Original Article

Efficacy of repetitive paravertebral block combined with medication in the treatment of zoster-related pain with different courses

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ABSTRACT

الأهداف : مقارنة نتائج العلاج السريري لمدى ارتباط الألم (ZP) بتطبيق العرقلة المتكررة للأعصاب على جانبي العمود الفقري (PVB) بالتزامن مع إعطاء الأدوية، لمواجهة الهربس النطاقي بمختلف عمليات العدوى

المنهجية : تم تقسيم 67 إصابة بـZP إلى 3 مجموعات حسب عملية عدوى الهربس النطاقي . المجموعة الأولى : 24 إصابة بألم أعصاب الهربس النطاقي المفاجئ (بدؤوا يتعرضون للمرض خلال الشهر الأخير) . المجموعة الثانية : 22 إصابةً بألم أعصاب الهربس النطاقي شبه المفاجئ (بدؤوا يتعرضون للمرض خلال الشهر الأخير إلى آخر الأشهر الثلاثة) . المجموعة الثالثة : 21 إصابةً بمضاعفات ألم أعصاب الهربس النطاقي (بدؤوا يتعرضون للمرض قبل 3 أشهر) . يتناول كل مصاب جابابنتين وحبات ترامادول المخففة، خاضعًا لعلاج PVB المتكرر فوق الصوتي . تم مقارنة مستويات VAS وQS، ومعدلات حدوث التورّم والدوخة والغثيان والخمول بعد يوم و3 أشهر و6 أشهر .

النتائج : تحسنت شدة الألم ونوعية النوم بمختلف المستويات لكل مجموعة من المجموعات الثلاث المذكورة، إلا أن أكبر تقدم ملحوظ في المجموعة الأولى، ثم المجموعة الثانية والمجموعة الثالثة .

الخلاصة : تختلف نتائج العلاج بـPVB المتكرر بالتزامن مع الأدوية في ظل الموجات فوق الصوتية، باختلاف عمليات عدوى الهربس النطاقي . كلما يتلق المُصاب العلاج مبكرًا، تتحسن نتيجة العلاج عليه . جمع PVB المتكرر مع الأدوية يُظهر نتيجةً مميزةً على الذين في مرحلتي الإصابة المفاجئة وشبه المفاجئة، إذ يخفف عن شدة الألم ويحسن نوعية النوع على التدريج، إلا أنه يساهم في التخفيف عن آلام الذين في مرحلة الإصابة المزمنة إلى حد معين فقط .

Objectives: To compare the clinical outcomes of repetitive paravertebral block (PVB) combining oral medication in the treatment of zoster-related pain (ZP) with different courses.

Methods: : Sixty-seven patients with ZP were divided into 3 groups based on their course of herpes zoster (HZ). Group I: 24 patients with acute herpetic neuralgia (within one month of disease onset); group II: 22 patients with subacute herpetic neuralgia (disease onset from 1 to 3 months); group III: 21 patients with postherpetic neuralgia (more than 3 months since disease onset). All patients received ultrasound-guided repetitive PVB with oral gabapentin and tramadol sustained-release tablets. The VAS and QS scores and the incidences of hematoma, dizziness, nausea, and drowsiness were compared at 1 day, 3 months, and 6 months after treatment.

Results: Pain intensity and sleep quality of the 3 groups improved to varying degrees after treatment. The best efficacy was achieved in the acute group, followed by the subacute group, and the poorest efficacy was observed in the chronic group.

Conclusion: The efficacy of ultrasound-guided repetitive PVB with oral medication varied with the courses of HZ. The shorter the time since onset, the better the efficacy. This combined treatment showed better efficacy in patients at the acute and subacute stages and significantly improved their pain and sleep quality, while demonstrating limited pain relief in chronic patients.

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Herpes zoster (HZ) is usually caused by reactivated varicella-zoster virus dormant in the sensory ganglia of the nervous system. Impairment of T

cell-mediated immunity caused by stress, aging, or immunosuppression usually leads to high susceptibility to herpes zoster.[1-3] Zoster-related pain (ZP) refers to neuralgia during the course of or after recovery from herpes zoster. The ZP is divided into 3 types based on the course of disease, namely, acute herpetic neuralgia (AHN) (within 1 month of disease onset), subacute herpetic neuralgia (SHN) (within 3 months of disease onset) and postherpetic neuralgia (PHN) (3 months or more after disease onset).[4] The pathophysiology of ZP is little known, and 2 potential mechanisms are more widely accepted. One is the sensitization mechanism, in which inflammatory mediators (e.g., substance P, histamine, and cytokines) lower the stimulus threshold of a nociceptor; the other is deafferentation, in which swelling caused by inflammation compresses the sensory ganglia in the intervertebral column, leading to ischemia and damage to nerve tissues. At present, the major treatments for ZP include medication and microinvasive intervention. Nerve block treatment is a widely used microinvasive technique for herpes zoster, offering an easy operation with few complications. A large number of reports have shown that nerve block treatment can achieve good clinical outcomes for ZP.[5-9] Paravertebral nerve block (PVB) is the easiest and fastest anesthetic method to inject local anesthetics into the space near the vertebrae to block the spinal nerves as they emerge from the intervertebral foramen. PVB and epidural anesthesia offer a similar pain-relieving effect, although PVB incurs fewer side effects.[10] It has been reported that PVB can temporarily relieve refractory PHN.[11] However, according to some case reports, transcatheter repetitive PVB can achieve long-term pain relief.[12] The present study investigates the efficacy of repetitive PVB combined with oral medication in the treatment of ZP with different courses to provide a scientific basis for clinical treatment.

Methods. *Baseline data.* Patients with ZP who visited the Pain Clinic of our hospital from April 2015 to November 2019 were recruited. The study was approved by the hospital ethics committee and performed according to the ethical standards of the Declaration of Helsinki. Before treatment, informed consent was signed by each subject.

Inclusion criteria were: (1) typical skin lesions and clinical symptoms of ZP in the acute stage; (2) NRS scores of ≥6; (3) skin lesions found in the region innervated by spinal nerves C4-L5, with 1-3 segments affected by skin lesions; and (4) a body mass index (BMI) of 18.5-24.0 kg/m^2.

Exclusion criteria: (1) minor skin lesions associated with HZ; (2) lesions located on the head/face and in the sacral nerve-innervated region; (3) a history of ablative treatment; (4) coagulation dysfunction; (5) severe heart, lung, kidney, and liver dysfunction; (6) unwillingness to receive PVB; (7) mental or psychological diseases or inability to cooperate with the treatment; (8) concurrent pain caused by diseases other than HZ; (9) long-term insomnia before HZ or administration of valium for insomnia during the observation period; (10) administration of other analgesics (e.g., nonsteroidal anti-inflammatory drugs and opioid) in addition to the test drug during the observation period (6 months); (11) administration of other treatments for ZP during the observation period; (12) inability to quit drinking alcohol during the observation period; (13) long-term diabetes and failing to control the blood glucose level; (14) depression or administration of long-term antidepressants.

A total of 71 patients were recruited, including 26 males and 45 females. Depending on the disease course, the patients were divided into three groups: 25 patients with AHN in group I, 24 patients with SHN in group II, and 22 patients with PHN in group III. All cases were followed as required except for 1 case in group I, 2 cases in group II, and 1 case in group III who were lost to follow-up due to loss of contact. There were no significant differences in age, sex, course of disease, BMI, VAS scores, quality of sleep (QS) scores, or distribution of affected sites upon admission (p=0.20, 0.27, 0.881, 0.20, 0.54, 0.89, respectively) (**Table 1**).

In addition, the PubMed and Web of Science databases were searched using the keywords "herpes zoster, repetitive paravertebral block, neuralgia, trial" to find related literature.

Intervention. (1) Basic medication: Gabapentin capsules, p.o., at a dose of 0.3 g after supper on the first day, and then 0.3 g at noon and in the evening on the second day; on the third day and beyond, the dose was 0.3 g in the morning, at noon and in the evening. For patients in group I, if no antiviral therapy was given within 2 weeks after the onset of HZ, 0.3 g of valaciclovir tid was given daily before a meal for 7 consecutive days. If the VAS score was 4, tramadol sustained-release tablets were prescribed (50-100 mg, Q12h, depending on body weight and tolerance) to

Table 1 - Comparison of baseline information among the 3 groups.

Items	Group I	Group II	Group III	Statistic
Cases	24	22	21	
Course of disease (days)	11.7±6.2	45.9±16.4	388.1±267.3	
Gender				
Male	6	6	10	X^2=2.63 *p*=0.27
Female	18	15	11	F=1.65 *p*=0.20
Age (years)	67.0±9.0	70.2±8.7	71.4±7.1	F=0.127 *p*=0.881
BMI (kg/m²)	21.8±1.2	21.8±1.2	22.0±1.1	
Affected sites				
Neck, shoulder and upper limbs	6	4	6	X^2=1.15 *p*=0.89
Chest, back and abdomen	10	12	9	
Waist and lower limbs	8	6	6	
VAS	7.3±0.9	7.0±0.9	6.9±0.7	F=1.64 *p*=0.20
QS	0.8±0.7	0.7±0.7	1.0±0.6	F=0.63 *p*=0.54
BMI - body mass index, QS - quality of sleep, VAS - visual analog scale				

Table 2 - Comparison of VAS Scores in the 3 groups before and after treatment.

Groups	Cases	Before treatment	At 1 day after treatment	At 3 months after treatment	At 6 months after treatment
I	24	7.3±0.9	2.5±1.1*,†	1.8±1.2*,†,††	1.3±1.3*,†,††,‡
II	22	7.0±0.9	2.8±1.0*,†	3.2±0.9*,**,†	3.1±0.9*,**,†
III	21	6.9±0.7	4.7±0.7†	4.5±0.5†	4.6±0.6†

*- *p*<0.05, compared with group III at the same time point; ** - *p*<0.05, compared with group I at the same time point; † - indicates the comparison within the group relative to the pretreatment value; †† - indicates the comparison within the group relative to the value at 1 day after treatment; ‡ - indicates the comparison within the group relative to the value at 3 months after treatment. VAS - visual analog scale

Table 3 - Comparison of QS scores in the 3 groups before and after treatment.

Groups	Cases	Before treatment	At 1 day after treatment	At 3 months after treatment	At 6 months after treatment
I	24	0.8±0.7	3.1±0.7*,†	3.3±0.6*,†	3.4±0.6*,†
II	22	0.7±0.7	3.1±0.5*,†	2.9±0.6*,**,†	3.0±0.7*,**,†
III	21	1.0±0.6	1.8±0.5†	1.9±0.5†	1.9±0.5†

* - *p*<0.05, compared with group I at the same time point; ** - *p*<0.05, compared with group III at the same time point. † - indicates the comparison within the same group relative to the value before treatment, *p*<0.0083. QS - quality of sleep

control the pain. If the VAS score became ≥5 2 days later, the dose of tramadol could be increased to 150 mg or above (Q12h). The daily maximum dose allowed was 400 mg. After patients reported signs of pain relief (VAS score of ≤3), the dose of tramadol was reduced by 50 mg (Q12h) every other day. Tramadol was discontinued if the pain was completely relieved. If the VAS score increased to more than 3, the patients were shifted to the last controllable dose of tramadol, and results were recorded in the patients' pain log.

(2) PVB: PVB was applied to different sites depending on the location of skin lesions and the nerves in the pain-affected regions guided by ultrasound: cervical PVB for neck, shoulder, and hip pain; thoracic PVB for chest, back, and waist pain; lumbar PVB for waist and lower limb pain. Ultrasound-guided PVB was performed using a GE Vivid e Ultrasound System (transducer: 12L, 8-13 MHz, GE, US). A puncture needle (17 G, 8 cm) was adopted, and the nerve block compound drug (5 mL of 2% lidocaine injection +

0.5 mg of methylcobalamin+10 mg f triamcinolone acetonide injection, diluted with 0.9% normal saline to 20 mL) was injected. The procedure was repeated once a week. If the pain relief lasted for more than 1 week, the treatment was discontinued. The treatment was provided for each patient four times at most.

Observation indicators. The VAS scores and QS scores were observed and compared among the 3 groups before treatment and at 1 day, 3 months, and 6 months after treatment. The VAS is a way to quantify the sensation of pain across a continuum of values ranging from 0 to 10: 0, no pain; 1-3 points, mild pain that doesn't interfere with work and daily life; 4-6, moderate pain that interferes with work and daily life; and 7-10, severe and intense pain that significantly interferes with work and daily life. The QS scores were evaluated by asking the question, "How did you sleep last night?" Responses were: 0, very bad sleep; 1, bad sleep; 2, fair sleep; 3, good sleep; 4, very good sleep.

Complications and adverse events. The incidence of hematoma at the puncture site was recorded at 24 h after treatment. Adverse events following the use of gabapentin and tramadol hydrochloride—including dizziness, nausea, drowsiness, and peripheral edema—were recorded.

Efficacy evaluation. Efficacy was evaluated by using the weighed value of VAS scores, which were calculated by VAS before treatment-VAS after treatment/VAS upon admission.

Statistical analysis. According to a literature review, the power of the test was $1-\beta=0.90$, and a significance level of $\alpha=0.05$ was chosen for the VAS score. Based on the preset parameters, the minimum sample size for each group was 16. Since the maximum drop-out rate was expected to be 20%, 20 cases for each group should meet the criteria.

Statistical analyses were performed with SPSS 21.0 software. Measurements were expressed as the mean ± standard deviation (x±SD). Data obtained at several time points before and after treatment were compared by one-way repeated measures ANOVA. Pairwise intergroup comparisons were carried out by one-way ANOVA, with the significance level set to $\alpha=0.05$. Comparisons across time points were conducted using t-tests. The total amount of tramadol administered was compared by one-way ANOVA. Count data such as efficacy indicators and the number of cases with hematoma and other adverse events were analyzed by the chi-square test or Fisher's exact test. The significance level was set to $\alpha=0.05$.

Results. *Comparison of VAS scores before and after*

treatments among the 3 groups. The results showed that the pretreatment VAS scores were 7.3±0.9, 7.0±0.9, and 6.9±0.7 for groups I, II and III, respectively, without showing a significant difference ($p>0.05$). At 1 day after treatment, the VAS scores did not differ significantly between group I and group II (2.5±1.1 versus 2.8±1.0), and the VAS scores of group (4.7±0.7) were significantly higher than those of groups (2.5±1.1) and (2.8±1.0) ($p<0.05$). At 3 months after treatment, there were significant pairwise differences in the VAS scores among groups I, II, and III (1.8±1.2 versus 3.2±0.9 versus 4.5±0.5). At 6 months after treatment, there were also significant pairwise differences in the VAS scores among groups I, II, and III (1.3±1.3 versus 3.1±0.9 versus 4.6±0.6). Intragroup comparisons were conducted within each group at different time points by using one-way repeated measures ANOVA. As the observation time was prolonged, VAS scores gradually decreased ($p<0.0083$). For groups II and III, there was also a significant reduction in the VAS scores after treatment ($p<0.0083$). However, there were no significant differences within each group at different time points ($p>0.0083$) (**Table 2**).

Comparison of QS scores among the 3 groups. There were no significant differences in the QS scores among the 3 groups before treatment ($p>0.05$). At 1 day after treatment, the QS scores did not differ significantly between group I and group II, and the QS scores of group III were significantly lower than those of groups I and II ($p<0.05$). At 3 months and 6 months after treatment, there were significant pairwise differences in the QS scores among the three groups. The highest QS score was found in group I, followed by group II and group III in descending order ($p<0.05$). Intragroup comparisons were conducted within each group at different time points by using one-way repeated measures ANOVA. The QS scores gradually increased in all 3 groups ($p<0.0083$). However, the differences were not statistically significant among the groups at each time point after treatment ($p>0.0083$) (**Table 3**).

Comparison of total amount of administered tramadol and incidences of hematoma and infection. The total amount of administered tramadol showed significant differences across the 3 groups ($p<0.05$). For example, it was lowest in group I (1779.2±3572.1 mg), followed by group II (5590.9±5014.4 mg), and group II (11644.6±2541.1). None of the cases in any of the three groups had hematoma or infection of the puncture site. The incidence of adverse events showed no significant differences among the 3 groups. No significant differences in the incidences of dizziness

(8.3% versus 4.5% versus 9.5%), nausea (8.3% versus 9.1% versus 4.8%) and drowsiness (8.3% versus 4.5% versus 9.5%) were observed among the 3 groups.

Discussion. Herpes zoster, usually caused by reactivated varicella-zoster virus dormant in the sensory ganglia of the nervous system, often presents as acute algesic zoster along the nerves.[13] Postherpetic neuralgia is a neuropathic pain caused by previous VZV infections and can last for 1 to 12 months.[14] Bouhassira et al.[15] pointed out that despite early antiviral therapy, ZP still persisted for 6 months in 8.5% of the patients and persisted for 12 months in 6% of the patients. Although HZ is not a lethal disease, it may cause severe ZP, including AHN and PHN. The ZP is associated with an increased sensitivity of segmental sensory neurons affected by the virus.[16] Reactivation of the virus damages relevant parts of the central and peripheral nervous systems, leading to inflammation, immune responses, and varying degrees of neuron loss in the affected spinal ganglia.[17,18] Following HZ, continuous stimulation of damaged primary efferent nociceptors induced by inflammation and damaged peripheral nerves may maintain the sensitized state of the central nervous system,[19] leading to the pathogenesis of PHN. Severe ZP usually affects patients' daily lives and greatly impairs their functional status and quality of life.[20-22] Thus, it is necessary to control ZP.

Gabapentin and tramadol are common medications for ZP.[23] As a first-line drug recommended in the guidelines,[24-25] gabapentin is associated with adverse events such as dizziness and drowsiness in a significant dose-dependent manner.[26] It has been reported that better pain relief can be achieved with a dose of 1800-2400 mg/d gabapentin, although the risk of dizziness and drowsiness increases dramatically. The incidence of dizziness can reach up to 24%-31%, and the incidence of drowsiness can reach up to 17%-27%.[25] In the present study, PVB was applied in combination with medication to treat ZP, and a good analgesic effect was achieved while avoiding the apparent side effects of large-dose gabapentin. Tramadol was used as a salvage analgesic in the present study, and its dose was adjusted depending on pain intensity. Nausea is a common adverse event associated with tramadol, but patients may develop tolerance. This study reported lower incidences of dizziness, drowsiness, and nausea, indicating the high safety of this combined therapy.

Previous studies have demonstrated that local anesthetics and/or corticosteroids can control AHN and PHN by blocking the sympathetic and somatic nerves while reducing the incidence of PNH.[27,28] The mechanism of a nerve block is to attenuate central sensitization by blocking the transmission of noxious efferent impulses into the central nervous system and to reduce nerve damage by improving blood flow in the efferent nerves. In addition, local anesthetics and corticosteroids may play an anti-inflammatory role in the affected nerves.[29]

The PVB is mainly intended to block the transduction of sympathetic nerve excitation so that the physiological response of pain will be disrupted. The use of adrenocorticotropic hormone can inhibit the generation of viral antibodies, thus reducing inflammatory damage to nervous tissues and relieving pain. The PVB can act on the dorsal root ganglia, blocking the transduction of pain signals from the periphery to the central nervous system. This procedure can also block the sympathetic nerves, improve local blood supply, promote restoration of the damaged ganglia, and finally reduce central sensitization. Cutaneous nerve block can achieve a good analgesic effect by blocking pain signal transduction through peripheral nerve block. Meanwhile, the immune and inflammatory responses of the peripheral nervous system are attenuated by medication. Therefore, the functional repair of peripheral nerves and pain relief can be effectively promoted.[30] Ultrasound-guided puncture has been proven to be a simple, safe, economic, and less painful microinvasive technique. With ultrasound guidance, doctors can more clearly observe the local structure of the target, the puncture pathway, and the real-time diffusion of local anesthetics, thus greatly improving the success rate of nerve block and reducing complications.[31] In the present study, none of the patients had infections/hematoma of the puncture site, demonstrating the safety and effectiveness of ultrasound-guided PVB.

Eo G and Oana Bulilete investigated the effect of gabapentin (900 mg/d and 1800 mg/d) as the major analgesic for pain relief of patients in the acute stage of herpes zoster. It was found that gabapentin could not significantly alleviate acute herpetic pain or prevent PHN.[32,33] However, many studies confirmed that gabapentin was effective in alleviating pain in patients in the chronic stage.[34,35] With reference to the existing literature, no control group was set up in this study. Instead, only the efficacy of paravertebral block combined with medication was compared among patients at different stages of herpes zoster. The pain of patients in the acute stage was relieved remarkably by the combined treatment. Moreover, none of the 24 patients underwent PHN. G. Ji and P. Zhao et al. also studied the combination of paravertebral block and medication.

Their results showed that after treatment, PHN occurred less frequently in patients in the acute stage of herpes zoster.[6,36] Nevertheless, there is controversy over the clinical effect of paravertebral block combined with medication on patients in the chronic stage of herpes zoster. In this study, the pain of patients in the chronic stage of herpes zoster was alleviated by 35%, similar to the reduction of 30%-33% after drug treatment only in previous studies.[35,37] Thus, it cannot be confirmed now whether the combination of paravertebral block and medication improves the efficacy in patients in the chronic stage of herpes zoster.

In this study, the combination of repetitive PVB and medication demonstrated the best outcomes in pain relief and sleep quality among patients in the acute stage, followed by those in the subacute stage, while the poorest outcomes were found in chronic patients. Moreover, the total amount of administered tramadol was the largest in patients in the chronic stage, followed by those in the subacute stage, while the total amount of administered tramadol was the smallest for those in the acute stage. The combined treatment was more effective for patients in the acute stage, who showed a significant reduction in VAS scores on the first day after treatment, and their VAS scores continued to decrease during the 6-month follow-up. Although patients in both the subacute and chronic groups achieved apparent pain relief on the first day after treatment, their pain intensity remained unchanged afterwards. However, pain relief was more obvious in the subacute group than in the chronic group, and the total amount of administered tramadol was also lower in the subacute group than in the chronic group. The reason may be that the combined treatment (antiviral drug, gabapentin, tramadol and repetitive GVB) could rapidly relieve inflammation and damage to the nerves while inhibiting central sensitization. Since the course of disease is longer in subacute patients than in acute patients, PVB with medication can only provide partial pain relief without completely inhibiting central sensitization. This explains the less satisfactory but still acceptable pain relief effect in the subacute group. However, central sensitization could not be properly controlled in the chronic group, leading to the worst pain relief outcome among the 3 groups. Taken together, it was suggested that this combined treatment worked better at the acute and subacute stages, so it is worthy of further clinical application. However, the efficacy of this combined treatment was limited in chronic patients. Thus, other therapeutic options, such as spinal cord stimulation and pulsed radiofrequency, should be considered for these patients.[38-40]

This study has several limitations. First, the sample size was limited. Second, no control group was set up for patients at different stages (e.g., paravertebral injection of normal saline with oral medication). Finally, patients were followed for only six months; long-term efficacy of the combined treatment remains to be investigated.

In conclusion, the efficacy of ultrasound-guided repetitive PVB with oral medication varied with the courses of HZ. The shorter the duration of onset, the better the efficacy. This combined treatment showed better efficacy in patients at the acute and subacute stages, as shown by significantly reduced pain and improved sleep quality. However, the combined treatment showed limited pain-relief for chronic patients. In the future, well-designed, and multicenter studies with a large sample size are needed to verify the findings of this study.

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