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Original Investigation

Clinical Study of Ultrasound-Guided Methylene Blue Thoracic Paravertebral Nerve Block for the Treatment of Postherpetic Neuralgia

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ABSTRACT

AIM: To investigate the effect of ultrasound-guided methylene blue (MB) thoracic paravertebral nerve block (TPVB) on the treatment of postherpetic neuralgia (PHN).

MATERIAL and METHODS: A total of 27 patients with PHN were treated with ultrasound-guided TPVB in the lesion innervation. The blocking drug used was an MB compound preparation, and several indexes were recorded, including pain visual analogue scores (VAS), dosage of oral analgesic required, plasma interleukin (IL)-6, tumor necrosis factor-alpha (TNF-α), and cortisol levels, basic viability, self-assessment, and satisfaction.

RESULTS: The patients' VAS after blocking were significantly reduced compared to those before blocking. Furthermore, dosage of oral analgesic required, levels of plasma IL-6, TNF-α, and cortisol were reduced, and basic viability and self-assessments were significantly improved ($p<0.05$). The treatment method was effective, did not cause any adverse effects, and patients reported higher degrees of satisfaction.

CONCLUSION: Ultrasound-guided TPVB exerts significant effects on PHN. The patients' degree of pain and dosage of oral analgesic required were reduced, basic patient viability was improved, and patients reported higher degrees of satisfaction.

KEYWORDS: Ultrasound, Thoracic paravertebral nerve block, Methylene blue, Postherpetic neuralgia

INTRODUCTION

Postherpetic neuralgia (PHN) is a neuropathic pain syndrome characterized by pain that persists for months to years after resolution of a herpes zoster (HZ) rash (22). It is a common complication of HZ, and occurs in the elderly (24). PHN stems from damage to peripheral and central neurons that may occur as part of the immune/inflammatory response accompanying varicella zoster virus reactivation (11,27). PHN is associated with reduced resistance and presents as spontaneous, persistent knife-like pain or paroxysmal burning that lasts several months to years. Patients with PHN report a decreased quality of life and interference with daily activities (8). Symptoms may include difficulty sleeping, low quality of life, and a higher incidence of cardiovascular and cerebrovascular accidents. The frequency and severity of PHN increases with advancing age, occurring in 20% of people aged 60-65 years who have had acute HZ infection, and in more than 30% of people aged >80 years (7). In addition to age, risk factors for developing PHN after HZ include the presence of a prodrome, severe rash, and severe pain during the acute phase (18). These symptoms should attract the attention of clinicians.

Ultrasound-guided thoracic paravertebral block (TPVB) is a conventional technique used to view anatomical structures, although the depth of the paravertebral space, the probe position, and the acute angle of the needle trajectory renders the tip and distal portion of the needle difficult to visualize (13,15). TPVB has been widely applied in anesthesia and

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postoperative analgesia (20). Methylene blue (MB) is a low-molecular weight, partially liposoluble vital dye that has been used in many different fields of clinical medicine. Different theories underlie the pharmacological and therapeutic mechanisms that may be responsible for the neuroprotective effects of MB (17,25). Because of its neurotropic effects, which enable it to inhibit nerve conduction or destroy nerve endings, the local injection of MB has been used to treat many different painful ailments (4,5).

In this study, we used ultrasound-guided TPVB, which involves the injection of local anesthetic into the thoracic paravertebral space under ultrasound guidance to achieve multiple ipsilateral somatic and sympathetic block, to treat PHN. We obtained a high success rate based on accurate positioning. Patients were satisfied with the analgesic effects achieved, and no adverse effects or complications related to nerve block were detected.

MATERIAL and METHODS

Patients

A total of 27 patients (14 male and 13 female) with PHN were enrolled from September 2014 to September 2015 in our hospital. Pain was mainly distributed in the chest and back, and one to two adjacent thoracic nerves were involved. These patients were 58-76 years old (mean age = 67.4 ± 8.5 years), and the course of disease was 1.5-12 months (mean duration = 3.6 ± 6.8 months). All patients fulfilled the clinical diagnostic criteria and were graded as level I-II according to the American Society of Anesthesiologists (ASA) classification. Exclusion criteria included severe heart, liver, lung, or kidney dysfunction, coagulation abnormality, and the presence of scars, infections, tumors, or spinal deformities at the puncture site. This study was approved by the ethics committee in our hospital, and informed consent was singed from each patient and family member.

Procedure

All patients were first treated with conventional nutrition nerve, anti-viral agents, increased body resistance, and analgesics (Tramadol, 0.1 g, national drug standard H19990062, Shandong Xinhua Pharmaceutical Co., Ltd.). Next, patients underwent TPVB, and the blocking drug used was a 0.2% MB complex solution containing 2 mL MB (20 mg, national drug standard H32024827, Jiangsu Jichuan Pharmaceutical Co., Ltd.), 5 mL 0.75% ropivacaine (10 mL, 75 mg, imported drug registration number H20140763, AstraZeneca, Cambridge, UK), and 3 mL 0.9% NaCl. The patients were taken to the operation room, venous access was opened, and electrocardiogram, blood pressure, and pulse oxygen saturation monitoring systems were connected.

The ultrasound-guided TPVB method included the following steps. Patients were placed with the affected side facing up, the arch was flexed, and TPVB guided by a Mindray Portable ultrasound system (UMT-500, Shenzhen Mindray Biomedical Electronics Co., Ltd.) was performed. The ultrasonic probe frequency was adjusted to 8 MHz and a strong echo pleura bright line moving with the breath was detected in the ultrasound window by adjusting the probe position. A sharp line on the upper edge of the pleura was identified as the transverse process of the vertebral body, and a wedge-shaped hypoechoic region of the thoracic paravertebral space was identified as the lateral pleura under the transverse process. A puncture point was selected next to the lower edge and 2-3 cm below the affected side of the corresponding vertebral body. The puncture needle position was adjusted to pass through the skin and intercostal muscles, and to reach the paravertebral space. After drawing back to confirm the absence of blood and gas, 10 mL 0.2% MB complex solution was injected. The drug solution spread outside the pleura, and the pleura moved downwards by action of the drug solution to the ventral side. After the operation was completed, patients were asked to lie flat for 30 min before returning to the ward if no adverse reactions were detected.

Observation Indexes

VAS and dosage of oral analgesics were recorded, including VAS before TPVB (T1), and after one day (T2), one week (T3), two weeks (T4), and one month (T5). Plasma inflammatory indexes, including interleukin (IL)-6, tumor necrosis factor-alpha (TNF-α), and cortisol levels, were recorded one day before and three days after ultrasound-guided TPVB. Other indexes, including adverse reactions such thoracic paraspinal nerve lag, basic living ability after one month (determined as patient's activity on the affected side, Table I), self-evaluation, and overall patient satisfaction, were evaluated.

Statistical Analysis

Measurement data are reported as means ± s, and a t-test was used to estimate the potential difference between the two groups. Counting data were estimated using χ^2 analysis, and $p<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS 17.0 software (IBM, Armonk, NY, USA).

RESULTS

Comparison of VAS and oral tramadol dose before and after TPVB

We evaluated the postoperative analgesic effects in the TPVB group at T1, T2, T3, T4, and T5. VAS significantly reduced in patients who had undergone ultrasound-guided TPVB ($p<0.05$, Table II). From T2 to T5, VAS decreased from 4.1 ± 1.3 to 1.5 ± 1.4. The doses of oral tramadol also significantly reduced ($p<0.05$, Table II). Compare to that in T1, the dose of oral tramadol decreased from 295.5 ± 45.7 to 157.6 ± 54.3 between T2 and T5, and a minimum value of 56.7 ± 35.8 was observed at T5.

Comparison of plasma IL-6, TNF-α, and cortisol levels before and after TPVB

Plasma levels of inflammatory markers including IL-6, TNF-α, and cortisol were evaluated in the TPVB group at T1, T2, T3, T4, and T5. Inflammatory indexes, including plasma IL-6, TNF-α, and cortisol levels, were all significantly reduced three

days after ultrasound-guided TPVB compared to those before blocking (p<0.05, Table III). Plasma IL-6 decreased from 157.6 ± 12.5 to 75.7 ± 8.9 (p=0.028), plasma TNF-α decreased from 3.5 ± 0.6 to 1.3 ± 0.2 (p=0.031), and plasma cortisol decreased from 282.1 ± 16.3 to 186.4 ± 10.2 (p=0.037).

Comparison of basic living ability and patient self-evaluation before and after TPVB

After blocking, the basic living ability of patients improved significantly (Table IV). The nerve block success rate was 100% in our study, and no paravertebral nerve blocking complications, such as pneumothorax, hematoma, nerve damage, and ropivacaine or MB poisoning reactions, such as dizziness, nausea, tinnitus, vertigo, chest tightness, or abdominal pain, were detected. Some patients felt slight skin numbness in the nerve block area, and these symptoms were maintained within the one-month follow-up period. Eighteen patients were very satisfied with the treatment and nine patients were satisfied (degree of satisfaction = 100%).

■ DISCUSSION

PHN mainly stems from an HZ infection that leads to primary skin lesions that have subsided or retain only slight pigmentation, and is characterized by persistent skin burning or knife-like neuralgia that lasts longer than one month (1,19). Here, the mean duration time was 15 months and studies indicate that the incidence of HZ is significantly higher in patients older than 60 years, with 9-34% of patients showing concomitant PHN sequelae (14), that seriously affect their quality of life, reduce basic living ability, and increase the incidence of cardiovascular and cerebrovascular accidents. The detailed mechanisms of pathogenesis remain unclear, but PHN is mainly extraspinal, and thoracic paraspinal nerve root injection is therefore an ideal method to control it (16).

Table I: Patient Activity Capacity Scale

Score	0	1	2	3	4
Description	No pain Unrestricted activity	Pain, but unrestricted activity	Pain with mild activity	Pain with extremely limited activity	Resting state with unbearable pain

Table II: VAS Scores and Dose of Oral Tramadol (mg) in Different Time Point ($\bar{x} \pm s$).

Time	**T_1**	**T_2**	**T_3**	**T_4**	**T_5**
VAS score	7.6 ± 1.5	4.1 ± 1.3*	2.8 ± 1.4*	1.6 ± 1.3*	1.5 ± 1.4*
p		**0.041**	**0.031**	**0.023**	0.18
Dose of oral tramadol	295.5 ± 45.7	157.6 ± 54.3#	123.7 ± 35.6#	75.3 ± 20.3#	56.7 ± 35.8#
p		**0.043**	**0.032**	**0.022**	0.17

Note: *Compared with indexes before blocking, VAS score reduces, *p<0.05. Compared with indexes before blocking, dose of oral tramadol reduces, #p<0.05.*

Table III: Plasma IL-6, TNF-α and Cortisol (ng·ml^{-1}) ($\bar{x} \pm s$).

	IL-6	**TNF-α**	**Cortisol**
Before blocking	157.6 ± 12.5	3.5 ± 0.6	282.1 ± 16.3
After blocking	75.7 ± 8.9*	1.3 ± 0.2*	186.4 ± 10.2*
p	**0.028**	**0.031**	**0.037**

Note: *at 3 days after blocking, Plasma IL-6, TNF-α and cortisol reduces, *p<0.05.*

Table IV: Basic Living Ability and Self-Assessment ($\bar{x} \pm s$).

Groups	**Basic living ability**					**Self-assessment**		
	0	**1**	**2**	**3**	**4**	**Excellent**	**Good**	**Poor**
Before blocking	0	3	5	10	9	0	3	24
After blocking	11*	10*	6	0*	0*	15*	12*	0*
p	**0.016**	**0.029**	0.610	**0.025**	**0.027**	**0.015**	**0.026**	**0.013**

Note: *Compared with indexes before blocking, *p<0.05.*

TPVB has been widely applied in clinical practice because of its high success rate and few related complications. The failure rate of traditional TPVB is 6.8%-10% (3), and its application may cause pleural, vascular, and nerve damage that further cause pneumothorax, hematoma, local anesthetic poisoning, and other complications. Renes et al. reported 100% block success rate in 36 patients with TPVB (21), with no complications. Our study involved the use of ultrasound-guided TPVB for real-time observation of the needle trajectory and the administration of local anesthetics under ultrasonic guide to accurately inject the drug into the paravertebral space of the corresponding lesion segment. Thus, this method can reduce the incidence of poisoning reactions caused by drugs entering the blood by avoiding damage to peripheral nerves, blood vessels, and pleura. In this study, 27 patients were successfully nerve-blocked, and no adverse effects or complications were detected.

MB is widely applied in analgesia to treat a variety of painful diseases because of its characteristic ability to block pain transmission (9,26). Low concentrations of MB cause no neurological damage (10,28), but patients may experience significant pain in the blocking region 3-4 hours after injection. Therefore, a complex comprising the novel amide local anesthetic ropivacaine and MB, which may be active for over 6 months, was used in this study (6,23). Baron believed that the persistent inflammatory response of the nerve trunk caused ectopic electrical activity in the primary afferent receptor, leading to spontaneous pain and hyperalgesia (2), and that a vicious cycle formed with pain aggravating the inflammatory reaction, and vice versa. Therefore, it is important to break this cycle using effective analgesic treatment. In this study, we found that plasma IL-6, TNF-α, and cortisol levels were significantly reduced 3 days after blocking, indicating that treatment reduced the inflammatory reaction, improved body resistance, contributed to damaged nerve recovery, and reduced the incidence rate of other inflammatory diseases. In this study, MB caused a significant reduction in postoperative pain in patients with thoracolumbar fractures 6 months after surgery. With pain reduction, the patients' social burden decreases and they can return to work and other normal activities. Similarly, in a multicenter prospective case series conducted in 2016, Kallewaard et al. showed that 40% of patients who underwent intradiscal MB injection for discogenic lower back pain (LBP) reported at least 30% pain relief 6 months after the intervention (12). Because surgical-site inflammation usually resolves 2 months after surgery, the pain also decreases significantly during this period. Therefore, we assumed that a 6-month follow-up period was sufficient to evaluate the safety and efficacy of MB in preventing postoperative pain. Thus, the aim of this study was to evaluate the efficacy of MB in the first 6 months after surgery. We demonstrated that MB can achieve adequate postoperative pain control during this period. In patients who responded well, physical function improved, and medication use diminished. We observed no procedural complications or adverse events.

CONCLUSION

Ultrasound-guided TPVB was used to treat PHN, and this method significantly reduced VAS, dose of oral analgesics required, and plasma inflammatory factor release, as well as enhanced body resistance, promoted organizational recovery, and improved patients' basic living ability and self-evaluation. More importantly, this treatment method did not cause any adverse effects and yielded higher satisfaction from the patients. Our study only investigated the treatment of a single or adjacent nerve in the chest, and may provide reference for multi-vessel disease and other areas of postherpetic pain.

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