Prospective Study

Reduction of Serum Substance P and Beta Endorphin in Herpes Zoster After Erector Spinae Plane Block

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Background: Acute herpes zoster (AHZ) is caused by the reactivation of varicella-zoster virus. This reactivation results in peripheral nerve fiber damage and triggers an immune reaction, which leads to the production of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-alpha). In the skin of patients affected with postherpetic neuralgia (PHN), high levels of calcitonin gene-related peptide (CGRP) have been found.

Objectives: The primary goal of this study was to compare changes in serum inflammatory cytokines (IL-6, IL-8) and pain neurotransmitters (substance P, CGRP) with those of a control group, and before and after fascial plane blocks.

Study Design: A prospective, nonrandomized, and case-control study.

Methods: The diagnosis of AHZ (< 2 months) and PHN (> 6 months) were determined based on the duration of each patient's pain since the onset of skin eruption. Healthy age- and gender-matched volunteers were included as the control group. For the sake of the enzyme-linked immunosorbent assay (ELISA), blood sampling was performed 2 or 3 times before and after the block. An ultrasound-guided erector spinae plane block (ESPB) was performed 2 or 3 times at an affected dermatome.

Results: The levels of IL-6 and pain neurotransmitters (substance P, CGRP) in HZ patients did not show any significant differences from those in the control group. However, the serum substance P (median, 24.0; IQR, 7.2-49.5) and beta-endorphin levels following the ESPBs (median, 237.8; IQR, 177.4-414.5) were significantly lower than they were prior to the ESPBs (median, 30.6; IQR, 13.3-71.6; $P = 0.009$).

Limitations: The AHZ patients in this study did not experience a very acute phase. Since the matter of whether or not the levels of serum inflammatory cytokines in AHZ patients can demonstrate a significant reduction or increase is uncertain, further study is required.

Conclusions: Between the HZ patients and the control group, the levels of inflammatory cytokines (IL-6) and pain neurotransmitters (substance P, CGRP) did not show any significant differences. However, a significant reduction of substance P and beta-endorphin following the ESPBs was observed.

Key words: acute herpes zoster, erector spinae plane block, enzyme-linked immunosorbent assay, inflammatory cytokine, postherpetic neuralgia, pain neurotransmitter

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Acute herpes zoster (AHZ) is caused by the reactivation of varicella-zoster virus that lies latent in the dorsal root ganglion. The distinctive rash that can be seen in AHZ develops into vesicles, pustules, and crusts (1,2).

The pain experienced by most patients with AHZ disappears as the skin rashes heal, which usually occurs within approximately one month. However, postherpetic neuralgia (PHN) develops in about 10% of AHZ patients even after their skin lesions heal. PHN is the

most important and common form of neuropathic pain caused by HZ infections (3). Due to the intractable and chronic nature of the pain, PHN results in considerable suffering and health care burden at both the individual and social levels. Patients with PHN experience reductions in their quality of life, physical and emotional functioning, and psychological well-being (3,4).

When an individual immune function declines, varicella-zoster virus is reactivated and enters the bloodstream via the sensory ganglia. This reactivation results in skin inflammation, triggers an immune reaction, and damages peripheral fibers (5-9). Moreover, infection from the varicella-zoster virus leads to the production of inflammatory factors, such as interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-alpha), from infected epidermal cells and fibroblasts. Tissue or nerve injury caused by the reactivation of the varicella-zoster virus can result in the release of inflammatory factors, which can increase the excitability of the nociceptive receptor membrane. Inflammation is known as one of the major factors that contribute to the pathogenesis of PHN (3,10).

According to the level A evidence suggested by the European Federation of Neurological Societies, the first- and second-line medication therapies for PHN include tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, pregabalin, tramadol, gabapentin, capsaicin patches, and lidocaine patches (1,11,12). Interventional treatments, such as fascial plane injections, peripheral nerve blocks, and neuraxial blocks, can be applied in cases of intractable PHN if one of the conservative medications described above is unsuccessful. Patients with medically intractable PHN can experience great benefits from various interventional procedures (1,8,13-18).

Calcitonin gene-related peptide (CGRP), a vasodilatory peptide, has been found at high levels in the blood, skin, and cerebrospinal fluid under various chronic and inflammatory pain conditions, derived from C and A-delta fibers. In the widespread area of the skin of patients infected with PHN, high levels of CGRP immunolabeling were found in epidermal keratinocytes (19). Additionally, it is uncertain whether the level of CGRP or other pain neurotransmitters can be changed after an ultrasound-guided injection into the fascial plane. One study suggested that the level of serum CGRP was lowered after ultrasound-guided greater occipital nerve blocks in patients with migraines (20).

The primary goal of this study is to compare the changes in serum inflammatory cytokines (IL-6, IL-8) and pain neurotransmitters (substance P, CGRP) undergone by the HZ patients to those in the control group before and after the administration of ultrasound-guided fascial plane blocks.

Methods

This prospective, case-control study was approved by our institutional review board (2023-04-059). The potential benefits and risks of this study were fully explained before patient enrollment, and all patients provided informed consent. This study was registered at ClinicalTrials.gov (NCT 05685797) before patient enrollment. In total, 30 HZ patients who received an ultrasound-guided erector spinae plane block (ESPB) were enrolled (from January 25th, 2023, to November 30th, 2023). Among the patients, 18 completed this study. Twelve patients refused to participate in the study because they had anxiety or fear about the needle puncture required for blood sampling. Fifteen healthy, age- and gender-matched patients were included for the control group.

Patient Selection

To meet the inclusion criteria, patients had to be 20-80 years old and have demonstrated minimal responses to conservative treatment for at least 4 weeks. The diagnoses of AHZ (< 2 months) and PHN (> 6 months) were determined based on the duration of the patients' pain since the onset of an acute skin eruption. Patients were excluded if they had allergic reactions to local anesthetics or coagulation abnormalities. The control group was composed of healthy age- and gender-matched volunteers. Patients who were taking nonsteroidal anti-inflammatory drugs, consuming immunosuppressive drugs, suffering from inflammatory disease, or had conditions (such as smoking or recent vaccination) that could affect inflammatory biomarkers were excluded from the control group.

Assessment of Clinical Outcomes

The 11-point numerical rating scale (NRS) (21) was used to measure the severity of each patient's zoster-related pain before the administration of an ultrasound-guided ESPB and then at 2, 4, and 8 weeks after the ESPB at an affected region. The physician who evaluated the NRS scores in this study asked the patients, "What was your average pain score over the 24 hours?"

During the 8 weeks of the study period, all patients received 2 or 3 sessions of an ultrasound-guided ESPB,

according to their pain severity. They were counseled strictly not to receive any other injection therapy.

Ultrasound-Guided ESPB

A physician who had more than 10 years of experience in administering ultrasound-guided nerve blocks performed this ESPB. A right- or left-sided unilateral ESPB was performed depending on the location of the pain region. For the thoracic and lumbar ESPBs, the patients were laid in a prone position. If pain severity prevented a patient from lying prone, a sitting position was used. In cases of HZ that presented at the cervical region, a high thoracic ESPB was used. A linear high-frequency (thoracic ESPB) or curved low-frequency (lumbar ESPB) probe (LOGIQ S8, GE HealthCare) was used in the longitudinal position. The probe was moved from the midline to the lateral side of the spine and serially identified the spinous process, lamina, and transverse process of the painful target vertebra. Once the location of the transverse process was confirmed, a 100-mm, 22-gauge echogenic ultrasound needle was inserted in the plane from the caudal to cephalad or cephalad to caudal direction. Twenty to thirty mL of 0.1% ropivacaine was injected after the contact of the transverse process. The linear spread of local anesthetics beneath the erector spinae muscle was identified during the injection. For at least 10 minutes, a patient was lying in bed, taking a monitor of any unwanted side effects.

Blood Sampling

Patients who were taking any anti-inflammatory or analgesic medications were made to stop taking those medications during the 48 hours before the procedure. Before the blood sample was collected, each patient took an overnight fast. The blood sampling was timed to take place just before the first ultrasound-guided ESPB and 2 weeks after the final ESPB. During each instance of blood sampling, 10 mL of blood was taken from the nondominant forearm. Collected blood was kept in an ethylenediaminetetraacetic acid (EDTA) tube (BD Vacutainer®, Becton, Dickinson and Company) to avoid any blood coagulation. As soon as the collected blood was centrifuged at 3000 rpm for 10 minutes to separate the serum, it was kept frozen in temperature of -30 °C. Finally, the enzyme-linked immunosorbent assay (ELISA) technique was used to evaluate the serum IL-6 (Human Interleukin 6 ELISA Kit, MyBioSource), IL-8 (Human InterLeukin 8 ELISA Kit, MyBioSource), CGRP (Human CGRP ELISA Kit, MyBioSource), substance P (Human Substance P, SP ELISA Kit, MyBioSource), and beta endorphin (Human beta Endorphin ELISA Kit, MyBioSource) levels. To determine the final level of each substance, ELISA was performed twice.

Statistics

The primary outcome variable was to compare the values of inflammatory cytokine and pain neurotransmitters in the HZ patients with those of the control group, and before and after the nerve blocks were administered. No earlier study had shown the comparative changes in pain neurotransmitters between HZ patients and a control group, and before and after the HZ patients received a nerve block. According to a previous study (22) that compared the levels of IL-6 in HZ patients to the levels of IL-6 in a control group, the mean intergroup difference in IL-6 between the former group (n = 43) and the latter (n = 47) was 1.63 ± 1.40. Considering an alpha error level of 0.05, a beta error level of 0.2, and a dropout rate of 15%, 15 patients were required for each group, with 80% power and a significance level of 5%.

All statistical analyses were performed using nonparametric methods because of the small sample size and non-normal distribution of the data. Continuous variables were summarized as median with interquartile range (IQR) and categorical variables as number and percentage.

Between-group comparisons (HZ vs. control) were performed using the Mann–Whitney U-test for continuous variables and Fisher's exact test or the chi-square test for categorical variables. Within-group comparisons (before block vs. after block in each group) were assessed using the Wilcoxon signed-rank test. All tests were 2-sided, and a P value < 0.05 was considered statistically significant.

Results

Clinical Data

Eighteen HZ patients who agreed to participate and a control group of 15 healthy age- and gender-matched patients were enrolled in this study. The 18 HZ patients comprised 10 individuals with AHZ (< 2 months) and 8 individuals with PHN (> 6 months) (Fig. 1). The median ages of the HZ and control groups were 62.0 (57.0-75.2) and 68.0 (58.0-74.0) years, respectively. Nine patients (50.0%) in the HZ group and 6 patients (40%) in the control group were women. The most commonly affected dermatome was the thoracic region (72.2%, Table 1).

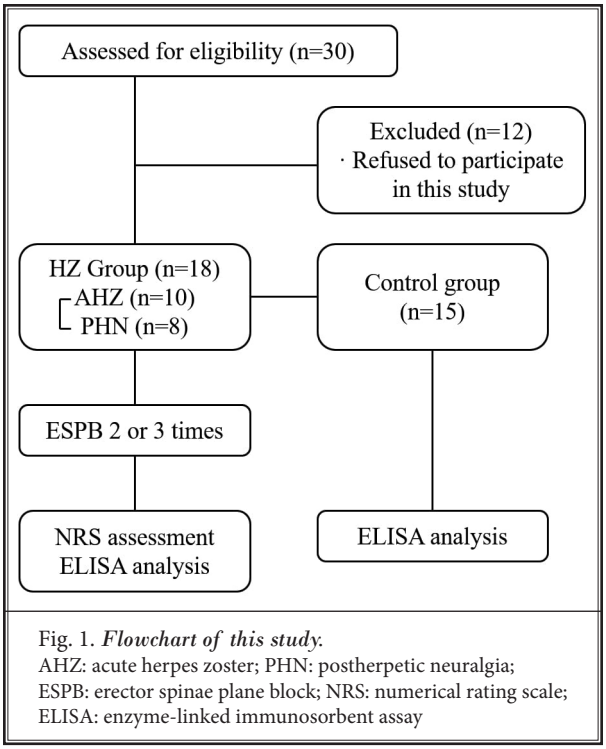


Fig. 1. *Flowchart of this study.*
AHZ: acute herpes zoster; PHN: postherpetic neuralgia; ESPB: erector spinae plane block; NRS: numerical rating scale; ELISA: enzyme-linked immunosorbent assay

Table 1. *Demographic data.*

	Herpes Zoster Group (n = 18)	Control Group (n = 15)	*P* value
Age (years)	62.0 (57.0-75.2)	68.0 (58.0-74.0)	0.469
Gender (M/F)	9 (50.0%) / 9 (50.0%)	9 (60.0%) / 6 (40.0%)	0.729
Body mass index (kg/m^2)	22.4 (20.5-23.5)	23.8 (21.9-26.0)	0.049
Pain duration (month)	2.0 (1.0-25.5)		
Affected dermatome			
Cervical	4 (22.2%)		
Thoracic	13 (72.2%)		
Lumbar	one (5.6%)		

Table 2. *Changes in numerical rating scale score among herpes zoster (HZ) patients after ultrasound-guided erector spinae plane blocks (ESPBs) at affected dermatomes.*

	Herpes Zoster (n = 18)
0 weeks	6.0 (6.0-7.0)
2 weeks	3.0 (1.8-4.2)
4 weeks	3.0 (0.8-3.2)
8 weeks	2.0 (0.8-3.0)*

Values are median (IQR).
*$P < 0.001$ compared to score at 0 weeks.

Clinical Response After ESPB

At 8 weeks after the ESPBs, the patients' NRS scores showed a significant reduction (median, 2.0; IQR, 0.8-3.0) from what they were before the block (median, 6.0; IQR, 6.0-7.0; $P < 0.001$, Table 2).

Serum Biomarker Comparison (HZ vs. Control Group)

The level of serum IL-6 (median, 36.5; IQR, 15.9-92.7) in the HZ patients was similar to the level in the control group ($P = 0.742$). However, the level of serum IL-8 in the control group was significantly higher ($P = 0.047$). The levels of serum CGRP (median, 157.1; IQR, 142.5-170.4), substance P (median, 30.6; IQR, 13.3-71.6), and beta endorphin (median, 375.4; IQR, 242.4-465.8) in the HZ patients were also similar to the control group's ($P = 0.928$ for CGRP; $P = 0.989$ for substance P; and $P = 0.871$ in beta endorphin levels, Table 3).

Serum Biomarker Comparison (AHZ vs. PHN)

The levels of serum IL-6 (median, 27.0; IQR, 14.7-76.5) and IL-8 (median, 8.5; IQR, 4.5-14.2) in patients with AHZ were similar to those found in patients with PHN ($P = 0.657$ for IL-6 and $P = 0.230$ for IL-8). The levels of serum CGRP (median, 159.2; IQR, 132.9–167.2), substance P (median, 35.5; IQR, 15.6-68.7), and beta endorphin (median, 390.4; IQR, 253.2-465.8) in AHZ patients were also similar to the levels thereof in PHN patients ($P = 0.594$ for CGRP, $P = 0.550$ for substance P, and $P = 0.722$ in beta endorphin levels, Table 4).

Serum Biomarker Comparison Before and After Ultrasound-Guided ESPB

The levels of serum IL-6, IL-8, and CGRP after the ESPB were similar to the levels thereof before the ESPBs ($P = 0.567$ for IL-6, $P = 0.825$ for IL-8, and $P = 0.824$ for CGRP, Figs. 2-4). The level of serum substance P following the ESPB (median, 24.0; IQR, 7.2-49.5) was significantly lower than it was prior to the ESPB (median, 30.6; IQR, 13.3-71.6; $P = 0.009$, Fig. 5). Also, the level of serum beta endorphin after the ESPB (median, 237.8; IQR, 177.4- 414.5) was significantly lower than it was before the ESPB (median, 375.4; IQR, 242.4-465.8; $P = 0.024$, Fig. 6).

Discussion

This study demonstrated a significant reduction of substance P and beta endorphin in HZ patients after they received an ESPB. However, the comparative levels of serum inflammatory cytokines (IL-6) and pain

neurotransmitters (substance P, CGRP) between the HZ patients and the control group did not show any significant differences. When the HZ patients were subdivided into the AHZ and PHN categories, the 2 subgroups showed no significant differences between their levels of serum inflammatory cytokines and pain neurotransmitters.

IL-6, as an early marker of tissue damage, becomes involved in various inflammatory processes and chronic immune-mediated diseases. As for the levels of IL-6 in patients infected with the varicella-zoster virus, however, contradictory results have been suggested (22-25). Several studies have demonstrated significantly higher levels of IL-6 in HZ patients who develop PHN than in those who do not develop PHN (10,25). Similarly, a study by Khazan et al (22) showed that AHZ patients had significantly greater levels of IL-6 and IL-18 than did the

Table 3. *Changes in serum IL-6, IL-8, calcitonin gene-related peptide (CGRP), substance P, and beta endorphins in HZ and control groups.*

	Herpes Zoster Group (n = 18)	Control Group (n = 15)	*P* value
IL-6 (pg/mL)	36.5 (15.9-92.7)	34.5.0 (15.3-41.3)	0.742
IL-8 (pg/mL)	8.9 (6.5-20.3)	17.0 (11.2–23.0)	0.047
CGRP (pg/mL)	157.1 (142.5-170.4)	159.1 (132.4-169.6)	0.928
Substance P (pg/mL)	30.6 (13.3-71.6)	34.6 (21.5-43.7)	0.989
Beta endorphins (pg/mL)	375.4 (242.4-465.8)	328.7 (257.0-500.3)	0.871

Values are median (IQR). Values in HZ patients were measured before the administration of any ultrasound-guided fascial plane injections.

Table 4. *Changes in serum IL-6, IL-8, CGRP, substance P, and beta endorphins among patients with acute herpes zoster (AHZ) and patients with postherpetic neuralgia (PHN).*

	AHZ (n=10)	PHN (n=8)	*P* value
IL-6 (pg/mL)	27.0 (14.7-76.5)	56.9 (16.7-105.0)	0.657
IL-8 (pg/mL)	8.5 (4.5-14.2)	15.8 (7.6-22.5)	0.230
CGRP (pg/mL)	159.2 (132.9-167.2)	154.2 (148.6-181.8)	0.594
Substance P (pg/mL)	35.5 (15.6-68.7)	14.2 (6.7-79.5)	0.550
Beta endorphins (pg/mL)	390.4 (253.2-465.8)	322.9 (223.3-452.8)	0.722

Values are median (IQR).

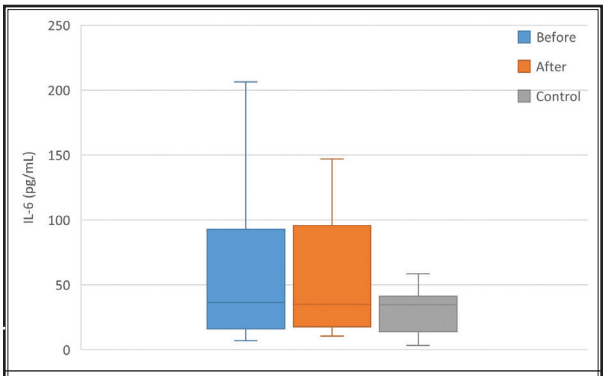


Fig. 2. *Box plot for serum IL-6 levels in HZ patients before and after ultrasound-guided ESPBs and in control group.*

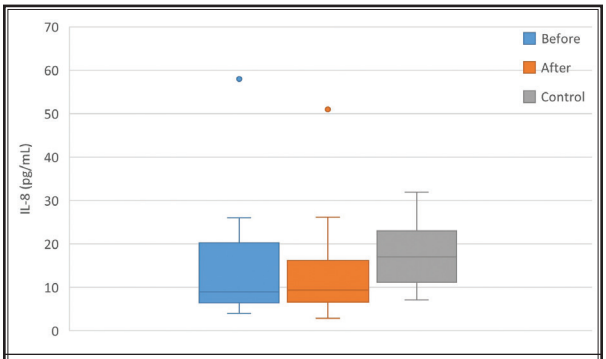


Fig. 3. *Box plot for serum IL-8 levels in HZ patients before and after ultrasound-guided ESPBs and in control group.*

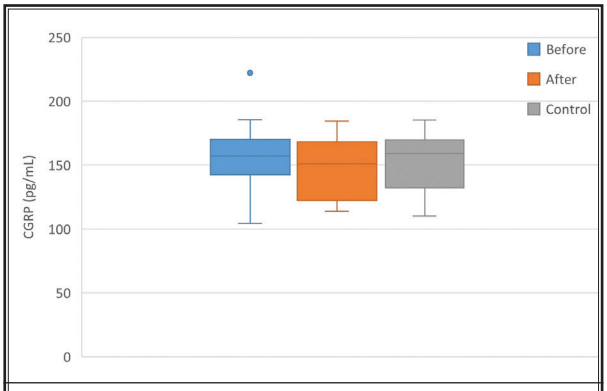


Fig. 4. *Box plot for serum CGRP levels in HZ patients before and after ultrasound-guided ESPBs and in control group.*

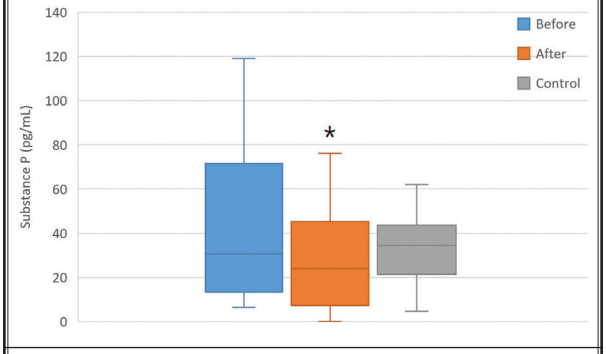


Fig. 5. *Box plot for serum substance P levels in HZ patients before and after ultrasound-guided ESPBs and in control group.*

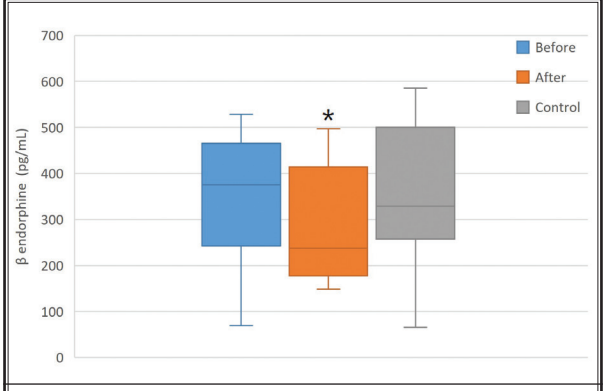


Fig. 6. *Box plot for serum beta endorphin levels in HZ patients before and after ultrasound-guided ESPBs and in control group.*

control group. Also, increased levels of all biomarkers were correlated significantly with higher levels of skin rash and pain severity (22). Contrasting with the results of the above studies, Uceyler et al (26) demonstrated no differences in IL-6 levels between PHN patients and the healthy control group or between affected and unaffected skin lesions.

In a study that showed a significantly higher level of serum inflammatory cytokines in AHZ patients than in the control group, the AHZ patients were within 7 days of the rash onset at their first visit (22). Also, a study by Hao et al (24) demonstrated that the serum cytokine level peaked at the first day of the patients' hospital admission. According to the results of those studies (22,24), a significant increase of serum inflammatory cytokines could be observed in a very acute phase of HZ. However, a study by Zak et al (25) demonstrated that inflammatory cytokine levels did not show any significant differences between a very acute phase (within 10 days of symptom development) and an acute phase (one week after a very acute phase). Accordingly, this study also demonstrated an insignificant increase of IL-6 in HZ patients from the levels seen in the control group. Moreover, IL-8 levels were significantly lower in the HZ patients than in the control group.

Persistent overproduction of IL-6 is associated with the development of acute inflammatory responses and chronic inflammatory diseases. IL-6 plays an important role in the pathophysiology of rheumatologic disease and is associated with disease severity and joint destruction (22,27). The protective or pathophysiological roles of IL-6 in HZ are still unclear and need further research.

Nerve blocks that use local anesthetics and steroids have been widely accepted as treatments for acute zoster-related pain and chronic PHN. This study showed a significant decrease in HZ patients' NRS scores after ultrasound-guided ESPBs. A previous study also demonstrated that ESPBs with local anesthetics and steroids could provide effective analgesia, reduce analgesic consumption, and decrease PHN incidences for patients with AHZ (28-30). HZ occurs most frequently in the thoracic dermatome, and the condition is localized. Unilateral, epidural, and paravertebral blocks have been widely used to manage it, as have ESPBs (28,29,31). Among such interventional treatments, the ESPB, rather than the paravertebral or neuraxial block, has been recommended due to its safety profile (28).

In accordance with the effective analgesia provided by the ESPBs in this study, levels of substance P and CGRP were reduced after the procedures, although the reduction of CGRP did not result in a significant difference from its pre-ESPB levels. According to the results of this study, the effective analgesia provided by the ESPBs was also confirmed by the reduced serum levels of pain neurotransmitters. An earlier study demonstrated high levels of CGRP immunolabeling in epidermal keratinocytes obtained from human skin (19). However, this study did not reveal an increase in the levels of serum CGRP from those seen in the control group.

Currently, no study shows the changes in HZ patients' levels of serum inflammatory cytokine and pain neurotransmitters before and after the administration of nerve blocks. One previous study of patients with chronic migraines demonstrated significant reductions in serum CGRP levels and number of headache days after greater occipital nerve blocks were given to the patients (20).

Compared to the pre-procedural values, levels of

serum beta endorphins decreased significantly after the ESPBs. In patients with chronic pain disorders, mu and kappa opioid receptors, the main targets of endogenous opioids, lose their sensitivity and become downregulated. This downregulation of receptors can lead to an elevated level of beta endorphins for compensatory pain control (32). The reduction in both NRS scores and beta endorphin levels after the ESPBs indicates that the technique effectively alleviated pain in patients with HZ, which meant the normalization of the chronically elevated beta endorphin levels in the HZ group.

This study includes several limitations. Most of the AHZ patients had been enduring their pain for one-2 months. Due to the severe skin lesions that occur in the very acute phase of AHZ, patients who have the condition tend to prefer to visit dermatologic physicians, not pain physicians. Therefore, this study could not include AHZ patients who were experiencing a very acute phase of the condition. Since it is uncertain if patients with very acute AHZ can experience any significant change, whether a reduction or an increase, in their levels of serum inflammatory cytokine, further study is required. Because of the invasive method used in this study (blood sampling) and the high costs of ELISA, only a small number of HZ patients could be included. Further study regarding serum biomarker changes in larger numbers of HZ patients is necessary.

Conclusions

In conclusion, the HZ patients and the control group did not show any significant differences between them in their levels of serum inflammatory cytokine (IL-6) and pain neurotransmitters (CGRP, substance P). However, a significant reduction of substance P and beta endorphin after the ESPBs was observed.

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