BCG Polysaccharide Nucleic Acid Interferes with the Mechanism of PHN Mediated by Inflammatory Factors

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Abstract: OBJECTIVE: To investigate the effect of BCG polysaccharide nucleic acid on pain and inflammatory factors of postherpetic neuralgia (PHN)METHODS: The included patients were randomly divided into the conventional treatment group and BCG-PSN group. Both groups were given conventional pain treatment. BCG-PSN group was treated with BCG-PSN nucleic acid. To observe and compare the changes of quality of life (QOL), visual analogue score (VAS), SP, inflammatory factors interleukin-1 Settings (il-1 Settings), interleukin-6 (il-6), interleukin-10 (il-10), and record the adverse reactions [RESULTS]: VAS and QOL scores after treatment showed that the pain symptoms of each group were significantly alleviated and the quality of life was good. The concentration of SP, the pain substance, was decreased by radioimmunoassay, and the expression levels of il-1 and il-6 and il-10 were significantly decreased by ELISA. The improvement of bcg-psn group was more likely to healthy people than the conventional treatment group ($P<0.05$). [CONCLUSION]: BCG-PSN can effectively reduce the neuroinflammatory pain response of PHN and relieve pain. The mechanism may be to improve the expression of serum inflammatory factors and regulate the local inflammatory environment caused by chronic pain.

Postherpetic Neuralgia (PHN) is a common peripheral neuropathic pain, with a high incidence rate and typical characteristics of spontaneous pain. Herpes virus has long been latent in the neurons of dorsal root ganglion after infection. When the body's immunity is reduced, the virus is activated, causing inflammation and degeneration of nerve cells and resulting in local neuropathic pain. Known analgesics, antidepressants and other drug treatment methods can only relieve symptoms, but cannot control the disease and eliminate the cause. What's more, with the clinical use of side effects, poor patient compliance and other problems gradually appear. At present, it is known that the low immunity is related to the destruction of spinal cord nerve cells by herpes zoster virus. The pathogenesis of postherpetic neuralgia may be related to peripheral neuropathy, including heterotopic conduction impulse after nerve injury and hyperalgesia caused by inflammation of peripheral nerve trunk. Cytokine is a kind of small molecular protein with extensive biological activity and a component of the immune system, it plays an important role in the induction and maintenance of neuropathic pain. The occurrence and aggravation of herpes zoster may be related to the abnormal level of cytokines secreted by helper Th cells in the body. BCG-PSN is an immunomodulator, which can improve the body's immunity and has a certain clinical effect on herpes zoster, but the mechanism of action is unknown. To study the regulation of inflammatory factors by immunomodulator BCG-PSN, and to explore the immunomodulatory effect of BCG-PSN

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on PHN patients, so as to reduce neurological damage, improve neuropathic pain and promote rehabilitation.

1. Introduction

1.1. Patient Selection

1.1.1. General Information

With signed informed consent ,60 patients with PHN in a hospital from November 2017 to September 2019 were randomly divided into BCG-PSN group and conventional treatment group (there was no significant difference in symptom scores between the two groups before treatment), and 30 healthy people were randomly selected as blank control group, and informed consent was signed. There were 34 males and 56 females, aged from 47 to 70 years old, with an average of (59.00 ± 5.88). There was no significant difference in general information between the two groups ($P > 0.05$).

1.1.2. Inclusion and Exclusion Standard

Inclusion criteria: Patients with VZV infection diagnosed as Hz and pain lasting more than one month after rash healing were regarded as PHN patients; the pain feeling of patients met the pain standard defined by PHN; the age was > 40 years old; VAS score was > 4 points; without treatment, there was no cognitive impairment; the lesion site had scab and fell off. Exclusion criteria: Recent use of other drugs or long-term use of immunosuppression; severe heart disease, cerebrovascular, liver and kidney injury; patients with hematopoietic system and other primary diseases or systemic failure; patients with malignant tumor; pregnant and lactating women; suffering from mental diseases; serious infection; serious central nervous system complications; not according to the requirements of medication, cannot judge the curative effect or inadequate information.

1.2. Therapeutic Method

Conventional treatment group: Gabapentin capsules (national medicine Zhunzi h20030662), 300mg, Po on the first day, 300mg, Po, bid on the next day, and 300mg, Po, TID later. Vitamin B12 injection, 1ml, Im, QOD. Two weeks in a row. BCG-PSN group: on the basis of conventional treatment group, BCG-PSN was given, 1ml each time, Im, QOD. In the blank control group, only blood samples were taken without any intervention.

1.3. Obvervational Index

（1）VAS was used to evaluate the pain before and after treatment, and QOL was used to evaluate the quality of life;

（2）Observation and record of the adverse reactions occurred in the two groups after medication;

（3）The levels of serum inflammatory factors and neurotransmitter SP in three groups;

（4）Record of the adverse reactions during medication;

（5）In the blank control group, blood samples were taken and evaluated by VAS.

1.4. Detection Method

Venous blood was collected before and after treatment, centrifuged at 4 ℃ and 1500rpm for 15min, and serum was stored in refrigerator at - 80 ° C for standby. In the blank control group, only blood samples were taken without any intervention. The serum levels of SP, IL-1 β, IL-6 and IL-10 were determined by ELISA.

1.5. Data Analysis

Spss22.0 software was used for statistical data, and the measurement data was expressed as (± s).

T test was used, and P < 0.05 showed that the difference was statistically significant.

2. Results

2.1. Comparison of pain degree between the two groups

VAS method was used to evaluate the pain of patients. The study showed that the VAS pain score of the conventional treatment group and BCG-PSN group before treatment was not statistically significant (P > 0.05), and the VAS pain score of each group after treatment and before treatment was lower than that before treatment, the difference was statistically significant (P < 0.05). After treatment, VAS pain score in BCG-PSN group was lower than that in conventional treatment group (P < 0.05). There was no obvious adverse reaction in each group. By comparing the VAS score and safety, the analgesic symptoms in each group were significantly alleviated, and the improvement in BCG-PSN group was better than that in conventional treatment group.

Tab 1 VAS pain score before and after treatment（$\bar{x}$±s，n=30）

group	before treatment	after treatment
Conventional treatment group	6.67±1.46	2.77±0.25*
BCG-PSN group	6.86±1.16	2.02±0.06*#

Note：*Compared with the same group before treatment*$P<0.05$, #compared with the conventional treatment group after treatment#$P<0.05$

2.2. Comparison of quality of life between the two groups

QOL method was used to evaluate the quality of life. There was no significant difference in QOL score between the conventional treatment group and BCG-PSN group before treatment (P > 0.05), but the QOL score of the same group increased after treatment (P < 0.05). After treatment, the QOL scores of the two groups were significantly higher (P < 0.05). See Table 2

Tab 2 QOL score before and after treatment（$\bar{x}$±s，n=30）

Tab 2 QOL Scores of Conventional treatment group and BCG-PSN group before and after treatment（ $\bar{x}$±s，n=30）

group	before treatment	after treatment
Conventional treatment group	63.73±5.74	88.50±5.04*
BCG-PSN group	66.50±5.05	90.80±2.52*#

Note：*Compared with the same group before treatment *P＜0.05, #compared with the conventional treatment group after treatment #P＜0.05

2.3. Effect of BCG-PSN on SP in PHN patients detected by ELISA

There was significant difference between the blank control group and the conventional treatment group and the BCG-PSN group (P < 0.05). There was no significant difference in the level of SP pain substance between the two groups before treatment, and the level of SP decreased significantly after treatment. Although the expression of SP was decreased, there was no significant difference between the conventional treatment group and BCG-PSN group (P > 0.05)

Tab 3 Pain substance before and after treatment（ $\bar{x}$±s，n=30）

group	before treatment SP（μg/mL）	after treatment SP（μg/mL）
blank control group	3.37±0.33	
Conventional treatment	6.03±0.69	3.52±0.13*

group		
BCG-PSN group	5.97±0.71	3.44±0.11*

Note：*Compared with the same group before treatment* $P<0.05$

2.4. Effect of BCG-PSN on the expression of inflammatory factors in PHN patients by ELISA

There was significant difference in the levels of inflammatory factors between the blank control group and the conventional treatment group and the BCG-PSN group ($P < 0.05$), but there was no significant difference in the levels of inflammatory factors between the two groups before treatment ($P > 0.05$); After treatment, the levels of IL-1 β and IL-6 in the two groups were lower than those in the blank control group, the levels of IL-10 in the BCG-PSN group were higher than those in the blank control group, and the improvement in the BCG-PSN group was more obvious than that in the conventional treatment group ($P < 0.05$).

Tab 4 The levels of inflammatory factors were compared before and after treatment（ $\bar{x}\pm s$，n=30 ）

group	IL-1βbefore（pg/ml）	IL-1βafter（pg/ml）	IL-6before（pg/ml）	IL-6after（pg/ml）	IL-10before（μg/ml）	IL-10after（μg/ml）
blank control group	10.26±0.32		336.59±12		177.54±9.28	
Conventional treatment group	20.03±0.53*	9.10±0.61*	517.24±18*	307.88±14*	135.54±6.27	165.66±8.78*
BCG-PSNgroup	19.91±0.66*#	10.00±0.28*#	508.47±24*#	332.41±13*#	134.56±6.51	184.47±7.92*#

Note：*Compared with the same group before treatment *P＜0.05, #compared with the conventional treatment group after treatment #P＜0.05

3. Discussion

PHN brings the biggest trouble to patients is pain, which seriously affects their quality of life. Postherpetic neuralgia is a common complication caused by varicella zoster virus infection. The main cause is that the virus invades the nerve, and the virus that lurks in the nerve is not completely removed from the body. With the increase of age, the patient's immunity decreases, and the patient's pain is lingering. The defense process that the body can control well is due to immune and inflammatory reactions. It is very important for the immune system to respond effectively to a certain pathological state of the body. There are many mechanisms in the balance of immune response and inflammatory response, one of which is to regulate the expression of cytokines to deal with inflammatory response. Researchers found that by reducing the expression of inflammatory factors and inhibiting the release of neurotransmitters, it mediates the pathological pain caused by nerve injury1. Substance P (SP) is an important neurotransmitter involved in neuropathic pain. The expression of SP in peripheral chronic neuropathic pain is increased, and SP can cause the secretion of inflammatory pain factors, thus participating in pain regulation 2. This study showed that the expression of SP was decreased, but the change was not significant ($P > 0.05$), but by comparing the VAS score and QOL method to evaluate the quality of life of patients, the pain symptoms of each group were significantly reduced, the quality of life was good, and the improvement of BCG-PSN group was better than that of conventional treatment group.

After herpes zoster virus infects human body, it lurks in neurons of dorsal root ganglion of spinal nerve for a long time. When the body's immunity is reduced, the virus is activated, causing

inflammation and degeneration of nerve cells, resulting in local neuropathic pain. Inflammatory factors are closely related to postnatal neuralgia, and cell activation participates in the reaction of neuroinflammatory pain. IL-1 is a polypeptide with extensive biological activity. IL-1 β participates in the immune response of the central nervous system and has nutritional effect on the central nervous system. At the same time, there is a high concentration of IL-1 β in the central inflammatory and painful reactions3. IL-1 β is involved in immune and inflammatory reactions. The serum IL-1 β level of patients with acute herpes zoster is significantly increased, and IL-1 β is closely related to the occurrence of PHN 4. IL-6 is a kind of proinflammatory factor, which can ensure the normal development of nerve and accelerate the function of nerve repair. The damage of nervous system is often due to the high concentration of IL-6 cytokines, which can induce pain by expanding the excitability of neurons. IL-6 can stimulate neuronal excitation, which can lead to persistent pain in patients with herpes zoster 5. Meanwhile, IL-1 β can induce the expression of inflammatory pain inducing substance IL-6. For PHN patients, BCG-PSN is added to the conventional treatment to regulate the immune function. BCG polysaccharide nucleic acid is a kind of substance with immunomodulatory function extracted from BCG. It can enhance the function of natural killer cells by regulating cellular immunity and humoral immunity, so as to improve the antiviral ability of the body. Through the study of PHN patients (before treatment) group and blank control group, the expression of related inflammatory factors was determined by ELISA. The levels of IL-1 β and IL-6 in patients with postherpetic neuralgia were significantly higher than those in blank control group ($P < 0.05$). After BCG-PSN intervened PHN, the results showed that the expression levels of IL-1 β and IL-6 cytokines in PHN patients decreased between groups before and after treatment ($P < 0.05$), and the mechanism of BCG-PSN on PHN was clarified.

IL-10 is an important anti-inflammatory factor with a variety of activities 6, which can not only change the autoimmune response, but also achieve immunosuppression through the expression of antigen by antigen-presenting cells. It plays an important role in anti-inflammation and immunosuppression 7. IL-10 is an inhibitory regulatory factor, and its high-level expression can inhibit the release of proinflammatory factors, so as to reverse neuralgia 8. The results showed that the level of IL-10 was higher than that before treatment, the difference was statistically significant ($P < 0.05$). IL-1 β can induce the expression of inflammatory pain inducing substance IL-6. The imbalance of IL-6 and IL-10 levels in patients with herpes zoster can lead to neuralgia. Some studies have shown that improving the levels of IL-1 β [9] and IL-10 [10] can reduce the incidence of postoperative neuralgia. The results of this study also showed that the level of IL-10 in the BCG-PSN group was more obvious than that in the conventional control group. The results further suggest that BCG-PSN treatment can effectively improve the level of inflammatory factors in patients with herpes zoster, reduce local inflammatory reaction, and achieve the effect of reducing pain. The study revealed the difference and correlation of the content changes and level changes of related indicators in serum, and alleviated the pain state of patients. The mechanism may be related to improving the expression of serum inflammatory factors, regulating the inflammatory environment caused by chronic pain, reducing pain and reducing neuroinflammatory pain response. It has a certain clinical value by improving the immune ability of patients, improving clinical symptoms and promoting rehabilitation, which provides a scientific basis for BCG-PSN intervention in PHN.

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