

# Effect and Immune Mechanism of BCG-PSN on Postherpetic Neuralgia: A Single-Masked, Randomised Controlled Trial

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## ABSTRACT

**Objective:** To investigate the therapeutic effect of the immune modulator Bacillus Calmette-Guerin polysaccharide and nucleic acid injection (BCG-PSN) on postherpetic neuralgia (PHN), and measure immune-related markers to elucidate the immune mechanism of BCG-PSN in treating patients with PHN with neuropathic pain.

**Study Design:** Single-masked randomised controlled trial.

**Place and Duration of the Study:** Department of Dermatology, Zhongnan Hospital, Wuhan University, Wuhan, Hubei, China, from January 2022 to December 2023.

**Methodology:** Ninety-eight patients with PHN were randomly assigned to receive oral administration of gabapentin (control group, n = 49), or a combination of gabapentin and locally injected BCG-PSN (BCG-PSN group, n = 49) for eight weeks. Two-sample and paired t-tests were used to measure the visual analogue scale (VAS) and quality of life (QOL) scores. Immune-related markers were measured in peripheral blood samples using flow cytometric staining. The  $\chi^2$  test was used to compare the incidence of adverse reactions.

**Results:** The VAS and QOL scores in the BCG-PSN group were significantly better than those of the control group ( $p < 0.001$  and  $p = 0.002$ ). The CD3<sup>+</sup>, CD4<sup>+</sup>, CD19<sup>+</sup>, and CD56<sup>+</sup> cells and the CD4<sup>+</sup>/CD8<sup>+</sup> ratio of the BCG-PSN group were statistically lower than those of the control group ( $p < 0.05$ ). No significant differences were observed in the incidence of adverse reactions between the two groups ( $p = 0.804$ ).

**Conclusion:** The results indicated that BCG-PSN could effectively alleviate pain and improve immune function in patients with PHN.

**Key Words:** BCG-PSN, Postherpetic neuralgia, Immune modulation, Neuropathic pain, Gabapentin.

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## INTRODUCTION

Postherpetic neuralgia (PHN) is the most annoying and common complication of herpes zoster (HZ) infection, caused by the varicella-zoster virus (VZV) that remains dormant in the posterior root ganglia or cranial ganglia of the spinal cord after primary varicella infection.<sup>1</sup> According to the German S2k-guidelines, PHN refers to pain lasting more than three months after HZ skin lesions healed.<sup>2</sup> The incidence of PHN in patients with HZ is 5-30%, and is more common in older and immunocompromised patients.<sup>3</sup> Patients who have been troubled by PHN for a long time are prone to chronic fatigue, sleep disorders, depression, anxiety, unemployment, and social isolation.<sup>4,5</sup>

Pharmacological pain management methods include analgesics, antidepressants, and other medications in clinical practice. However, this can only alleviate symptoms and cannot control or eliminate the underlying causes. In addition, the impact of poor patient adherence behaviour will increase due to reduced clinical effectiveness as doctors continue to rely on a prescriptive approach.<sup>6</sup> The underlying pathology and pathogenesis of PHN are unknown, but it is possibly linked to immunopathological processes within the sensory ganglia.<sup>7</sup> For example, in a study, mice with IFN- $\gamma$  gene knockout have been shown to have lower hyperalgesia and allodynia. IFN- $\gamma$  is an immune regulatory cytokine in spinal cord tissue, increasing its level can relieve pain in PHN rats.<sup>8</sup>

Bacillus Calmette-Guerin polysaccharide and nucleic acid injection (BCG-PSN) is a relatively new generation, bacterial lipopolysaccharides fraction extracted from BCG vaccines using a BCG-based hot phenol method.<sup>9</sup> As an immune regulator, BCG-PSN has been used to treat skin diseases such as vitiligo, neurodermatitis, urticarial, and systemic lupus erythematosus.<sup>10</sup> It acts on intracellular signalling pathways by secreting different cytokines, activating the immune function

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of monocytes macrophages and reducing inflammation secretion.<sup>11</sup> Previous studies have shown that BCG-PSN is relatively safe for clinical use, and its immune regulatory function can play a role in treating and relieving pain caused by viral infections.<sup>12</sup> Despite intensive research on the clinical evaluation of treatment effectiveness, its potential therapeutic mechanism has not been thoroughly explored.

Several studies focused on the pathogenesis of neuropathic pain through immune response.<sup>6,7,10</sup> It was presumed that the immune function may be disrupted during the formation of PHN, and that treatment with BCG-PSN could alleviate neuropathic pain by stabilising immune function. The aim of this study was to investigate whether BCG-PSN treatment provides recovery and regulates immune cells balance in patients with PHN. To the authors' knowledge, this is the first study to investigate the effect of BCG-PSN on immune function.

## METHODOLOGY

This prospective single-masked randomised controlled trial was conducted in the Department of Dermatology, Zhongnan Hospital of Wuhan University, Wuhan, China, from January 2022 to December 2023. This study was conducted in accordance with the tenets of the 2013 revision of the Declaration of Helsinki. It was approved by the Institutional Ethics Committee of the Zhongnan Hospital of Wuhan University (Approval No: 2022047; Date: January 2022) and was registered with the China Drug Clinical Trial Registration Platform (CTR20211651).

The inclusion criteria were as follows: Patients diagnosed with HZ due to VZV infection who continued to experience pain for more than a month after the rash had healed and were considered as having PHN, the visual analogue scale (VAS) score exceeded 4 points; the patients were aged 18–80 years; had not been treated, had no cognitive impairment, understood the intervention measures used in the experiment, and agreed to participate in the experiment, with the affected area having scabbed and the scab having fallen off. Patients with a history of long-term immunosuppression therapy, chronic renal failure, psychiatric disease, severe organ dysfunction, malignant tumour, autoimmune diseases, or immunodeficiency or who were pregnant or breastfeeding were excluded from the study.

For randomisation, participants were selected using the sealed envelope method without external notations or identification that might affect group allocation. The randomisation process followed the CONSORT guidelines. Masking for researchers who implemented the intervention was not possible, as the drug prescription required supervision.

The control group was given gabapentin capsules. Gabapentin dosages were increased to 900 mg/d within one week due to its analgesic properties, using the approved protocol [Day 1: 300 mg quaque die (qd); Day 3: 300 mg bis in die (bid); Day 7: 300 mg ter in die (tid)]. Patients continued on a stable dosage of 900 mg/d for an additional seven weeks. The approved BCG-PSN dosage schedule [1 ml each time, intramuscular (Im), quaque

omni die (QOD)] was added to the treatment plan of the control group for the experimental group. In addition, two groups were given methyl adenosine cobalamin, an oral neuroprotective vitamin B12 agent. The patients' VAS scores, physical tolerances, and medication side effects were checked every week, and the dosages were adjusted. After 8 weeks of treatment, the nurse contacted the patients telephonically, requesting them to visit the hospital so that the efficacy could be evaluated.

The VAS score, which has a 10-step linear scale ranging from no pain to the worst pain, was used to assess the intensity of neuropathic pain in patients with PHN upon completion of the test. The Cronbach's alpha value was 0.83, ensuring its internal consistency.

The participants' quality of life (QOL) was measured using the summary version of the WHOQOL-100, with six domains appraising overall QOL (bodily well-being, mental well-being, socialisation, environment, independence, and beliefs), including 100 entries.<sup>12</sup> The highest score is 100 points. Those with a total score <60 have poor QOL, those with 60–70 points have average QOL, those with 70–80 points have good QOL, and those with 80–100 points have good QOL. Overall, Cronbach's alpha for each domain and the general QOL facet ranged from 0.76 to 0.90.

Blood samples (5 ml) were collected from a median cubital vein, allowed to clot for 45 minutes and centrifuged at 3000 rpm for 10 minutes. The samples were stored at -80°C for backup. Venous blood (100 µL) was mixed with fluorescently labelled antibodies for surface staining and incubated for 30 minutes in the dark. Erythrocytes lysing reagent (5 ml) was then added, incubated for 10 minutes, and centrifuged. The supernatant was discarded, and the pellet was washed twice with phosphate buffer solution. CD3<sup>+</sup>, CD4<sup>+</sup>, CD4<sup>+</sup>/CD8<sup>+</sup>, CD19<sup>+</sup> (B cells), and CD56<sup>+</sup> (natural killer [NK] cells) cells were detected using flow cytometry. All the reagents were purchased from Beckman Coulter (Brea, CA, USA).

Adverse reactions (ADRs) were recorded during the trial period. An independent data monitoring committee (DMC) reviewed the safety findings, evaluated all available accumulated safety data, investigated compliance with the trial, and monitored adverse events.

G\*Power version 3.1.9.7 was used to estimate the required sample size, with an alpha of 0.05, an effect size of 0.8, a test power of 0.95, and a target sample size of 84. Based on the centre's previous clinical trial experience with PHN, a 10% sample loss was considered. Therefore, the minimum sample size was ultimately estimated required to be 97 cases. SPSS software, version 26.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. The test of normality can be observed through the Shapiro-Wilk's test. Quantitative data that conformed to a normal distribution were expressed as mean ± standard deviation. The categorical data was presented as percentages, with comparisons being made using the  $\chi^2$  test. A paired t-test was used for analysis before and after treatment, and a two-sample

t-test was used for comparison between groups. Statistical significance was set at  $p < 0.05$  on both sides.

## RESULTS

A total of 106 patients were initially recruited, of whom 98 patients met the eligibility criteria for inclusion. Eight of the total 106 patients were excluded due to refusal, failure to meet inclusion criteria, and loss of follow-up. No dropouts occurred after drug allocation. The baseline data for gender, age, disease duration, and comorbidities were consistent between the two groups ( $p > 0.05$ , Table I).

Considered as a whole, both the control and BCG-PSN group treatments significantly affected the patients' symptomatology and QOL. The pre-treatment VAS scores of the control and BCG-PSN group patients were  $7.03 \pm 1.68$  and  $6.89 \pm 1.82$ , respectively (Table II). While scores were significantly reduced ( $p < 0.001$ ), a more pronounced decrease was observed in the BCG-PSN group ( $p < 0.001$ ). There was a significant increase in the QOL values ( $p < 0.001$ ), and the improvement was more pronounced in the BCG-PSN group ( $p = 0.0016$ , Table III). No adverse reactions led to treatment interruption or suspension during the trial period.

When immune-related markers, including  $CD3^+$ ,  $CD4^+$ ,  $CD4^+/CD8^+$ ,  $CD19^+$ , and  $CD56^+$  cells, were compared before and after treatment, the BCG-PSN group showed a more significant increase ( $p < 0.05$ , Figure 1).

During the routine treatment of the control group, five patients experienced adverse reactions, including nausea, vomiting, and dizziness. In comparison, six patients in the BCG-PSN group displayed adverse reactions, including high body temperature, nausea, vomiting, and visual impairment. The ADR incidence between the two groups was similar (10.2% vs. 12.2%,  $\chi^2 = 0.062$ ,  $p = 0.804$ ). One patient with medicine intolerance showed significant improvement in adverse reactions after adjusting the dosage. The other ten patients did not receive special treatment and gradually improved with the treatment process. The patient with ADR underwent routine blood, urine, liver, and kidney examinations, and no abnormalities were found.

## DISCUSSION

PHN, a complication of HZ caused by recurrent latent VZV infection, is characterised by chronic neuropathic pain mainly affecting older people, severely impacting their lives.<sup>1</sup> The incidence and severity of PHN increase with age, and up to 30% of people over the age of 80 years who contract HZ will develop PHN.<sup>13</sup> For years, the pathogenesis of neuropathic pain has been believed to be related to pro-inflammatory cytokines, and many scholars have focused on the anti-inflammatory treatment effects of cytokines.<sup>14,15</sup> However, recent research evidence increasingly suggests that immune system deficiencies promote the occurrence of neuropathic pain.<sup>16</sup>

**Table I: The baseline characteristics of patients.**

Demographic variables	Control group (n = 49)	BCG-PSN group (n = 49)	t /c2	p-value <sup>a</sup>
Age (years)				
18-60	7	9	0.3500	0.8395
61-70	21	19		
$\geq 71$	21	21		
Gender				
Male	23	24	0.1650	0.6846
Female	26	25		
PHN duration (day)	$51.36 \pm 9.79$	$50.48 \pm 9.47$	0.4758	0.6353
At least one comorbidity				
No	19	12	2.3120	0.1284
Yes	30	37		

a: Comparison between control group and experimental group using two sample t-test and  $\chi^2$  test.

**Table II: Comparison of VAS scores of patients.**

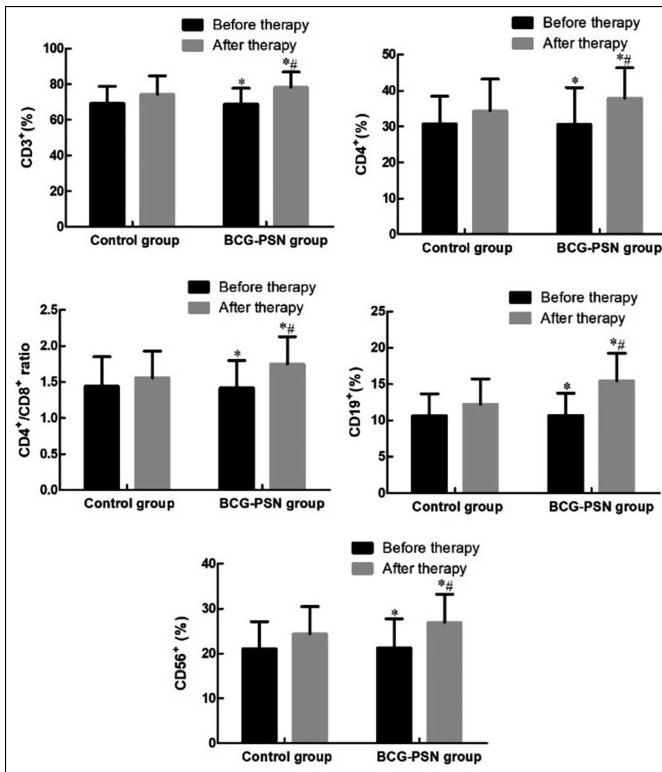
Group	Before therapy	After therapy	95% CI	t	p-value <sup>a</sup>
Control group (n = 49)	$7.03 \pm 1.68$	$3.09 \pm 0.53$	3.4581, 4.4219	15.6561	<0.001
BCG-PSN group (n = 49)	$6.89 \pm 1.82$	$2.42 \pm 0.47$	3.9177, 5.0211	16.6462	<0.001
95% CI	-0.5624, 0.8424	0.4686, 0.8702			
t	0.3957	6.6208			
p <sup>b</sup>	0.6932	$\square 0.001$			

a: Comparison before and after treatment using paired t-test; b: Comparison between control group and experimental group using two sample t-test.

**Table III: Comparison of QOL scores.**

Group	Before therapy	After therapy	95% CI	t	p-value <sup>a</sup>
Control group (n = 49)	$58.49 \pm 6.89$	$79.23 \pm 10.55$	17.3267, 24.1534	11.5217	<0.001
BCG-PSN group (n = 49)	$60.47 \pm 7.37$	$86.49 \pm 11.59$	22.1525, 29.8867	13.2612	<0.001
95% CI	-4.8411, 0.881	2.8159, 11.7052			
t	1.3738	3.2426			
p <sup>b</sup>	0.1727	0.0016			

a: Comparison before and after treatment using paired t-test; b: Comparison between control group and experimental group using two sample t-test.



**Figure 1: Comparison of immune-related markers.**  
\*Compared with before treatment,  $p < 0.05$ ; #Compared with the control group,  $p < 0.05$ ; #Compared with the control group and experimental group using two-sample t-test and  $\chi^2$  test paired t-test.

BCG-PSN is a bioactive substance extracted from BCG after protein removal. Its main components are lipopolysaccharides and nucleic acids, which maintain the immune function of BCG and reduce adverse reactions.<sup>9</sup> BCG-PSN has been studied for use in clinical immuno-therapy applications.<sup>10,11</sup> Previous studies have shown that pain can be alleviated in patients with PHN by reducing the expression of the serum inflammatory factors interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-10 (IL-10) in the neuro-inflammatory pain response.<sup>12</sup>

Zhou *et al.*'s study has shown that age is the biggest risk factor for developing PHN in patients with HZ.<sup>17</sup> A cross-sectional study in China showed that 80% of PHN occurs in people over the age of 50 years.<sup>18</sup> In this study, the proportion of patients aged over 60 years in the BCG-PSN group and control group was 81.6% and 85.7%, respectively, which is consistent with Zhou *et al.*'s conclusion. Although previous studies have confirmed that PHN is more prevalent in women, a recent study involving 21 female patients and 19 male patients indicated no difference between genders (52.5% vs. 47.5%).<sup>19</sup>

Compared to those before treatment, the QOL scores of both groups increased and VAS scores decreased, indicating that the patients' symptoms and QOL improved after eight weeks of treatment. The QOL score of the BCG-PSN group was higher than that of the control group, and the VAS

score was lower than that of the control group, suggesting that the BCG-PSN group had a better analgesic effect on patients. In addition, the most direct clinical significance of the increase in VAS and QOL scores was that patients felt their disease was improving, which can significantly improve patients' overall self-confidence.

Patients with PHN have lower CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells, as well as CD4<sup>+</sup>/CD8<sup>+</sup> T cell ratio than patients without PHN.<sup>20</sup> Wang *et al.* found CD4<sup>+</sup>/CD8<sup>+</sup> ratio is an independent risk factor for determining whether patients with HZ develop PHN.<sup>21</sup> BCG-PSN can inhibit the expression of substance P and neuropeptide Y in peripheral blood mononuclear cells of patients with PHN, thereby reducing the release of pain neurotransmitters and alleviating pain hypersensitivity. It can also upregulate the expression of nerve growth factor (NGF) to protect damaged neurons and accelerate the recovery of damaged nerve areas.<sup>12</sup> Lack of these cytokines triggers cross-reactive immunity against VZV, leading to an increased risk of HZ and the subsequent development of PHN.<sup>22</sup> BCG-PSN treatment resulted in an increase in CD3<sup>+</sup>, CD4<sup>+</sup>, and CD4<sup>+</sup>/CD8<sup>+</sup> T cells and a significant decrease in VAS scores, indicating relief of neuropathic pain symptoms. Therefore, it was concluded that a low immune-related marker level, such as CD3<sup>+</sup>, CD4<sup>+</sup>, and CD4<sup>+</sup>/CD8<sup>+</sup> ratio, is a risk factor for promoting the development of PHN. The increase in immune-related markers after BCG-PSN treatment significantly reduces the neuropathic pain symptoms. However, the specific mechanism of the increase in immune markers is still uncertain, which may be a topic for future research. Subsequently, the authors measured B and NK cell levels. The results from this study indicated that treatment with BCG-PSN can effectively improve the immune function of patients with PHN, achieving the goal of reducing pain and improving the patients' QOL.

As a first-line therapy for PHN, gabapentin, being both efficacious and safe, reduces the release of excitatory neurotransmitters by binding to the  $\alpha 2\delta$  subunit of voltage-gated calcium channels. In cases where monotherapy is insufficient, the implementation of combination therapy with opioids or antidepressants (as second-line or third-line treatment) is used.<sup>23</sup> Despite widespread use and an increasing number of randomised controlled trials,<sup>24</sup> so far, there is no strong and convincing evidence to demonstrate the superiority of any combination over its respective monotherapies. Combination therapy raises concerns related to the potential drug safety. Therefore, BCG-PSNs can be used in combination with gabapentin. Although BCG-PSN cannot replace opioid analgesics or antidepressants as a first-line treatment, it can be used in combination with analgesics to provide a synergistic effect during acute attacks and help reduce recurrence during stable periods. Compared with existing treatment methods, it has high clinical safety and low usage cost and can be used as a powerful supplementary tool for PHN medicine treatment plans.

Firstly, the single-centre design limited the research findings to other centres or the entire population. The sample size was relatively small, resulting in possible bias in the results. Resulting in possible bias in the results. Second, among the 98 patients, 77 had at least one chronic disease. It is unclear whether the combined diseases affect the prognosis of patients. The results were not subjected to stratified analysis on whether there were comorbidities, making it impossible to determine the impact of comorbidities on the therapeutic effect of BCG-PSN, which may lead to bias. Lastly, the study had an eight-week treatment period and lacked long-term follow-up evaluation of treatment efficacy and recurrence, which will be an important direction for expanding sample studies in the future. Considering this possible bias, this study was published as a pilot study. Future large, multi-centre, well-designed randomised controlled trials are needed to clearly demonstrate the effects of BCG-PSN on the mechanisms and long-term effects of PHN treatment.

## CONCLUSION

This study found that BCG-PSN therapy significantly affected immune-related markers in patients with PHN, especially CD3<sup>+</sup>, CD4<sup>+</sup>, CD4<sup>+</sup>/CD8<sup>+</sup>, CD19<sup>+</sup>, and CD56<sup>+</sup> cells. These differences in immune-related markers indicate that the system's role in the mechanism of PHN occurrence is much more important than previously believed. BCG-PSN has specific clinical values by regulating patients' immune function, improving clinical symptoms, and promoting recovery, and is expected to be used for PHN.

### ETHICAL APPROVAL:

This study was conducted in accordance with the tenets of the 2013 revision of the Declaration of Helsinki. It was approved by the Institutional Ethics Committee of the Zhongnan Hospital of Wuhan University (Approval No: 2022047; Date: January 2022) and was registered with China Drug Clinical Trial Registration Platform (CTR20211651).

### PATIENTS' CONSENT:

Participants are aware of the potential risks associated with this study protocol and have signed an informed consent form.

### COMPETING INTEREST:

The authors declared no conflict of interest.

### AUTHORS' CONTRIBUTION:

YW, MG: Analysed the data, prepared the first draft, revised the manuscript, and confirmed the authenticity of all the raw data.

YW, JW: Conceived and designed the study; confirmed the authenticity of all the raw data.

All authors approved the final version of the manuscript to be published.

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