Retrospective Case Series

Clinical Efficacy of Tender Point Infiltration (TPI) for Management of Acute and Subacute Zoster-Associated Pain: A Retrospective Analysis

Ying Shen, MD[1], Xiangjun Zhou, MD[1], Nan Ji, MD[2], and Fang Luo, MD[1]

From: [1]Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, China; [2]Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

Address Correspondence:
Fang Luo, MD
Department of Pain Management
Beijing Tiantan Hospital, Capital Medical University
119 South Fourth Ring Road West, Fengtai District
Beijing, China
E-mail: luofangwt@yahoo.com

Disclaimer: The study is funded by the Capital's Funds for Health Improvement and Research (grant No. 2020-2-2046). The funders have had no role in the study design, data collection, and analysis, decision to publish, or preparation of the manuscript. Ying Shen and Xiangjun Zhou contributed equally to this work and should be considered as co-first author. Nan Ji and Fang Luo contributed equally to this work. All authors read and approved the final manuscript

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 08-26-2022
Revised manuscript received: 11-11-2022
Accepted for publication: 11-16-2022

Free full manuscript: www.painphysicianjournal.com

Background: Zoster-associated pain (ZAP) represents an important medical, social, and economic problem. The treatment approach for ZAP continues to be challenging. Tender point infiltration (TPI) with local anesthetic and steroids has been demonstrated to have potential in the treatment of severe pain, but there are rare reports of the efficacy and security of TPI for acute and subacute ZAP.

Objectives: The aim of this study was to retrospectively analyze the efficacy of TPI for pain control in acute and subacute ZAP.

Study Design: Retrospective case series.

Methods: Medical records of 152 patients who underwent TPI for acute and subacute herpes zoster pain were reviewed. The patients were divided into 2 groups: acute TPI group (TPI within 30 days after zoster onset) and subacute TPI group (TPI between 30 and 90 days after zoster onset). The numeric rating scale (NRS), effective rate, frequency of TPI and rate of medication discontinuation during the follow-up period of 3 months were retrospectively analyzed.

Results: The NRS score significantly decreased from 7.80 ± 1.05 before TPIs to 0.97 ± 0.68 in the acute TPI group ($P < 0.001$) and was decreased from 5.76 ± 1.07 to 1.12 ± 0.70 in subacute TPI group ($P < 0.001$). The effective rate was 92.2% in acute TPI group and was 90.7% in subacute TPI group ($P = 0.734$). The rate of medication discontinuation at month 1 and month 3 was higher in the acute TPI group than in the subacute TPI group ($P < 0.05$). The frequency of TPI in acute TPI group (1.49 ± 0.79) was less than subacute TPI group (3.09 ± 1.02) ($P < 0.001$). A small proportion of the patients had mild complications, and all resolved over time after TPIs. No severe adverse events occurred during or after TPI procedures.

Limitations: Retrospective design without a control group, short period of follow-up, and the small number of patients.

Conclusions: TPI can be a useful and safe option for the control of acute and subacute ZAP with high feasibility. Early application of TPI in the acute phase of herpes zoster pain may show better clinical outcomes.

Key words: Tender point infiltration, herpes zoster, zoster-associated pain, acute pain, Diprospan

Pain Physician 2023: 26:E63-E72

Herpes zoster (HZ) is caused by reactivated varicella-zoster virus, which induces inflammation of the ganglion and peripheral nerve, and local tissue injury along the descending sensory nerve. The incidence rate of HZ ranges between 3 and 5/1000 person-years in North America, Europe, and Asia-Pacific (1). According to

current research, 3 phases can be distinguished in zoster-associated pain (ZAP): acute herpetic neuralgia (AHN), subacute zoster neuralgia, and postherpetic neuralgia (PHN) (2). AHN is characterized by a specific quality of pain in association with the outbreak of a herpes zoster rash within one month. The pain is associated with hyperalgesia, allodynia, burning, prickling, and tingling sensations or an electric shock-like sensation and usually disappears with rash regression. AHN occurs in ≥ 95% of patients aged > 50 years, and 60% to 70% of patients continue to have persistent pain 1 month after the episode, with 40% of those considered to be severe (3). Pain that persists for more than 3 months after rash onset is typically considered PHN. Subacute herpes zoster is defined as the presence of zoster symptoms beyond the acute phase before PHN is diagnosed (4). Intractable severe pain can lead to depression, fatigue, and sleep disturbances; as the intensity of pain and discomfort increase, its impact on functional status and health-related quality of life (HRQL) becomes increasingly severe (5). If an appropriate degree of pain reduction and anti-inflammation therapy is not established in the acute and subacute phase of herpes zoster, acute and subacute herpetic neuralgia may progress to PHN (6); pain may continue over for 3 months following the viral infection. PHN has a complex etiology and is difficult to cure. Therefore, early medical interventions for the pain of acute and subacute herpes zoster are essential for better clinical outcomes and prognosis.

Antiviral therapy in combination with adequate pain management should be given to all patients as soon as herpes zoster is diagnosed (7). Patients with mild to moderate pain may be managed with acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs), alone or in combination with a weak opioid analgesic (e.g., codeine) or tramadol as a recommendation for supplementing antiviral therapy in the acute stage of HZ (8). Although analgesia is included in the standard treatment of HZ, medications are not completely effective. Studies show that pulsed radiofrequency (9), lidocaine patch (10), capsaicin cream (11), acupuncture (12), transcutaneous electrical nerve stimulation (13), and subcutaneous botulinum toxin-A injection (14) can be used to provide pain relief as a supplement to the basic analgesic treatment regimen. Undoubtedly many patients have benefited from it, however, some have not. Given the lack of high-quality studies, there is insufficient evidence and expert agreement to make recommendations for these intervention strategies as first-line treatments in guidelines (15).

Based on the European consensus-based guideline and in line with previous investigations (3,16), in patients with severe AHN that is not controlled by any other means, a local anesthetic nerve block with steroids is recommended, which may provide pain relief and possibly reduce the development of PHN (17,18). Interventional treatment options of nerve block for AHN are mostly epidural, paravertebral, erector spinae plane, and intercostal block (16,19-22) with multiple or continuous administration (23), which are complex and difficult procedures with possible tissue damage. This may lead to an increase in the failure rates and the risk of localized inflammation, local infection, abscess formation, and sepsis. Indwelling catheters come with the risk of complications such as prolapse or obstruction of the catheter, leading to patient suffering, poor compliance, and poor quality of life. Studies on the therapeutic effects of subcutaneous and intracutaneous injection with local anesthetic and steroids in the management of acute herpes zoster pain are scarce (24,25). Further research is needed to demonstrate the safety and effectiveness of subcutaneous and intracutaneous injections in patients with AHN. While the effectiveness of the aforementioned interventions in controlling AHN is promising, they cannot completely relieve pain and prevent PHN, and risks may occur. Considering invasiveness, price, effectiveness, and safety, it is necessary to explore other compatibilities of options with lower incidence of side effects, higher feasibility, and longer duration in the management of acute and subacute herpes zoster pain.

A tender point denotes a focal nodule that produces pain directly under the area of palpation (26). Tender point infiltration (TPI) is a type of local infiltration with anesthetics and steroids injected into the most painful region, healed scars, and pigmented spots. Compared to traditional ways of nerve block, TPI has the advantages of easier orientation, lower risk of complications or misplacement of the needle. Many studies showed the therapeutic effects of TPI in the management of inguinal neuralgia, fibromyalgia, and back pain (27,28). A case report by Chen et al reported immediate pain relief after injections to tender points with lidocaine in 2 patients who developed allodynia 1 to 3 months after zoster onset; the effect of pain relief lasted 1 to 2 weeks after the initial injection and lasted up to 2 months after repeated injections (29). However, this study only included 2 patients with subacute herpes zoster, and the solution for TPI was simplex lidocaine. The effectiveness of TPI with the

combination of local anesthetic and steroids in more patients with acute and subacute herpes zoster pain has not been investigated yet. In the present study, we retrospectively analyzed the efficacy of TPI with local anesthetic and steroids for control of ZAP in patients with acute and subacute herpes zoster to explore a safe, impactful, and convenient option for acute and subacute herpes zoster pain.

Methods

Study Setting and Patients

This study was approved by Capital Medical University. Medical records of patients who underwent TPI with local anesthetic and steroids for acute or subacute zoster-associated pain between April 2019 and February 2022 were collected retrospectively from the Department of Pain Management, Bejing Tiantan Hospital information systems.

Patients who met the following inclusion criteria were included in the study: (1) TPI performed in patients over 18 years of age with moderate to severe zoster pain; (2) The herpetic skin lesions involving the dermatome from the lumbosacral to cervical segment and limbs; (3) Cases in which TPI was performed within 90 days from zoster onset. Patients with an insufficient 3-month follow-up period after TPI or with missing data were excluded from the study. Patients were followed up after TPI due to the need for medical quality control. Routine follow-up was done through telephone interviews or when patients revisited the clinic. Antiviral therapy (for example, Famciclovir 250 mg was administered 3 times daily orally for 7 days within the first 72 hours of eruption) was used as the first line treatment of HZ in the acute zoster phase. Acetaminophen, ibuprofen or other NSAIDs, tramadol, oxycodone/acetaminophen combination tablet, and topical analgesics were used as analgesics. Amitriptyline or duloxetine were used as antidepressants. Gabapentin or pregabalin were used as anticonvulsants.

Interventions

The assessment of tender points was done before TPI. Each tender point was identified on a physical exam, and up to 20 tender points with the worst pain were selected for TPI at one time. Before the treatment, the skin of the participant was marked with a permanent marker at the assessed tender points and disinfected with Aner iodine skin disinfectant. The infiltration solution was prepared with 4 mL of 2% lidocaine and diprospan (0.5 mL, betamethasone propionate 2.5 mg, and betamethasone sodium phosphate 1 mg), diluted to a total volume of 20 mL with normal saline (30). The injected volume into each tender point was 1 mL. The total volume needed of the solution for injections was calculated by the number of tender points. The injections were administered perpendicular to the skin surface over the chosen tender point using a 25G needle (BD PricisionGlide™, 30 Tuas Avenue 2, Singapore). The solution was administered into each tender point as a single shot in 10 seconds, and stretching was done after all the injections in order to help distribute the solution across the muscle. The injections were repeated after 2 weeks in the most painful tender points at that time when patients obtained effective but incomplete pain relief. If necessary, up to 5 injections were administered 2 weeks each. All TPI procedures were conducted by experienced physicians in pain management.

Data Collection

The demographic, perioperative, and follow-up data were collected and analyzed: Patient characteristics (age, gender, body mass index [BMI], dermatomal level of vesicles, previous medication, and comorbidities), duration of disease (time to initiate TPI from zoster onset), block characteristics (number of block points each time, doses of betamethasone propionate and betamethasone sodium phosphate used each time, frequency of TPI procedures performed, as well as the proportion of patients who received repeated TPI). ZAP in the last 24 hours was assessed using a numeric rating scale (NRS), with 0 representing "no pain" and 10 representing "worst pain imaginable." The intensity of pain and doses of analgesics, anticonvulsants, and antidepressants were assessed and recorded prior to TPI, at 2 weeks, 1 month, and 3 months after TPI. Self-tapering of medication was recommended unless pain increased again after effective TPI procedures. Satisfactory pain relief was defined as "medication discontinuation." Responders were defined as patients who had a reduction of NRS > 50% after TPI (31). We calculated the following data: effective rate (number of responders/total number of patients*100%) at each time point, the time required for a positive response as reported by patients following TPI therapy, and the proportion of patients who were able to discontinue the prescribed medication at 2 weeks, 1 month and 3 months after TPI. Patients who were refractory to TPI and offered additional intervention strategies were recorded and excluded from further analysis.

Patients were divided into 2 groups: patients who underwent first TPI within 30 days after zoster onset (acute phase of herpes zoster) were classified as the acute TPI group, whereas patients who underwent first TPI between 30 and 90 days after zoster onset (subacute phase of herpes zoster) were classified as the subacute TPI group. The aforementioned data were compared between the 2 groups.

Statistical Analysis

Data are presented as mean ± standard deviation (SD) for continuous variables. Data normality was evaluated using the Kolmogorov-Smirnov test. Outcomes between the groups were compared using the independent t-test or Mann-Whitney U test for continuous variables. The chi-square test or Fisher's exact test was used to evaluate the significant difference of categorical variables. All data were analyzed using SPSS version 25.0 (SPSS Inc., Chicago, IL), and P values < 0.05 were considered statistically significant.

Results

Medical records of 158 patients who met the inclusion criteria were reviewed. Medical records of 6 patients were insufficient for analysis and were excluded from the study. Among 152 patients, 77 underwent the first TPI within 30 days after zoster onset (acute TPI group), and 75 underwent the first procedure at 30 to 90 days from zoster onset (subacute TPI group). As a result, a complete review of the medical records of 152 patients was available for 3 months after the first TPI (Fig. 1).

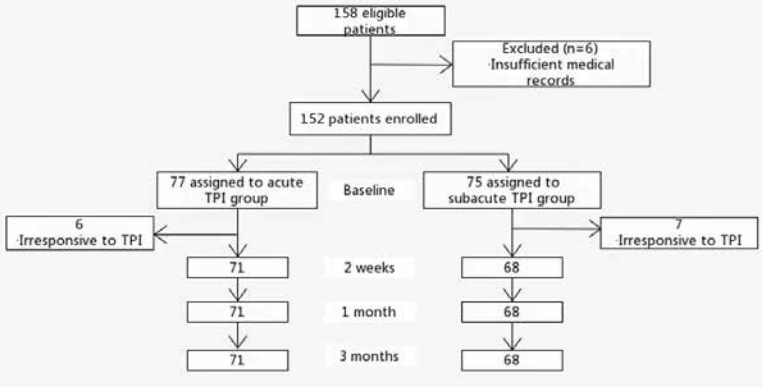

Fig. 1. *Enrollment and follow-up.*
All patients who had undergone TPI were included in the primary outcome analysis.

Patient Demographics

The demographic data of patients are summarized in Table 1. There were no significant differences in age, gender, BMI, involved dermatome, side, medical history and previous analgesics between the 2 groups. Time from zoster onset to initiation of TPI was 19.81 ± 9.49 days in the acute TPI group and 49.07 ±15.57 days in the subacute TPI group (P < 0.001). NRS before the procedure was 7.83 ± 1.03 and 5.68 ± 1.07 for the acute TPI group and the subacute TPI group, respectively (P < 0.001).

Effective Rate

The effective rates of the acute TPI group at 2 weeks, 1 month, 3 months after the first TPI treatment were all 92.2% (71 patients) in the acute TPI group, and 90.7% (68 patients) were in the subacute TPI group. The effective rate was similar in both the acute and subacute groups (P = 0.734). A total of 13 patients, including 6 patients in the acute TPI group and 7 patients in the subacute TPI group, were refractory to TPI and were offered additional intervention strategies in the study. Positive responses were reported by patients with effective TPI therapy shortly after the injections in both the acute TPI group and the subacute TPI group. There was no significant difference between the 2 groups.

Block Characteristics

A total of 334 TPIs procedures were performed in 152 patients. One hundred thirty-nine patients responded to treatment which included 71 patients from the acute TPI group with 106 TPIs and 68 patients from the subacute TPI group with 210 TPIs. The number of block points, number of patients, and doses of diprospan (betamethasone propionate and betamethasone sodium phosphate) used each time significantly decreased in both the TPI groups, with the increase in times of TPI administration (Table 2). The frequency of TPI during the follow-up period in the acute TPI group was less than that in the subacute TPI group (acute TPI group 1.49 ± 0.79 vs subacute TPI group 3.09 ± 1.02, P < 0.001) (Table 2, Fig. 2). A higher proportion of patients who received repeated TPI treatment was observed in the subacute TPI group when compared to the acute TPI group.

Table 1. *Demographic data of patients*.

Characteristic	Acute TPI group n = 77	Subacute TPI group n = 75	*P* value
Age, years	63.62 ± 9.70	65.89 ± 9.32	0.143
Gender, n (%)			0.370
Male	30 (39.0%)	24 (32.0%)	
Female	47 (61.0%)	51 (68.0%)	
BMI	20.99 ± 2.89	20.79 ± 2.91	0.673
Involved dermatome			0.843
Cervical, n (%)	29 (37.7%)	25 (33.3%)	
Thoracic, n (%)	27 (35.1%)	29 (38.7%)	
Lumbosacral, n (%)	21 (27.2%)	21 (28.0%)	
Side			0.623
Left, n (%)	39 (50.6%)	35 (46.7%)	
Right, n (%)	38 (49.4%)	40 (43.3%)	
Underlying disease			0.485
Hypertension (HTN), n (%)	21 (27.3%)	25 (33.3%)	
Diabetes mellitus (DM), n (%)	9 (11.7%)	7 (9.3%)	
HTN and DM, n (%)	12 (15.6%)	18 (24.0%)	
Depressive disorder, n (%)	6 (7.8%)	4 (5.3%)	
None, n (%)	29 (37.7%)	21 (28.0%)	
Previous medications			
Anticonvulsants (gabapentin or pregabalin), n (%)	77 (100.0%)	75 (100.0%)	
Antidepressants (amitriptyline or duloxetine), n (%)	12 (15.6%)	15 (20.0%)	0.476
Analgesics, n (%)	77 (100.0%)	75 (100.0%)	
NSAIDs, n (%)	76 (98.7%)	70 (93.3%)	0.114
Tramadol, n (%)	12 (15.6%)	16 (21.3%)	0.361
Oxycodone/acetaminophen combination tablet, n (%)	30 (39.0%)	21 (28.0%)	0.152
Topical analgesics, n (%)	44 (57.1%)	54 (72.0%)	0.056
NRS before TPI	7.83 ± 1.03	5.68 ± 1.07	< 0.001
Time to 1st TPI from zoster onset, days	19.81 ± 9.49	49.07 ± 15.57	< 0.001

a: Continuous variables are presented as mean ± standard deviation (SD); categorical variables are presented as number (%).
b: *P* value compares acute TPI group and subacute TPI group.
c: t-test used to compare means and chi-squared test used to compare proportions.

NRS and Medication Use

In patients with persistent ZAP who reported effective TPI, NRS showed a positive change in both groups. Patients who were refractory to TPI and were offered additional intervention strategies were not within consideration. The mean pain score of responders after TPI decreased more than 50% at 2 weeks in both groups when compared to the baseline and the score continued decreasing at 1 month and 3 months. NRS at 2 weeks and 1 month after TPI was lower in the acute TPI group than in the subacute TPI group, whereas NRS at 3 months after TPI was not significantly different between the 2 groups (Fig. 3). The proportion of patients who were able to discontinue anticonvulsants, antidepressants, and analgesics was significantly higher in the acute TPI group than that in the subacute TPI group at month 1 and month 3 after the procedure (Table 3).

Complications

Minor surgical complications included skin bruises and hematoma. No steroid-related complication or severe complications were observed. A 22.1% minor complication rate was observed in the acute TPI group

Table 2. *Block characteristics*.

	Acute TPI group n = 71		Subacute TPI group n = 68		*P* value
Times of TPI	1.49 ± 0.79		3.09 ± 1.02		< 0.001
Number of patients Time 1, n (%) Time 2, n (%) Time 3, n (%) Time 4, n (%) Time 5, n (%)	 71 (100.0%) 24 (33.8%) 9 (12.7%) 2 (2.8 %) 0 (0.0%)		 68 (100.0%) 60 (88.2%) 55 (80.9%) 24 (35.3%) 3 (4.4%)		 < 0.001
Number of block points Time 1, points Time 2, points Time 3, points Time 4, points Time 5, points	 15.15 ± 2.35 12.42 ± 1.67 6.56 ± 1.67 4.50 ± 0.71 0		 11.60 ± 2.23 11.22 ± 2.46 6.20 ± 1.42 4.04 ± 1.52 3.67 ± 1.16		 < 0.001 0.012 0.499 0.680
Doses of diprospan used each time (mg)	betamethasone propionate	betamethasone sodium phosphate	betamethasone propionate	betamethasone sodium phosphate	< 0.001
Time 1 Time 2 Time 3 Time 4 Time 5	1.89 ± 0.29 1.55 ± 0.21 0.82 ± 0.21 0.56 ± 0.09 0	0.76 ± 0.12 0.62 ± 0.08 0.33 ± 0.08 0.23 ± 0.04	1.45 ± 0.28 1.40 ± 0.31 0.76 ± 0.18 0.51 ± 0.19 0.46 ± 0.14	0.58 ± 0.11 0.56 ± 0.12 0.31 ± 0.71 0.20 ± 0.08 0.18 ± 0.58	< 0.001 0.120 0.499 0.680
Proportion of patients who received repeated TPI n (%)	24 (33.8%)		60 (88.2%)		< 0.001

a: Continuous variables are presented as mean ± standard deviation (SD); categorical variables are presented as number (%).
b: *P* value compares acute TPI group and subacute TPI group
c: t-test used to compare means and chi-squared test used to compare proportions

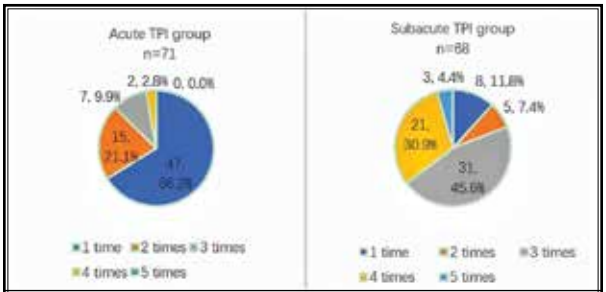

Fig. 2. *Frequency of TPI procedures performed in Responders*.
Number and Proportion of responders who received different times of TPI procedures from acute TPI group and subacute TPI group.

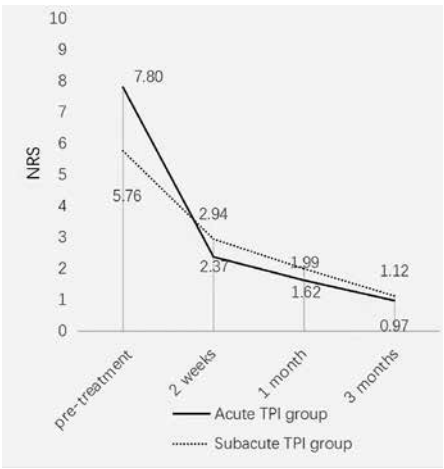

Fig. 3. *NRS of patients with effective TPI at different time points*.
Mean NRS of patients with effective TPI at 2 weeks, 1 month, and 3 months.

(skin bruise [n = 15] and hematoma [n = 2]). A 18.7% minor complication rate was observed in the subacute TPI group (skin bruise [n = 10] and hematoma [n = 4]). All resolved over time.

Discussion

Although many interventional treatments for the relief of ZAP have been studied, to the best of our knowledge, this is the first report demonstrating the efficacy of TPI with the combination of local anesthetic and steroids for the management of pain in acute and subacute herpes zoster. The findings of this retrospective study show that tender point infiltrations with betamethasone propionate and betamethasone sodium

Table 3. *Medication discontinuation rate in patients*.

	Anticonvulsants			Antidepressants			Analgesics		
	Acute TPI group, n (%)	Subacute TPI group, n (%)	*P*	Acute TPI group, n (%)	Subacute TPI group, n (%)	*P*	Acute TPI group, n (%)	Subacute TPI group, n (%)	*P* value
2 weeks	19/77 (24.7%)	10/75 (13.3%)	0.075	5/12 (41.7%)	2/15 (13.3%)	0.185	28/77 (36.4%)	18/75 (24.0%)	0.097
1 month	36/77 (46.8%)	20/75 (26.7%)	0.010	8/12 (66.7%)	3/15 (20.0%)	0.022	42/77 (54.5%)	26/75 (34.7%)	0.014
3 months	53/77 (68.8%)	35/75 (46.7%)	0.006	10/12 (83.3%)	5/15 (33.3%)	0.019	57/77 (74.0%)	39/75 (52.0%)	0.005

a: categorical variables are presented as number (%).
b: *P* value compares acute TPI group and subacute TPI group
c: chi-squared test used to compare proportions

phosphate added to lidocaine significantly alleviate acute and subacute ZAP.

Both the acute and subacute ZAP patients who received TPIs obtained a high effective rate of more than 90% 2 weeks after the treatment, and the effective rate maintained above 90% during the follow-up period of 3 months. A comparable decrease in NRS and the increased withdrawal rates in patients also demonstrate the therapeutic efficacy of TPI in the acute and subacute phases of ZAP. An immediate analgesic effect was observed in patients who were responsive to TPIs. The number of block points, the total capacity of the solution, and doses of diprospan used each time decreased significantly with the increase in the number of TPI performed in the patient, which indicates that some of the tender points were cured in the progress of TPI treatment. Besides, although NRS at baseline in the acute TPI group was significantly higher than NRS in the subacute TPI group before treatment, pain intensity in the acute TPI group was significantly lower than subacute TPI group at 2 weeks and one month after TPI, with a lower frequency of TPI performed for pain relief, and a higher discontinuation rate of prescribed medication was found in the acute TPI group compared with the subacute TPI group. The above findings suggest that the sooner we perform TPI in ZAP patients, the better the response and a higher effective rate may be reached in patients with only one TPI treatment.

In previous studies, the benefits of administering nerve blocks with local anesthetic and steroids for relieving severe pain in the acute phase of herpes zoster have been reported (32,33). Instead of using local anesthetic and steroids for nerve blocks, the mixture used in our study for TPI obtained a relatively good analgesic effect. Certainly, further studies must be designed to demonstrate the difference between TPI and conventional nerve blocks. Studies investigating whether advanced outcomes can be observed with TPI and nerve blocks combined for acute and subacute herpes zoster pain are warranted. Compared with previous methods of nerve block, such as epidural injection, paravertebral block, and intercostal nerve block, TPI is more feasible and convenient. Besides, unlike previous studies suggesting the effectiveness of nerve block only for AHN, we also found the therapeutic effect of TPI in subacute herpes zoster, while the best therapeutic time window still requires thorough investigation in the future. A study by Albert et al (34) showed that one epidural injection of methylprednisolone and bupivacaine has a modest effect on acute herpes zoster pain (rash < 7 days) for 1 month. Different from their reports, we found that 47 out of 71 patients who responded to treatment in the acute TPI group obtained satisfactory pain relief for 3 months through a single application of TPI procedure; the other 24 responders also attained 3-month-long pain relief after repeated TPIs. Because TPI has the advantages of high feasibility and high compliance among patients with repetitive treatments, multiple operations of TPIs may show a cumulative benefit for further clinical advancement. With TPI, the needle tip is inserted in close proximity to the focal nodule that produces pain directly under the area of palpation. Therefore, proper delivery of drugs to any affected area can be achieved with a lower dose of injection resulting in less tissue damage.

In general, the acute pain experienced by patients during the acute phase of herpes zoster is attributed to inflammatory swelling of affected nerve and tissue damage; neuropathic changes such as central sensitization might not be established yet in herpes zoster within a month after zoster onset. It is possible that patients with acute zoster develop a guarded movement pattern that fosters the development of myofascial pain. Weiner et al reported that adequate treatment

of myofascial pain may not only alleviate pain related to myofascial pathology itself but also facilitate the treatment of sensory neuropathy (35). According to the study by Haanpaa et al, mechanical allodynia was common in acute herpes zoster and was associated with the presence of intense pain (36). A combination of antiviral therapy with effective relief of acute pain during this period may decrease the development of chronic neuropathic conditions such as PHN (6). In clinical trials of topical agents and in the clinical use of these agents for herpes zoster, therapy is typically delivered to the area of maximal pain (37). Besides, the use of local anesthetic allows an adequate block of ongoing pain signals through the direct action of local anesthetics on spinal nerves. The addition of steroids promotes a membrane-stabilizing effect on C-fiber transmission resulting in hindering the transmission of the nociceptive signal and reducing or even preventing the arousal of ectopic neural discharge. Epidural injection and paravertebral block with a local anesthetic plus methylprednisolone (25,34,38,39) or dexamethasone (21,40) showed significant pain relief in patients who had herpes zoster affecting the cervical to sacral dermatomes of less than a 1-month duration from the onset. In our study, we used the combination of betamethasone propionate and betamethasone sodium phosphate instead of the more commonly used dexamethasone or methylprednisolone, as the steroid added to local anesthetic although the optimal medication and concentration are yet to be reported. Soluble betamethasone disodium phosphate takes effect shortly after injection. Betamethasone dipropionate also becomes a reservoir due to the difficult absorption, which gradually decays and releases the steroid, so the effect lasts for a long time (41,42). A study by Liu et al. showed that intra-substance injection into the rupture area of the supraspinatus tendon with diprospan and xylocaine relieved pain and improved function scores more when compared to normal saline and xylocaine, and the therapeutic effect lasted for at least 6 months (43). The long-acting anti-inflammatory effect of diprospan may be due to its modulation of reducing the level of pro-inflammatory cytokines and stimulating the expression of the anti-inflammatory cytokine (44).

In the current study, only minor complications, such as skin bruises and skin hematoma, were incidentally noted after TPI, all of which resolved over time. Moreover, we delivered the needle tip to tender points in the muscle of maximal pain to minimize the potential for vascular injury or tissue damage, which contributed to high safety and little complications of repeated infiltrations. Different from the reported complications of epidural injections and selective nerve blocks such as infections, hypotension, seizure, stroke, spinal cord injury, or even death (45,46), TPI in our study had little complications, and all recovered quickly. Possible devastating complications of epidural injections were reported in a retrospective single-center study with a complication rate of < 3% (47). The potential for serious complications due to epidural blockade or paravertebral block and the invasiveness of these procedures must be given serious consideration. Compared to the interlaminar epidural injection and other selective nerve blocks, TPI has the advantages of cost-effectiveness, easy operation, high safety, and high compliance among patients. Also, steroid-related complications such as facial flushing, vasovagal episodes, nausea, vomiting, and hypotensive episode were not observed in our study since the steroids would not enter the blood or cerebrospinal fluid. Another reason is that we used very small amounts of steroids for each TPI in our study. Moreover, the required dose of steroids appeared to be decreased in patients who received repetitive TPIs, and steroid-related complications are expected to be negligible. Although severe complications associated with TPI were not observed in the present analysis, further prospective controlled study is needed to determine the safety of this procedure in herpes zoster.

Limitations

The present study has some limitations, which are expected to be improved in further studies. The primary limitation of this study is the relatively short follow-up period and small number of patients. Also, since this was a retrospective study dependent on the review of medical records, it was not possible to enroll an appropriate control group, and selection bias during data acquisition was unavoidable. Based on the results of the present retrospective study, further randomized controlled trials with long-term follow-up should be conducted with patients divided into a TPI group and a non-TPI group to determine whether the analgesic effect is due to local infiltrations or oral medications. Another limitation is that our study only included the values for NRS, rate of medication discontinuation, and effective rate. Assessing the effect of this treatment should simultaneously focus on PHN incidence and quality of life. In the current study, we only investigated a single combination of a local anesthetic and

steroid. The more appropriate medications are worthy of profound study. Additionally, predictors of impactful TPI ought to be explored to provide a reference for the clinical selection of applicable treatment options.

Conclusions

In conclusion, TPI has significant effectiveness and safety of pain relief in both acute and subacute herpes zoster neuralgia and may show a better clinical outcome in acute herpes zoster. Based on the results of this study, further randomized prospective comparative trials with an appropriate sample size should be conducted to further demonstrate the usefulness of TPI in herpes zoster and explore the optimal therapeutic time point, or even the ideal kind and dosage of medications, to provide guidance for clinical decision making.

References

1. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: Towards a global perspective. *BMJ Open* 2014; 4:e004833.
2. Zhou J, Sun W, Liu Y, et al. Clinical characteristics, treatment effectiveness, and predictors of response to pharmacotherapeutic interventions among patients with herpetic-related neuralgia: A retrospective analysis. *Pain Ther* 2021; 10:1511-1522.
3. Werner RN, Nikkels AF, Marinović B, et al. European consensus-based (S2k) guideline on the management of herpes zoster - guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV), Part 2: Treatment. *J Eur Acad Dermatol Venereol* 2017; 31:20-29.
4. Forbes HJ, Thomas SL, Smeeth L, et al. A systematic review and meta-analysis of risk factors for postherpetic neuralgia. *Pain* 2016; 157:30-54.
5. Forbes HJ, Bhaskaran K, Grint D, et al. Incidence of acute complications of herpes zoster among immunocompetent adults in England: A matched cohort study using routine health data. *Br J Dermatol* 2021; 184:1077-1084.
6. Kramer S, Baeumler P, Geber C, et al. Somatosensory profiles in acute herpes zoster and predictors of postherpetic neuralgia. *Pain* 2019; 160:882-894.
7. Schmader K. Herpes zoster. *Clin Geriatr Med* 2016; 32:539-553.
8. Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. *Clin Infect Dis* 2007; 44:S1-26.
9. Kim K, Jo D, Kim E. Pulsed radiofrequency to the dorsal root ganglion in acute herpes zoster and postherpetic neuralgia. *Pain Physician* 2017; 20:E411-E418.
10. Bianchi L, Piergiovanni C, Marietti R, et al. Effectiveness and safety of lidocaine patch 5% to treat herpes zoster acute neuralgia and to prevent postherpetic neuralgia. *Dermatol Ther* 2021; 34:e14590.
11. Tyring SK. Management of herpes zoster and postherpetic neuralgia. *J Am Acad Dermatol* 2007; 57:S136-S142.
12. Liu L, Chen Q, Yang J, et al. Fire needling acupuncture for adult patients with acute herpes zoster: Protocol of a systematic review and meta-analysis. *J Pain Res* 2022; 15:2161-2170.
13. Stepanović A, Kolšek M, Kersnik J, Erčulj V. Prevention of post-herpetic neuralgia using transcutaneous electrical nerve stimulation. *Wien Klin Wochenschr* 2015; 127:369-374.
14. Hu Y, Zou L, Qi X, et al. Subcutaneous botulinum toxin-A injection for treating postherpetic neuralgia. *Dermatol Ther* 2020; 33:e13181.
15. Gross GE, Eisert L, Doerr HW et al. S2k guidelines for the diagnosis and treatment of herpes zoster and postherpetic neuralgia. *J Dtsch Dermatol Ges* 2020; 18:55-78.
16. Benzon HT, Chekka K, Darnule, Chung B, Wille O, Malik K, Chung B, Wille O, Malik K. Evidence-based case report: The prevention and management of postherpetic neuralgia with emphasis on interventional procedures. *Reg Anesth Pain Med* 2009; 34:514-521.
17. Kim HJ, Ahn HS, Lee JY, et al. Effects of applying nerve blocks to prevent postherpetic neuralgia in patients with acute herpes zoster: A systematic review and meta-analysis. *Korean J Pain* 2017; 30:3-17.
18. Makharita MY, Amr YM. Effect of repeated paravertebral injections with local anesthetics and steroids on prevention of post-herpetic neuralgia. *Pain Physician* 2020; 23:565-572.
19. Tekin E, Ahiskalioglu A, Aydin ME, Sengun E, Bayramoglu A, Alici HA. High-thoracic ultrasound-guided erector spinae plane block for acute herpes zoster pain management in emergency department. *Am J Emerg Med* 2019; 37:375.e1- 375.e3.
20. Ahiskalioglu A, Alici HA, Ari MA. Ultrasound guided low thoracic erector spinae plane block for management of acute herpes zoster. *J Clin Anesth* 2018; 45:60-61.
21. Lee HJ, Park HS, Moon HI, Yoon SY. Effect of ultrasound-guided intercostal nerve block versus fluoroscopy-guided epidural nerve block in patients with thoracic herpes zoster: A comparative study. *J Ultrasound Med* 2019; 38:725-731.
22. Lin CS, Lin YC, Lao HC, Chen CC. Interventional treatments for postherpetic neuralgia: A systematic review. *Pain Physician* 2019; 22:209-228.
23. Kim YN, Kim DW, Kim ED. Efficacy of continuous epidural block in acute herpes zoster: Incidence and predictive factors of postherpetic neuralgia, a retrospective single-center study. *Medicine (Baltimore)* 2016; 95:e4577.
24. Nguyen DT, Dang TC, Nguyen QA, et al. The effect of subcutaneous injection of methylprednisolone acetate and lidocaine for refractory postherpetic neuralgia: A prospective, observational study. *Health Sci Rep* 2021; 4:e271.
25. Cui JZ, Zhang JW, Yan F, et al. Effect of single intra-cutaneous injection for acute thoracic herpes zoster and incidence of postherpetic neuralgia. *Pain Manag Nurs* 2018; 19:186-194.
26. Hammi C, Schroeder JD, Yeung B. Trigger Point Injection. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.
27. Verhagen T, Loos MJ, Mulders LG, Scheltinga MR, Roumen RM. A step up therapeutic regimen for chronic post-Pfannenstiel pain syndrome. *Eur J Obstet Gynecol Reprod Biol* 2018;

231:248-254.

28. de Souza RC, de Sousa ET, Scudine KG et al. Low-level laser therapy and anesthetic infiltration for orofacial pain in patients with fibromyalgia: A randomized clinical trial. *Med Oral Patol Oral Cir Bucal* 2018; 23:e65-e71.
29. Chen SM, Chen JT, Kuan TS, Hong CZ. Myofascial trigger points in intercostal muscles secondary to herpes zoster infection of the intercostal nerve. *Arch Phys Med Rehabil* 1998; 79:336-338.
30. Jia Y, Zhao C, Ren H, Wang T, Luo F. Pre-emptive scalp infiltration with dexamethasone plus ropivacaine for postoperative pain after craniotomy: A protocol for a prospective, randomized controlled trial. *J Pain Res* 2019; 12:1709-1719.
31. Wijayasinghe N, Ringsted TK, Bischoff JM, Kehlet H, Werner MU. The role of peripheral afferents in persistent inguinal postherniorrhaphy pain: A randomized, double-blind, placebo-controlled, crossover trial of ultrasound-guided tender point blockade. *Br J Anaesth* 2016; 116:829-837.
32. Zheng S, Li X, Yang X, He L, Xue Y, Yang Z. Ultrasound-guided cervical nerve root block for the treatment of acute cervical herpes zoster: A randomized controlled clinical study. *Pain Practice* 2019; 19:500-509.
33. Yang F, Liao P, You Y, Liang Y, Hu Y. The effectiveness of repetitive paravertebral block with ropivacaine and dexmedetomidine for the prevention of postherpetic neuralgia in patients with acute herpes zoster. *Postepy Dermatol Alergol* 2022; 39:116-120.
34. van Wijck AJ, Opstelten W, Moons KG, et al. The PINE study of epidural steroids and local anaesthetics to prevent postherpetic neuralgia: A randomised controlled trial. *Lancet* 2006; 367:219-224.
35. Weiner DK, Schmader KE. Postherpetic pain: more than sensory neuralgia? *Pain Med* 2006; 7:243-250.
36. Haanpää M, Laippala P, Nurmikko T. Pain and somatosensory dysfunction in acute herpes zoster. *Clin J Pain* 1999; 15:78-84.
37. Dworkin RH, Gnann JW Jr, Oaklander AL, Raja SN, Schmader KE, Whitley RJ. Diagnosis and assessment of pain associated with herpes zoster and postherpetic neuralgia. *J Pain* 2008; 9:S37-S44.
38. Beydoun N, Brunner P, De La Torre Y, et al. Effectiveness of CT-guided epidural infiltration of steroids and local anesthetics for acute and chronic herpes zoster neuralgia. *Diagn Interv Imaging* 2021; 102:525-530.
39. Ji G, Niu J, Shi Y, Hou L, Lu Y, Xiong L. The effectiveness of repetitive paravertebral injections with local anesthetics and steroids for the prevention of postherpetic neuralgia in patients with acute herpes zoster. *Anesth Analg* 2009; 109:1651-1655.
40. Makharita MY, Amr YM. The effect of repeated paravertebral injections with local anesthetics and steroids on prevention of post-herpetic neuralgia. *Pain Physician* 2020; 23:565-572.
41. Xu P, Yu Q, Huang H, Zhang W, Li W. A self-controlled study of intralesional injection of diprospan combined with topical timolol cream for treatment of thick superficial infantile hemangiomas. *Dermatol Ther* 2018; 31:e12595.
42. Yuan SM, Zhang M, Guo Y, Cui L, Hong ZJ, Jiang HQ. Intralesional injection of diprospan is effective for infantile hemangioma. *J Craniofac Surg* 2015; 26:422-424.
43. Liu CT, Yang TF. Intra-substance steroid injection for full-thickness supraspinatus tendon rupture. *BMC Musculoskelet Disord* 2019; 20:569.
44. Xie W, Liu X, Xuan H, et al. Effect of betamethasone on neuropathic pain and cerebral expression of NF-kappaB and cytokines. *Neurosci Lett* 2006; 393:255-259.
45. Hwang B, Lee J, Park BJ. Neurological complication rates of epidural injections and selective nerve blocks: A comparison of steroid use patterns. *Clin J Pain* 2020; 36:449-457.
46. Emanuel EJ. Reform of clinical research regulations, finally. *N Engl J Med* 2015; 373:2296-2299.
47. Lee JW, Lee E, Lee GY, Kang Y, Ahn JM, Kang HS. Epidural steroid injection-related events requiring hospitalisation or emergency room visits among 52,935 procedures performed at a single centre. *Eur Radiol* 2018; 28:418-427.