ABSTRACT

Introduction: Postherpetic neuralgia (PHN) is the most common complication of herpes zoster. Methylene blue (MB) is an inhibitor of nitric oxide synthesis with potentially analgesic and anti-inflammatory properties. Studies have demonstrated that thoracic paravertebral single MB injection is effective in treating chronic pain. However, there are rare reports of the efficacy of continuous thoracic paravertebral infusion of MB for pain management in PHN patients. The purpose of this study was to evaluate the therapeutic effects of continuous thoracic paravertebral infusion of MB on PHN.

Methods: A total of 104 PHN patients were randomly divided into two groups: the control group (continuous thoracic paravertebral infusion of 5% lidocaine in a total volume of 300 ml) and the MB group (continuous thoracic paravertebral infusion of 5% lidocaine plus 0.2% MB in a total volume of 300 ml). All patients were evaluated using the Numerical Rating Scale (NRS), Insomnia Severity Index (ISI), Patient Health Questionnaire-9 (PHQ-9), 36-Item Short-Form Health Survey (SF-36), and medication doses before and after the procedure. The effective treatment rate and adverse complications were recorded 6 months after the procedure.

Results: In both groups, the NRS scores, ISI scores, PHQ-9 scores, and rescue medication dosages were significantly decreased at different time points after treatment compared to baseline, while the SF-36 scores were evidently improved at different time points after treatment compared to baseline. Compared with the control group, the MB group had significantly reduced NRS scores, ISI scores, PHQ-9 scores, and rescue medication dosages at each observation time point. Furthermore, the SF-36 scores in the MB group were significantly higher than those in the control group at each observation time point. The total effective treatment rate of the MB group was higher than that of the control group 6 months after the procedure. No severe adverse complications were observed in either group.

Conclusions: Ultrasound-guided continuous thoracic paravertebral infusion with MB is a safe and effective therapy for PHN. Continuous
infusion with MB can significantly reduce pain intensity, improve pain-related depression, increase quality of life, and decrease the amount of rescue medicine with no serious adverse complications.

**Keywords:** Postherpetic neuralgia; Methylene blue; Ultrasound guidance; Thoracic paravertebral infusion; Pain

### Key Summary Points

**Why carry out this study?**

Postherpetic neuralgia is the most frequent chronic complication of herpes zoster, and is manifested by neuropathic pain after the rash has healed [1]. Recent studies have shown that the annual incidence of HZ is approximately 3.4 cases per 1000 persons, and it rises sharply from the age of 50 years to approximately 10.9 cases per 1000 person in the ≥ 80 age group [2, 3]. It is estimated that approximately 20% of HZ patients develop PHN [4]. In China, a higher proportion (29.8%) of patients develop PHN, and the prevalence increases with age [5]. PHN can last from several months to several years, even up to 10 years. PHN substantially affects patient quality of life and can cause physical disability, emotional distress, and social isolation; it also presents a serious economic burden and public health problems for society [6, 7]. Therefore, a therapy that can effectively alleviate PHN is urgently needed.

The goal of PHN treatment is to improve quality of life by relieving pain. Currently, the main strategies for PHN management are medication and invasive interventional therapies. Pharmacological agents include opioids, antiviral drugs, nonsteroidal anti-inflammatory drugs, antiepileptic drugs, anticonvulsants, tricyclic antidepressants, and invasive interventional therapies, including pulsed radiofrequency of the dorsal root ganglion, electrical stimulation of the spinal cord, morphine pump implantation, peripheral neurotomy, autologous fat grafting, and acupuncture therapy [8–10]. However, these approaches have many adverse effects and risks, such as respiratory depression, nausea, vomiting, addiction, allergy, bleeding, infection, pneumothorax, and

### DIGITAL FEATURES

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### INTRODUCTION

Postherpetic neuralgia (PHN) is the most frequent chronic complication of herpes zoster (HZ), and is manifested by neuropathic pain after the rash has healed [1]. Recent studies have shown that the annual incidence of HZ is approximately 3.4 cases per 1000 persons, and it rises sharply from the age of 50 years to approximately 10.9 cases per 1000 person in the ≥ 80 age group [2, 3]. It is estimated that approximately 20% of HZ patients develop PHN [4]. In China, a higher proportion (29.8%) of patients develop PHN, and the prevalence increases with age [5]. PHN can last from several months to several years, even up to 10 years. PHN substantially affects patient quality of life and can cause physical disability, emotional distress, and social isolation; it also presents a serious economic burden and public health problems for society [6, 7]. Therefore, a therapy that can effectively alleviate PHN is urgently needed.

The goal of PHN treatment is to improve quality of life by relieving pain. Currently, the main strategies for PHN management are medication and invasive interventional therapies. Pharmacological agents include opioids, antiviral drugs, nonsteroidal anti-inflammatory drugs, antiepileptic drugs, anticonvulsants, tricyclic antidepressants, and invasive interventional therapies, including pulsed radiofrequency of the dorsal root ganglion, electrical stimulation of the spinal cord, morphine pump implantation, peripheral neurotomy, autologous fat grafting, and acupuncture therapy [8–10]. However, these approaches have many adverse effects and risks, such as respiratory depression, nausea, vomiting, addiction, allergy, bleeding, infection, pneumothorax, and
spinal cord injury. Therefore, it is important to find another effective and safe treatment for PHN. Recently, numerous studies have reported favorable outcomes with early nerve blocks and confirmed a positive impact on the prevention and treatment of PHN [11–13]. After the advent of ultrasound imaging in nerve blocks, ultrasound-guided thoracic paravertebral block (USG-TPVB) has become increasingly popular for perioperative pain management and neuropathic pain treatment. The ultrasound-guided approach is a preferred method due to easy visualization and accurate puncture of the paravertebral space. USG-TPVB can effectively mitigate acute postoperative pain and chronic neuropathic pain, and the incidence of undesirable complications of this approach, such as nausea, vomiting, extradural hematoma, pulmonary complications, and nerve injury, is low [14–17].

Methylene blue (MB) is a guanylyl cyclase inhibitor that can suppress the production of superoxide radicals. Several studies have shown that MB can be used as an antioxidative and anti-inflammatory agent for the treatment of malaria, psychotic disorders, osteoarthritis-associated pain, methemoglobinemia, cardiopulmonary bypass, shock, neurodegenerative diseases, and traumatic brain injury [18–22]. Recently, it was reported that ultrasound-guided thoracic paravertebral single methylene blue injection can significantly reduce pain intensity and plasma proinflammatory cytokine levels in PHN patients, and can improve their basic living ability and self-evaluation without incurring obvious adverse side effects [23].

The abovementioned research indicated that ultrasound-guided MB thoracic paravertebral injection is one possible choice for the treatment of PHN. However, whether continuous MB thoracic paravertebral infusion can provide safe, effective, and long-term analgesia for PHN patients is still unclear. Therefore, this prospective randomized study was conducted to evaluate the efficacy and safety of ultrasound-guided continuous MB thoracic paravertebral infusion in PHN patients.

METHODS

Ethics and Patients

This study was approved by the Institutional Review Board and Ethics Committee of Shanghai East Hospital (2019, No. 006). The present clinical research was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients before inclusion. A total of 106 patients with PHN were enrolled from January 2019 to January 2020 at the pain clinic of Shanghai East Hospital. The PHN diagnosis was based on the diagnostic criteria of the International Association for the Study of Pain (IASP). The inclusion criteria were as follows: (1) age > 18 years, (2) course of chronic pain > 30 days, (3) pain distributed in T1–T12, and (4) numeric rating scale (NRS) score > 6. The exclusion criteria were as follows: (1) severe dysfunction of the heart, lung, liver, and kidney, (2) acute systemic infection or serious immune disorders, (3) infection of the skin overlying the vertebra of the affected dermatome, (4) coagulation abnormalities, (5) allergy to the drugs used in this study, and (6) psychiatric diseases. Eligible patients were randomly assigned to one of the two groups (the MB group or the control group) using a computer-generated random number list.

Procedure

After the patients were admitted to the hospital, routine examinations, including blood tests for coagulation, blood glucose, liver function, and kidney function, were performed. All treatment procedures were performed in the operating room. Standard monitors, including electrocardiogram, noninvasive blood pressure, pulse oximetry, and heart rate, were applied. A blinded theater nurse who did not participate in the present study opened the envelopes and determined the group assignment. The patients were placed in the prone position, and a thin pillow was placed under the patient’s anterior lower thorax. The painful area on the body surface was labeled. Following standard skin asepsis, a
sterile surgical towel was placed on the patient. Precise paravertebral catheter placement was performed using an S-Nerve ultrasound machine (Sonosite, Bothell, WA, USA) with a linear 5–10 MHz ultrasound transducer at the thoracic level, using an in-plane approach. Prior to needle insertion, the skin was infiltrated with 3 ml of 1% lidocaine. The ultrasound transducer was positioned parallel to the rib along with the targeted intercostal space. By moving the transducer position, we identified the wedge-shaped thoracic paravertebral space, which is a hypoechoic area containing the costotransverse ligament, parietal pleura, and transverse process on an ultrasound image. An 18-gauge Tuohy needle (Tuoren, Xinxiang, Henan, China) was inserted into the paravertebral space, approximately 5 ml of normal saline was injected through the needle to dilate the paravertebral space, and a concomitant ventral shift of the pleura was confirmed. Subsequently, a 20-gauge epidural catheter (Tuoren, Xinxiang, Henan, China) was threaded through the needle into the paravertebral space 3–4 cm beyond the needle tip under real-time ultrasound surveillance. An aspiration test was performed to ensure that there was no intravascular or intrapleural puncture. The Tuohy needle was withdrawn, and the catheter was fixed to the skin. Finally, the catheter was connected to an electronic infusion pump and infused at a rate of 5 ml/h. Patients in the MB group received a medication cocktail of 60 mg methylene blue 6 ml + 1.5 g lidocaine hydrochloride 75 ml + 0.9% NaCl 219 ml. Patients in the control group received a medication cocktail of 1.5 g lidocaine hydrochloride 75 ml + 0.9% NaCl 225 ml. The inserted catheter was maintained in position for 2.5 days.

Outcome Measurement

Preoperative data, including gender, age, weight, height, body mass index (BMI), duration of PHN, preoperative NRS, preoperative ISI, preoperative PHQ-9 score, and dosage of rescue medication, were recorded. Follow-up assessments were performed 1 week, 1 month, 3 months, and 6 months after the operation (Fig. 1). Patients were evaluated at follow-up visits by a pain physician who did not participate in the surgery.

Primary Outcome

Pain intensity was assessed using the NRS. NRS scores were recorded in the two groups and ranged from 0 (no pain) to 10 (worst pain imaginable).

Secondary Outcome

Depression Assessment

The Patient Health Questionnaire-9 (PHQ-9) is a reliable and valid instrument for making diagnoses and assessing the severity of depressive disorders, and is scored as follows: 5–10 points indicates mild depression, 10–15 points indicates moderate depression, 15–20 points indicates moderately severe depression, and > 20 points indicates severe depression.

Sleep Quality

The Insomnia Severity Index (ISI) questionnaire was used to evaluate the severity of insomnia. The ISI is a validated 7-item self-report questionnaire that assesses insomnia severity over the past 2 weeks. A sum score was calculated (range 0–28), with lower scores indicating fewer insomnia symptoms.

Effective Treatment Rate

The treatment effect was assessed 6 months after the surgery according to the following criteria: “remarkable effect (RE)” — the symptoms and physical signs of the disease disappeared, with good quality of life restored; “valid effect (VE)” — the symptoms and physical signs of the disease were relieved, with quality of life improved; “invalid effect (IE)” — no improvement in the symptoms, signs, or quality of life. Total effective rate (%) = [(RE + VE)/n] × 100%.

Quality of Life

Patient quality of life was accessed by the 36-Item Short-Form Health Survey (SF-36), which included the following domains:
physical function, role-physical, bodily pain, general health, vitality, social function, role-emotional, and mental health.

**Dosage of Rescue Medication**
Tramadol 50–100 mg twice a day and pregabalin 75–150 mg twice a day orally were administered as rescue agents if the pain was not controlled sufficiently.

**Adverse Complications**
Possible complications, such as vascular puncture, hypotension, bradycardia, pleural puncture, pneumothorax, vertebral nerve puncture, catheter breakage, and lidocaine or methylene blue poisoning, were evaluated throughout the observation period.

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**Statistical Analysis**

**Sample Size**
Because there was no reference for the effectiveness of continuous thoracic paravertebral infusion with MB in PHN patients, a preliminary trial was conducted before starting the formal research, as suggested and approved by the Institutional Review Board of Shanghai East Hospital. The preliminary trial indicated that the effective rate of treatment was 65% (13/20) in the control group and 90% (18/20) in the MB group. Therefore, the sample size calculation was based on a 65% effective rate in the control group and a 90% effective rate in the MB group. Assuming a two-sided \( \alpha = 0.05 \) and a statistical power of 0.8, the sample size was calculated to
be 40 for each group. Considering a 10% loss to follow-up, the sample size was at least 44 in each group.

**Data Analysis**

Numerical variables are presented as the mean ± standard deviation (SD), and categorical variables are reported as numbers or percentages. The Kolmogorov–Smirnov test was used to assess the normality of measurement data. Normally distributed data were analyzed using the independent t-test and repeated measures analysis of variance (ANOVA), and nonnormally distributed data were compared using the Mann–Whitney U test. Differences between count data were calculated using the chi-square test or Fisher’s exact test. A p value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software (version 22; SPSS Inc., Chicago, IL, USA).

**RESULTS**

**Preoperative Patient Characteristics**

The demographic characteristics of the patients, including gender, age, height, weight, BMI, disease duration, pain intensity, and ISI and PHQ-9 scores, were recorded before surgery, and no significant differences were found in these parameters between the two groups (p > 0.05, Table 1).

**NRS Scores**

Compared with the preoperative baseline scores, the NRS scores at different time points were significantly decreased in both groups. The NRS scores were the lowest in the control group at 1 week and then gradually increased, but they were still lower than the preoperative baseline. Similarly, the NRS scores significantly declined at each time point after treatment in the MB group and were the lowest at 6 months. Compared with the control group, the MB group showed significantly lower NRS scores at each postoperative observation time point (p < 0.05, Fig. 2).

**ISI Scores**

There was no significant difference in baseline ISI scores before the operation between the two groups. The ISI scores of the patients in the control group and MB group decreased significantly at each time point compared with the preoperative baseline. The ISI scores of the

| Table 1 | General preoperative characteristics of the patients (mean ± SD) |
|---------|---------------------------------------------------------------|
| Variable | Control group (n = 48) | MB group (n = 50) | p-value |
| Gender | | | | 0.689 |
| Female | 28 | 27 | |
| Male | 20 | 23 | |
| Age | 62.21 ± 7.15 | 61.22 ± 11.37 | 0.632 |
| Height (cm) | 167.28 ± 12.32 | 168.93 ± 12.17 | 0.355 |
| Weight (kg) | 57.65 ± 9.28 | 59.11 ± 12.38 | 0.474 |
| BMI | 20.81 ± 2.95 | 21.02 ± 3.18 | 0.298 |
| PHN duration (months) | 3.89 ± 2.02 | 3.96 ± 1.78 | 0.524 |
| Preoperative NRS | 7.21 ± 1.03 | 7.40 ± 0.97 | 0.661 |
| Preoperative ISI | 21.31 ± 4.27 | 22.65 ± 4.06 | 0.494 |
| Preoperative PHQ-9 | 18.04 ± 3.09 | 18.92 ± 3.03 | 0.520 |

△ Adis
control group were higher than those of the MB group at each time point ($p < 0.05$, Table 2).

### PHQ-9 Scores

There was no significant difference in preoperative baseline PHQ-9 scores between the two groups. The PHQ-9 scores of the patients in the two groups decreased significantly at each time point compared with the preoperative baseline. The PHQ-9 scores of the control group were higher than those of the MB group at each time point ($p < 0.05$, Table 3).

### Total Effective Rate

The total effective rate was 64.58% in the control group 6 months after the surgery. In the MB group, the total effective rate was 88.00% 6 months after the surgery ($p < 0.05$, Table 4).

### SF-36 Assessment

There was no significant difference between the groups in the preoperative baseline SF-36 score, but the SF-36 scores in domains including general health, body pain, physical function, role-physical, vitality, mental health, role-emotional, and social function evidently improved in the two groups at each observation time point compared to the preoperative baseline ($p < 0.05$; Fig. 3); the difference between the

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**Table 2** Comparison of ISI scores in the two groups (mean ± SD)

| ISI score            | Control group ($n = 48$) | MB group ($n = 50$) | $p$-value |
|----------------------|--------------------------|---------------------|-----------|
| Preoperative         | 21.31 ± 4.27             | 22.65 ± 4.06        | 0.494     |
| 1 week postoperative | 15.40 ± 2.53             | 13.10 ± 2.13        | 0.040     |
| 1 month postoperative| 16.00 ± 2.63             | 11.33 ± 2.06        | < 0.01    |
| 3 months postoperative| 16.13 ± 3.48            | 9.93 ± 1.97         | < 0.01    |
| 6 months postoperative| 15.82 ± 3.62            | 9.26 ± 1.93         | < 0.01    |

* $p < 0.05$ versus the preoperative value within the same group

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**Table 3** Comparison of PHQ-9 scores in the two groups (mean ± SD)

| PHQ-9 score          | Control group ($n = 48$) | MB group ($n = 50$) | $p$-value |
|----------------------|--------------------------|---------------------|-----------|
| Preoperative         | 18.04 ± 3.09             | 18.92 ± 3.03        | 0.520     |
| 1 week postoperative | 11.71 ± 2.06             | 10.70 ± 2.58        | 0.351     |
| 1 month postoperative| 13.37 ± 2.50             | 6.63 ± 2.012        | < 0.01    |
| 3 months postoperative| 12.20 ± 4.21            | 5.64 ± 1.85         | < 0.01    |
| 6 months postoperative| 12.66 ± 3.57            | 4.05 ± 1.76         | < 0.01    |

* $p < 0.05$ versus the preoperative value within the same group
control group and MB group was statistically significant after 1 week, and a statistically significant difference was maintained for 6 months ($p < 0.05$; Fig. 3).

Dosage of Rescue Medication

The rescue drug (pregabalin and tramadol) daily dosages were both significantly reduced at each time point after the operation compared to the preoperative baseline. The daily dosages of pregabalin and tramadol were lower in the MB group than in the control group at each time point after surgery ($p < 0.05$; Fig. 4).

Adverse Complications

No adverse complications, such as vascular puncture, hypotension, bradycardia, pleural puncture, pneumothorax, vertebral nerve puncture, catheter breakage, and lidocaine or methylene blue poisoning, occurred in either group during the follow-up period. No patients withdrew from the treatment because of adverse complications.

DISCUSSION

Postherpetic neuralgia (PHN) is the most frequent chronic complication of herpes zoster (HZ) and is characterized by persistent skin burning or knife-like neuralgia in the affected area. PHN is a chronic neuropathic pain syndrome that can persist for more than 3 months after the initial onset of a HZ rash. PHN seriously affects patient quality of life and can cause physical disability, anxiety, depression, insomnia, and social isolation; it also presents serious economic burdens and public health problems for society [1, 24, 25]. Although there are various treatments for PHN, they are not fully effective at relieving PHN.

Methylene blue (MB) is an inhibitor of nitric oxide synthase (NOS) and soluble guanylate cyclase (sGC), which can be used in the treatment of methemoglobinemia [18], cyanide poisoning [26], carbon monoxide poisoning [27], pruritus ani [28], vasoplegia [28], malaria [29], osteoarthritis [19] and ifosfamide-induced encephalopathy [30]. In addition, Miclescu et al. showed that intravenous infusion of MB effectively decreased pain levels in patients with chronic therapy-resistant neuropathic pain [31]. Several studies have demonstrated that injection of MB into a painful disc is a safe, effective, and minimally invasive method for the treatment of intractable and incapacitating discogenic low back pain [32, 33]. Recently, Carlos et al. found that MB oral rinse significantly reduced refractory neuropathic pain from oral mucositis related to cancer treatment [34]. The abovementioned evidence indicates that MB is a safe and useful analgesic for various painful conditions. In the present study, we comprehensively assessed the analgesic effects of continuous MB thoracic paravertebral infusion in patients with moderate-to-severe PHN. We found that the NRS scores of PHN patients in both of the studied groups were significantly lower over the 6-month follow-up period than at baseline. Furthermore, NRS scores were significantly lower in the MB group than in the control group from 1 to 6 months after the surgery. We also found that continuous thoracic paravertebral infusion with MB can effectively reduce the daily doses of oral rescue drugs (pregabalin and tramadol).

Several possible mechanisms may be involved in the relief of neuropathic pain by MB. First, activation of N-methyl-D-aspartate (NMDA) receptors in the spinal cord dorsal horn can increase calcium conductance and activate

| Group          | Remarkable | Valid | Invalid | Total effective rate |
|----------------|------------|-------|---------|----------------------|
| Control group  | 10         | 21    | 17      | 64.58%               |
| MB group       | 21         | 23    | 6       | 88.00%$^a$           |

$^a$ $p < 0.05$ versus the control group
Fig. 3 Comparison of quality of life scores (SF-36) in the two groups. The data are expressed as the mean ± SD. *p < 0.05; **p < 0.01 versus the preoperative value within the same group. #p < 0.05; ##p < 0.01 versus the control group.
NOS, ultimately modulating the NO/cyclic guanosine monophosphate (cGMP)-dependent pathway, which enables low-threshold mechanosensitive Aβ- and Aδ-afferent fibers to activate central pain pathways. MB, as an inhibitor of NOS and sGC, can effectively block these pathways and shows antinociceptive effects [35–37]. Second, neuroinflammation contributes significantly to the development and maintenance of neuropathic pain, which results from the activation of glial cells, including microglia and astrocytes. Activated microglia and astrocytes release proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and chemokines, to activate and sensitize spinal cord nociceptive neurons [38–40], while MB has been reported to have anti-inflammatory properties in a series of disease models [41–43]. Recently, Ping et al. found that MB thoracic paravertebral single injection effectively inhibited the levels of plasma IL-6, TNF-α, and cortisol in PHN patients [23], indicating that the analgesic effect of MB may be related to its anti-inflammatory properties. Furthermore, some studies found that MB exerted its beneficial effect by attenuating mitochondrial dysfunction-induced oxidative stress [44–46]. However, the therapeutic mechanism of MB for PHN needs to be further investigated.

PHN may persist for years and is difficult to treat. Current guidelines suggest that treatment with alpha-2 delta ligands, tricyclic antidepressants, opioid analgesics, lidocaine patch, or capsaicin cream should be initiated. In addition, nerve block, intrathecal glucocorticoid injection, local botulinum toxin A injection, pulsed radiofrequency, spinal cord stimulation, dorsal root ganglion stimulation, and physical therapy are routine treatments for PHN [8, 9, 46, 47]. Thoracic and cervical dermatome involvement is reportedly most common in patients with HZ [48, 49]. TPVB can produce ipsilateral somatosensory and sympathetic nerve blockade in the thoracic dermatome; therefore, it is an ideal and effective therapy for the treatment of acute thoracic HZ pain and PHN. Several studies have proven that TPVB can remarkably lower the pain intensity in thoracic acute HZ pain, and it also effectively decreases the incidence of PHN [50–52]. More recently, Ping et al. indicated that a single thoracic paravertebral injection with MB can effectively lower the pain levels of PHN patients within 1 month after treatment [23]; however, this study lacked a control group, and the long-term analgesic efficacy of MB for the treatment of PHN needs further investigation. In the present study, we found that continuous thoracic paravertebral injection with MB can evidently decrease the NRS scores in PHN patients, and this therapeutic effect can last for at least 6 months, indicating that continuous paravertebral injection with MB can provide a longer postoperative analgesic effect in PHN patients.

Chronic pain can dramatically increase the risk of developing insomnia, anxiety, and depression, while it has a negative effect on the...
Several studies have proven that PHN patients have abnormal activities in brain regions related to anxiety and depression, such as the limbic system and frontal lobe \cite{55, 56}. Therefore, we investigated the effect of continuous MB infusion on insomnia, depression, and quality of life in PHN patients. Our results showed that the PHN patients in both groups obtained significantly decreased insomnia (ISI) scores and depression (PHQ-9) scores and experienced improved quality of life. In addition, patients in the MB group had lower insomnia scores and depression scores and better quality of life than those in the control group. Currently, ultrasound-guided nerve blocks are widely performed for regional anesthesia, postoperative analgesia, and chronic pain management. Traditionally, TPVB mainly uses either the “landmark technique” or “loss of resistance” methods to locate the thoracic paravertebral space; this is a difficult technique among ultrasound-guided nerve blocks because the paravertebral space is not visualized in real time \cite{57–59}. The failure rate of traditional TPVB is 7–10%, and its application may lead to pleural, vascular, and nerve damage that further causes pneumothorax, hematoma, and other adverse complications \cite{60}. In contrast to traditional TPVB, ultrasound guidance has significantly improved the safety and efficacy of TPVB, and ultrasound-guided TPVB (USG-TPVB) can provide real-time and accurate visualization of the needle tip and precise placement of catheters to allow continuous anesthesia and pain management. In this study, the catheter was successfully inserted into the thoracic paravertebral space and fixed to the skin of PHN patients, and no adverse effects or complications were reported in either group.

There are also several limitations to our study. First, the patients were recruited from a single center and the sample size was small. Second, the patients were only followed for 6 months after treatment. Third, double blinding was not used in this research.

**CONCLUSIONS**

In conclusion, ultrasound-guided continuous thoracic paravertebral infusion with MB is a novel, safe, and effective therapy for PHN. Continuous infusion with MB can significantly reduce pain intensity, improve pain-related depression, increase quality of life, and decrease the amount of rescue medicine needed while incurring no serious adverse side effects.

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**Authorship Contributions.** Mingxia Wang, Jinyuan Zhang, Li Zheng contribute to study design, analysis, and manuscript drafting. Hongwei Fang, Yiguo Zhang, Huimin Deng contribute to data analysis and manuscript editing. Mansi Wang, Xiuqin Yu, Qingxiang Meng, Yuanli Chen contribute to patient...
follow-up, data collection. Lijun Liao, Xin Lv contribute to study concept, design. Hao Yang, Xiangrui Wang contribute to study concept, design, analysis, and manuscript editing.

Disclosures. Mingxia Wang, Jinyuan Zhang, Li Zheng, Hongwei Fang, Yiguo Zhang, Huimin Deng, Mansi Wang, Xiuqin Yu, Qingxiang Meng, Yuanli Chen, Lijun Liao, Xin Lv, Hao Yang, and Xiangrui Wang have nothing to disclose.

Compliance with Ethics Guidelines. This study was approved by the Institutional Review Board and Ethics Committee of Shanghai East Hospital (2019, No.006). The present clinical research was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients before inclusion.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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