and Treatment of Bronchial Asthma* (2016 *Edition*)[3] formulated by the Asthma Group of Respiratory Branch of Chinese Medical Association.

2.2.2 Diagnosis of TCM syndromes. The TCM syndrome differentiation standards for lung qi deficiency syndrome refer to the TCM syndrome differentiation standards for asthma syndrome in the *Guiding Principles for Clinical Research of New Traditional Chinese Medicines* (*Trial*)[4]: (i) chest tightness or wheezing, shortness of breath or cough, the symptoms are aggravated when moving; weariness or fatigue; (ii) spontaneous sweating, sensitive to the cold; (iii) pale tongue, or weak or intermittent pulse. (i) is required, and two of (ii) – (iv) are added.

2.3 Inclusion criteria

2.3.1 Inclusion criteria for patients with bronchial asthma in remission. (i) Meet the above diagnostic criteria; (ii) classified as mild or moderate disease; (iii) aged 19 – 65 years old; (iv) no serious primary diseases such as cardiovascular, liver, kidney and hematopoietic system diseases; (v) patients who volunteer to take the test and sign the informed consent agreement.

2.3.2 Inclusion criteria for healthy volunteers. (i) Aged 26 – 65 years old; (ii) volunteers without basic diseases during physical examination (no genetic diseases, infectious diseases, diabetes, kidney diseases, liver diseases and mental diseases, *etc.*); (iii) no participation in any other clinical trials within 3 months.

2.4 Exclusion criteria (i) Pregnant and breastfeeding women; (ii) those who have used systemic glucocorticoids within 2 weeks; (iii) those with severe diabetes or diseases of heart, liver, kidney and hematopoietic system; (iv) those with mental abnormalities, history of skin allergy, and bleeding tendency.

2.5 Drop-out criteria (i) Those with poor compliance and inability to cooperate in treatment; (ii) patients with severe cardiopulmonary insufficiency or severe adverse reactions during clinical studies.

2.6 Treatment regimen

2.6.1 Healthy group. No intervention is given.

2.6.2 Control group. Budesonide and Formoterol Fumarate Powder for Inhalation [AstraZenecaAB (Sweden), specifications: (320 μg + 9 μg) × 60 inhalations] was administered, 1 inhalation once, 2 times/d, for 1 year.

2.6.3 Observation group. On the basis of the treatment of the control group, liquid nitrogen cryotherapy was performed at acupoints during the "dog days" period every year[5]: Feishu, Shanzhong and Fengmen were taken, and liquid nitrogen acupoint freezing was performed with a flexible hypothermia therapy apparatus; the head of the treatment gun is a copper plane freezing head with a diameter of 1 cm, after starting the therapy apparatus, the cold head quickly became an ice ball, and it was used to touch the acupuncture points and exert pressure, and then the skin shrank slightly and the pores were stacked, so at this time, due to vasoconstriction, the skin surface was pale and slightly sunken; the central skin temperature dropped rapidly from 33 – 36 ℃ to about 10 ℃, and each point was frozen for 10 sec. The same point area needed to be frozen again, and the interval should be about 15 – 20 d, with twice a year as a course of treatment. Treatment lasted for 1 course.

Patients in both groups were followed up for more than 1 year.

2.7 Detection indexes 10 mL of blood samples were collected from healthy volunteers (5 mL of blood samples were collected by disposable vacuum collection tubes containing anticoagulant heparin solution, and the remaining blood samples were collected by disposable vacuum collection tubes without anticoagulant); blood samples were collected from patients in the observation group and control group before treatment and before the third acupoint cryotherapy in the second year, respectively, with the same method as that in the healthy group. The blood samples were left to stand at room temperature for 1 h, centrifuged at 3 500 r/min for 10 min, and the centrifugation radius was 200 px. The supernatant was taken in a cryopreservation tube and stored at −80 ℃. Serum immunoglobulin E, A, G (IgE, IgA, IgG) content was detected by immunoturbidimetry, cytokines were detected, serum interleukin-4 (IL-4), interleukin-10 (IL-10), tumor necrosis factor-a (TNF-ct), interferon-7 (IFN-γ) content was detected by enzyme-linked immunosorbent assay, and the plasma vasoactive intestinalpeptide (VIP) and substance P (SP) content was detected by radioimmunoassay. All operations were tested in strict accordance with the kit instructions.

2.8 Statistical methods All the data were sorted out by Excel, and the data were analyzed by SPSS 22.0 statistical software. The data were expressed by $\bar{x} \pm s$, and the homogeneity test of variance and one-way analysis of variance were carried out. The *LSD* method was used to compare pairwise between groups, and the difference was statistically significant when $P < 0.05$.

3 Results and analysis

3.1 Comparison of serum IgA, IgE, and IgG levels before and after treatment in different groups As shown in Table 1, before treatment, compared with the healthy group, the serum IgA and IgG content of the observation group and the control group was significantly reduced ($P < 0.05$), and the serum IgE content was significantly increased ($P < 0.05$); compared with this group before treatment, the serum IgA and IgG content of observation group and control group increased significantly ($P < 0.05$) and IgE content decreased significantly ($P < 0.05$) after treatment,

and the IgA and IgG content of observation group was significantly higher than that of control group ($P<0.05$), and the IgE content of observation group was significantly lower than that of control group ($P<0.05$).

3.2 Comparison of serum cytokine IL-4, IL-10, TNF-α and IFN-γ levels before and after treatment in different groups

As shown in Table 2, before treatment, compared with the healthy group, the serum IL-4 and TNF-α levels in the observation group and the control group were significantly increased ($P<0.05$), while the serum IL-10 and IFN-γ levels were significantly decreased ($P<0.05$); compared with this group before treatment, the serum IL-4 and TNF-α levels in the observation group and the control group were significantly reduced after treatment ($P<0.05$), and the levels in the observation group were significantly lower than those in the control group ($P<0.05$); the serum IL-10 and IFN-γ levels in the observation group and the control group were significantly increased ($P<0.05$), and the levels in the observation group were significantly higher than those in the control group ($P<0.05$).

3.3 Comparison of plasma neuromediators VIP and SP levels before and after treatment in different groups

As shown in Table 3, before treatment, compared with the healthy group, the plasma VIP content in the observation group and the control group decreased significantly ($P<0.05$), and the SP content increased significantly ($P<0.05$); compared with this group before treatment, the plasma VIP content of the observation group and the control group increased significantly after treatment ($P<0.05$), and the plasma VIP content of observation group was significantly higher than that of the control group ($P<0.05$); the plasma SP content of the observation group and the control group decreased significantly after treatment ($P<0.05$), and the plasma SP content of the observation group was significantly lower than that of the control group ($P<0.05$).

Table 1 Comparison of serum IgA, IgE, and IgG levels in different groups ($\bar{x}\pm s$, $n=50$)

Group	Time	IgA//g/L	IgE//IU/mL	IgG//g/L
Healthy	–	3.46±0.59	67.11±18.32	12.12±2.56
Control	Before treatment	1.59±0.55*	179.66±25.77*	8.65±0.54*
	After treatment	2.31±0.51△	126.45±26.39△	9.23±1.11△
Observation	Before treatment	1.61±0.72*	171.19±23.83*	8.12±1.31*
	After treatment	3.21±0.31△▲	88.77±21.74△▲	10.12±0.87△▲

NOTE Compared with the healthy group, *$P<0.05$; compared with the group before treatment, △$P<0.05$; compared with the control group in the same period, ▲$P<0.05$. The same below.

Table 2 Comparison of serum cytokine IL-4, IL-10, TNF-α and IFN-γ levels in different groups ($\bar{x}\pm s$, $n=50$, ng/mL)

Group	Time	IL-4	IL-10	TNF-α	IFN-γ
Healthy	–	44.67±20.45	20.54±4.33	6.23±0.56	29.14±5.81
Control	Before treatment	82.34±24.33*	9.78±2.36*	16.56±2.87*	19.10±2.45*
	After treatment	69.87±26.61△	14.55±3.32△	12.34±6.78△	22.34±6.70△
Observation	Before treatment	80.76±26.65*	10.44±3.26*	17.11±3.32*	17.68±4.33*
	After treatment	52.32±22.56△▲	17.11±2.21△▲	9.45±3.75△▲	25.65±4.33△▲

Table 3 Comparison of plasma neuromediator VIP and SP levels in different groups ($\bar{x}\pm s$, pg/mL, $n=50$)

Group	Time	VIP	SP
Healthy	–	217.23±10.43	35.45±11.82
Control	Before treatment	161.23±9.56*	53.23±8.11*
	After treatment	170.45±5.46△	49.60±7.43△
Observation	Before treatment	160.40±6.45*	55.34±6.33*
	After treatment	183.76±9.45△▲	38.19±4.55△▲

4 Discussion

"Summer treatment of winter disease" is a characteristic external treatment method of traditional Chinese medicine. Its theory has derived a variety of treatment means and methods, including acupoint application, acupoint acupuncture, acupoint moxibustion, acupoint liquid nitrogen freezing, acupoint injection, acupoint scraping and acupoint cupping[6-7]. Its mechanism of action is to take advantage of the favorable opportunity of high temperature in summer and abundant yang in the body to adjust the balance of yin and yang in the human body, so that some chronic diseases, especially those that are easy to recur after having a cold in winter, can be recovered[8]. The acupoint liquid nitrogen cryotherapy for "summer treatment of winter disease" carried out by the Department of Traditional Chinese Medicine of People's Hospital of Xinjiang Uygur Autonomous Region is an external treatment method to prevent and treat respiratory diseases by stimulating the acupoints with low-temperature liquid nitrogen, which falls into the category of "crude herb moxibustion" therapy of traditional Chinese medicine. Its low-temperature liquid nitrogen stimulates specific acupoints and parts, causing skin frostbite, then blisters or suppuration, wound healing, local tissue hyperplasia and repair and other processes, which is basically similar to traditional dog days drug application. In previous studies, it was found that the clinical efficacy of treating winter diseases in summer with liquid nitrogen freezing for bronchial asthma at acupoints was significantly better than that of conventional crude herb moxibustion therapy[9], but its mechanism of action is not yet clear. According to the overall concept of traditional Chinese medicine, we studied the effect of acupoint liquid nitrogen cryotherapy on immunoglobulin, cytokines and nerve mediators in patients with bronchial asthma in remission, and discussed the mechanism of acupoint liquid nitrogen cryotherapy in treatment of bronchial asthma in remission from the nerve-endocrine-immune network system.

Western medicine generally believes that bronchial asthma is a multi-heterogeneous disease in which a variety of inflammatory cytokines and immune cells participate in recurrent attacks. At

present, the pathogenesis is still unclear, but the research results show that bronchial asthma is a Th1/Th2 lymphatic disorder disease[10-11]. Serum IgE level is one of the important indicators to measure the immunopathological changes of bronchial asthma. IgE can activate basophils and mast cells, and at the same time activate cells involved in antigen presentation in vivo. It is generally believed that IgE is the core link in inducing asthma attacks[12]. One of the important mechanisms of asthma attack is airway hyperresponsiveness and airway inflammation caused by the regulation of specific IgE production by Th2 lymphocytes and the allergic reaction induced by the accumulation of eosinophils in the airway and lung tissue. Under physiological conditions, the regulatory function of Th2 cells is checked and balanced by the function of Th1 cells, and it cannot produce too much specific IgE. However, the imbalance of Th1/Th2 cells may produce a large amount of specific IgE, resulting in abnormal immune response and inflammatory response of airway, thus inducing asthma. The imbalance of Th1/Th2 cells in asthma patients is characterized by low function of Th1 cell subsets and hyperfunction of Th2 cell subsets[10, 12]. Cytokines IFN-γ and IL-4 are characteristic cytokines of Th1 and Th2 cells, respectively, and their abnormal content plays an important role in the pathogenesis of asthma[14-15]. IL-4 plays a very important role in the inflammatory response of asthma. It can regulate IgE levels to promote the increase of basophils and mast cells, cause and aggravate the inflammatory immune allergy of asthma, and IFN-γ can antagonize this effect of IL-4[16-17]. Studies have shown that serum IFN-γ levels are negatively correlated with IgE content, and IL-4 levels are positively correlated with IgE content. The results of this study showed that compared with the healthy group, the serum IgE and IL-4 levels in the observation group and the control group before treatment were significantly increased, and the IFN-γ levels were significantly decreased ($P<0.05$), indicating that the function of Th1/Th2 cells in asthma patients was imbalanced and induced to produce a large amount of IgE. Therefore, correcting the imbalance of Th1/Th2 cells and regulating immune function are important links in preventing and treating asthma. After acupoint liquid nitrogen cryotherapy intervention, the serum IgE, IL-4 and IFN-γ levels in the observation group were significantly improved compared with the control group ($P<0.05$), indicating that this method can regulate the secretion of cytokines, correct the imbalance of Th1/Th2 cells and inhibit IgE-mediated allergy. There are also many cytokines related to Th1 and Th2 cell subsets, among which IL-10 can inhibit T cell activation by inhibiting antigens[18]. TNF-α is mostly secreted by monocytes-macrophages, which promotes the secretion of other inflammatory factors and can mediate a series of pathophysiological reactions in the body, causing the body to have different degrees of inflammatory reactions[19]. The pathogenesis of asthma is closely related to the immune mechanism, and the weakening of Th1 function in asthma patients may lead to the decrease of IgA and IgG content[20]. Therefore, monitoring the serum immunoglobulin content is of great significance to understanding the overall immune status of patients and the trend of asthma occurrence and development. The results of this study showed that the serum IgA and IgG levels of patients in the control group and observation group decreased[21]. After treatment, the serum IgA, IgG levels in the observation group were significantly higher than those in the control group ($P<0.05$), indicating that this method can improve the overall immunity of asthma patients to prevent and treat asthma. This result is basically consistent with the report of Li Bolin *et al.*[22].

The neuroendocrine system can jointly regulate the immune system through peripheral nerve synapses, neurotransmitters, endocrine hormones and cytokines secreted by nerve cells, and have important effects on bronchoconstriction, blood circulation, airway mucus secretion, *etc.* VIP and SP are neurotransmitters released by nervous system, which play an important role in regulating the pathogenesis of asthma. Studies have found that VIP and SP are metabolized abnormally in the immune response of asthma patients, causing the increase of IgE. Participating in allergic reaction SP can promote bronchoconstriction, mucus secretion and plasma exudation, leading to airway stenosis, airflow obstruction, aggravation of airway inflammation, and stimulation of IgE production. VIP has a relaxing effect on bronchial smooth muscle. It is the strongest endogenous bronchodilator discovered at present. It has a strong effect of inhibiting the release of inflammatory mediators and resisting injury, regulating serum IgE levels, and participating in the regulation of immune response. The imbalance between VIP and SP often leads to the occurrence and aggravation of asthma. The results of this study showed that the plasma VIP content decreased and the SP content increased in the observation group and the control group before treatment ($P<0.05$), indicating that the neuromodulation mechanism of asthma patients was abnormal. After treatment, the increase of plasma VIP content and the decrease of SP content in the observation group were significantly improved compared with the control group ($P<0.05$), indicating that this method can regulate the release of neuromediators and achieve the purpose of preventing and treating asthma. This study shows that the pathogenesis of asthma is involved by many factors, and each factor does not exist alone, but influences each other, restricts each other, and breaks the balance of the body to lead to the occurrence of the disease. Acupoint liquid nitrogen cryotherapy improves immune function by interfering with the secretion of cytokines and the release of nerve mediators in the body, and then plays a role in preventing and treating bronchial asthma. This result is basically consistent with the report of Wang Dong *et al.*[9] The liquid nitrogen acupoint cryotherapy is used in Xinjiang to treat bronchial asthma in remission period, and the curative effect is remarkable, and it is superior to conventional crude herb moxibustion therapy.

Acupoint liquid nitrogen cryotherapy for summer treatment of winter disease has definite curative effect on bronchial asthma in remission, but it is difficult to explain its mechanism of action from a single mechanism. Whether it is immune function, cytokines or nerve mediators, they all interact with each other, form a network, and participate in the whole process of disease occurrence and development. Therefore, our research group explored its possible mechanism from the neuro-endocrine-immune network system, in order to make a reasonable explanation of its mechanism from a holistic perspective. Through the above research, it is shown that acupoint liquid nitrogen cryotherapy for summer treatment of winter

disease can improve the protective factors of the body, reduce the pathogenic factors, and improve the immune function by regulating the secretion of cytokines and the release of nerve mediators, thus achieving the effect of preventing and treating bronchial asthma. Due to the limitation of objective conditions, it is not possible to study the intervention effect of this method on patients with acute attack of bronchial asthma. Moreover, the research on neuro-endocrine-immune network system is still in the preliminary stage, and its internal relationship needs to be further studied.

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