

Effect of 2% lidocaine continuous epidural infusion for thoracic or lumbar herpes-zoster-related pain

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Abstract

Few treatments are effective to manage herpes-zoster (HZ)-related pain. This retrospective study focused on the efficacy of 2% lidocaine continuous epidural infusion on pain control and quality of life in patients with thoracic or lumbar HZ.

A total of 256 patients with thoracic or lumbar HZ were reviewed for this study. Patients included in the study were divided into continuous epidural infusion (70 mL 2% lidocaine + 180 mL 0.9% normal saline) and medical therapy group (group1) and only medical therapy group (group2). European Organization for Research and Treatment of Cancer and Izbicki pain score were used to evaluate the pain control and quality of life before therapy, and 6 and 9 months after therapy.

For 256 patients with HZ (thoracic HZ = 162, lumbar HZ = 94), 53.1% was women. Mean \pm standard deviation age was 69.4 ± 9.5 (range, 38–85) years. Significant differences between the 2 groups in terms of quality of life and pain control were detected after 6 and 9 months follow-up ($P < .001$). For patients with HZ at 1 to 3 months after rash onset, the pain score was significantly lower in group 1 ($P < .001$). Sixteen patients with postherpetic neuralgia (PHN) underwent continuous epidural infusion therapy. Only 4 patients achieved satisfactory pain relief. Seven patients required analgesic drugs, and 6 patients still were unable to work, 10/16 (62.5%) patients had readmission. In addition, the pain score was higher in patients with HZ with diabetes ($P < .001$). Epidural infection occurred in 6 patients (8.8%), catheter dislodgement in 4 patients (5.8%), and catheter leakage in 3 patients (4.4%). There was no spinal epidural abscesses occurred.

2% lidocaine continuous epidural infusion therapy can lead to sustained pain relief and improve the quality of life in patients with thoracic or lumbar HZ at 1 to 3 months after rash onset. Epidural lidocaine is avoided for the treatment PHN, and the level of glucose might be associated with zoster-related pain.

Abbreviations: CF = cognitive function, EF = emotional function, EORTC = European Organization for Research and Treatment of Cancer, HZ = herpes zoster, PF = physical function, PHN = postherpetic neuralgia, QL = global health score, QLQ = quality of life questionnaire, RF = role function, SF = social function, VAS = visual analog scale.

Keywords: continuous epidural infusion, diabetes, herpes-zoster-related pain, lidocaine

1. Introduction

Herpes zoster (HZ) is caused by reactivation of varicella zoster virus that remains latent in the sensory ganglia.^[1] It is characterized by dermatomal pain and vesicular rash with burning, itching, or aching. Generally, HZ is involved in a single sensory nerve (usually cranial or spinal nerve).^[2] HZ-associated pain has serious health risks for adults, particularly after the age of 50 years. With increasing age, the incidence of HZ rises.

Studies reported that about 20% to 30% individuals developed opportunistic infection of HZ during their lifetime.^[3,4]

Postherpetic neuralgia (PHN), one of the most commonly serious complications of HZ, is defined as pain persisting ≥ 3 months after rash onset. The major clinical manifestations of PHN is spontaneous pain characterized by constant burning or stabbing sensation with allodynia. The pain can last for months or even multiple years. Based on the previously available data, half of persons with HZ aged ≥ 60 years developed PHN.^[5] Studies confirmed that older age, ophthalmic involvement, prodromal pain, greater severity of pain were risk factors for PHN.^[6,7]

Unlike other clinical symptoms of HZ and PHN, continuous or intermittent pain can profoundly affect the quality of life and the ability to work. This unpleasant sensory can also lead to stress, anxiety, emptiness, even depression. Moreover, severe acute pain is considered as a risk factor for PHN.^[6] Therefore, pain control is the primary evaluation of therapeutic options in the course of HZ treatment. Currently, acute HZ is usually treated with medical treatments such as antiviral drugs, analgesia. Most patients with these agents had rash healing and pain relief, even pain loss in the acute phase of HZ (≥ 30 days after rash onset). Disappointingly, a few patients with systemic therapy still present persistent pain after 30 days. Notably, antiviral drugs have no effect on pain control despite of chronic pain not persisting for ≥ 3 months. At this phase, medical therapy such as anticonvulsants

Editor: Sergio Gonzalez Bombardiere.

The study was conducted in accordance with the principles of the Declaration of Helsinki and the guidelines of Wuhan First Hospital.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2018) 97:32(e11864)

Received: 12 March 2018 / Accepted: 23 July 2018

<http://dx.doi.org/10.1097/MD.00000000000011864>

(gabapentin or pregabalin), topical lidocaine, and tricyclic antidepressants may relieve the pain, but these therapeutic effects seem to be limited. According to our experience, this group of patients tends to be more easily developing PHN if achieving unsatisfied pain relief despite of no available data reported previously. Hence, we focused on a therapy that 2% lidocaine continuous epidural infusion to reduce zoster-related pain. This study aimed to evaluate pain control and the quality of life in patients with HZ (pain persisting at 1–3 months) and PHN undergoing 2% lidocaine continuous epidural infusion therapy.

2. Methods

2.1. Patient selection

This was a retrospective study conducted between September 2015 and September 2017 in the Department of Pain Management of Wuhan First Hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki and the guidelines of Wuhan First Hospital. Three hundred eighty patients with HZ were reviewed for this study.

Inclusion criteria were: chronic pain persisting for ≥ 30 days after rash onset, and pain score at least 4 on the visual analog scale (VAS). Exclusion criteria were: age under 18 or over 85 years, refusal or irregular drug treatment, incomplete data due to patients treating in other medical centers, the failure of continuous epidural infusion therapy for pain control in the first time.

2.2. Measurements

The HZ is diagnosed by a typical rash in the dermatomal distribution of a segmental nerve.^[8] The disease is usually difficult to diagnose in the prodromal period. Antiviral therapy was used as the first line in the treatment of HZ in the acute zoster phase. Most patients could benefit from antiviral therapy and other drug therapy (gabapentin was commonly used in dosages of 1800 mg daily, pregabalin in dosages of 150 mg daily, amitriptyline in dosages of 25 mg daily, oxycodone in dosages of 30 mg daily, and tramadol in dosages of 300 mg daily). But still a few patients who developed severe pain required analgesics. Clinically, we found that once chronic pain persisted for ≥ 30 days after rash onset, the therapy of HZ was extremely difficult.

The procedure of continuous epidural infusion therapy is described as follows. Under the guidance of X-rays, puncture point was selected at thoracic or lumbar nerve root in accordance with the dermatomal distribution of a segmental nerve, and puncture needle was inserted into the epidural space. After the success of puncture, catheter was placed closely to thoracic or lumbar nerve root. Meanwhile, the contrast medium was injected into the epidural space to ensure catheter arriving at the destination point. Then 5 mL of mixture liquid (2% lidocaine + betamethasone + 0.9% normal saline) was injected to the thoracic or lumbar nerve root. Finally, catheter was connected with analgesic pump with 250 mL another mixture liquid (70 mL 2% lidocaine + 180 mL 0.9% normal saline) for continuous pump at infusion of 3 mL/h. The continuous infusion was continued for 1 week.

According to different treatments, all the selected patients were classified into 2 groups: group 1 (medical therapy + epidural infusion group), group 2 (medical therapy). Medical therapy included gabapentin, pregabalin, amitriptyline, tramadol, and oxycodone. If the drugs were ineffective to the intractable pain, patients were treated with continuous epidural infusion therapy.

2.3. Questionnaire

The European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ) and the Izbicki pain score system were used to subjectively assess health-related quality of life and pain intensity.^[9,10] The EORTC questionnaire contains 30 items including functional scale, symptom scale, emotional and social scale, financial strain scale, and a global quality of life scale.^[9] The Izbicki pain score was related to 2 subjective items (a VAS, frequency of pain attacks) and 2 objective items (analgesic medication use and disease-related inability to work). Both the EORTC questionnaire and the Izbicki pain score had previously been identified with high standards of reliability and validity. In this study, all patients were assessed before therapy (baseline) at intervals of 6 and 9 months after therapy.

2.4. Statistics

Statistical analyses were performed using SPSS software (version 22.0 SPSS). Chi-squared test or Fischer exact test was used to analyze categorical variables. Descriptive data were presented as mean \pm standard deviation. Pain scores and quality of life scores were assessed using Mann–Whitney *U* test. Graphical representations were performed with Microsoft Excel (Redmond, WA) or GraphPad Prism software (La Jolla, CA). A value of $P < .05$ was considered statistically significant.

3. Results

3.1. Demographics and disease-related data

Between September 2015 and September 2017, a total of 380 patients were diagnosed HZ, of which 256 patients (162 [63.3%] thoracic HZ, 94 [36.7%] lumbar) were enrolled in the study (Fig. 1). About 124 patients were excluded from the study (108 due to the HZ ≥ 30 days rash onset, 15 due to other therapies, 1 patient died during the study due to septic shock following urinary infection with severe pulmonary infection). Of the enrolled patients, 69 patients treated by medical therapy and continuous epidural infusion therapy, and 187 patients treated by simple medical therapy. Loss to follow-up was 5 patients at 6 months and 13 patients at 9 months. Figure 2 showed the duration of time between onset of HZ and therapy in our center. We found that 195/256 (76.2%) patients were treated in 1 to 3 months. And data about the duration of time in 2 groups had no difference.

Baseline characteristics of the HZ in 2 groups (120 men, 136 women; mean age 69.4 years, range 38–85) are summarized in Table 1. Of the enrolled patients, 67 (26.2%) patients with HZ present with diabetes. Most of the patients presented ≥ 1 chronic condition (98 cardiovascular diseases, 48 pulmonary diseases, 11 cancers, 1 HIV, 21 others). There were 195 (76.2%) patients treated at the phase of 1 to 3 months after rash onset. Sixty-one (23.8%) patients were diagnosed PHN, of which 16 (6.3%) patients suffered from chronic pain persisting for > 6 months (Fig. 2). There were no significant difference between the 2 groups ($P > .05$) (Table 1).

3.2. Quality of life assessment

All the patients with HZ had high levels of symptom scales and low levels of functional scales. No significant difference was detected between the 2 groups in quality of life at baseline

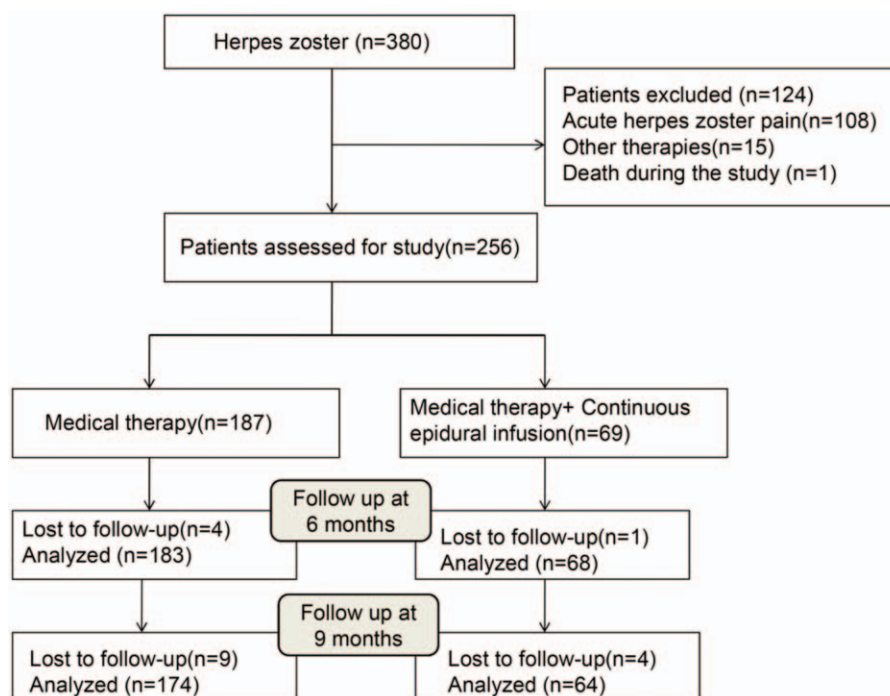


Figure 1. Study enrollment.

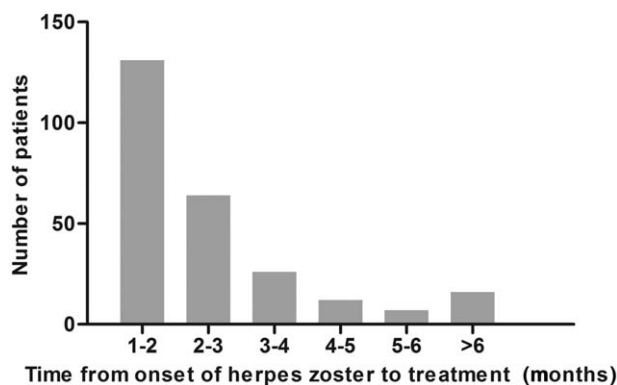


Figure 2. Duration of time between onset of herpes zoster and therapy in our center 195/256 (76.2%) patients were treated in 1 to 3 months. And data about the duration of time in 2 groups had no difference.

Table 1

Clinical characteristic of patients with herpes zoster in 2 groups.

Variable	Group 1 (n=69)	Group 2 (n=187)	P
Age, mean ± SD, range	68.2 ± 19.4 (45–85)	70.6 ± 23.6 (38–72)	.215
Men/women	37/32	83/104	.189
Smoking, n (%)	32 (46.4%)	66 (35.3%)	.106
Alcohol intakes, n (%)	24 (34.8%)	55 (29.4%)	.409
Primary dermatome affected			.248
Thoracic, n (%)	40 (58.0%)	122 (65.2%)	
Lumbar, n (%)	29 (42.0%)	65 (34.8%)	
Duration of prodromal pain			.729
≤3d, n (%)	10 (14.5%)	24 (12.8%)	
>3d, n (%)	59 (85.5%)	163 (87.2%)	
Description of rash			.151
Limited rash	12 (17.4%)	20 (10.7%)	
Extensive rash	57 (82.6%)	167 (89.3%)	

SD = standard deviation.

($P > .05$) (Fig. 3). After the 6-month follow-up, there were 68 patients in group 1 and 183 patients in group 2 (Table 2). The 2 groups demonstrated an equal distribution of age, gender, the history of smoking, and alcohol intakes. For the health-related quality of life, social function (SF, 60.17 ± 26.39 vs 51.34 ± 19.15), physical function (PF, 64.29 ± 18.32 vs 39.37 ± 21.35), role function (RF, 56.70 ± 21.34 vs 45.37 ± 27.85), emotional function (EF, 60.43 ± 25.47 vs 37.13 ± 11.32), cognitive function (CF, 58.12 ± 27.25 vs 40.53 ± 16.73), and global health score (QL, 61.42 ± 19.14 vs 51.64 ± 23.37) were significantly higher in group 1. In contrast, scores on the symptom scales showed lower in group 1. Fatigue symptom (37.09 ± 11.54 vs 62.41 ± 22.57), pain symptom (57.82 ± 26.58 vs 70.42 ± 31.52), insomnia symptom (60.37 ± 16.19 vs 78.63 ± 35.72), and appetite loss symptom (57.32 ± 29.64 vs 71.43 ± 26.72) were improved in group 1 patients ($P < .001$). However, pruritus symptom and

financial burden shown no statistically significant differences between the groups ($P = .627$, $P = .517$, respectively).

After 9 months follow-up, 238 patients were included in this trial (group 1, $n = 64$; group 2, $n = 174$). Similarly, scores on the functional scales revealed a statistically significant higher in group 1. As for the symptom scales after 9 months follow-up, no significant differences could be obtained for pruritus symptom and financial burden between the 2 groups.

3.3. Pain assessment

At baseline, mean pain score was found to be 58.92 ± 6.56 in group 1 and 59.64 ± 6.17 (range 0–96) in group 2 ($P = .625$) (Fig. 4). Overall, there was a significant reduction in Izbicki pain score at 6 and 9 months follow-up. At 6 months follow-up, pain scores were obviously lower in those treated with medical therapy and epidural

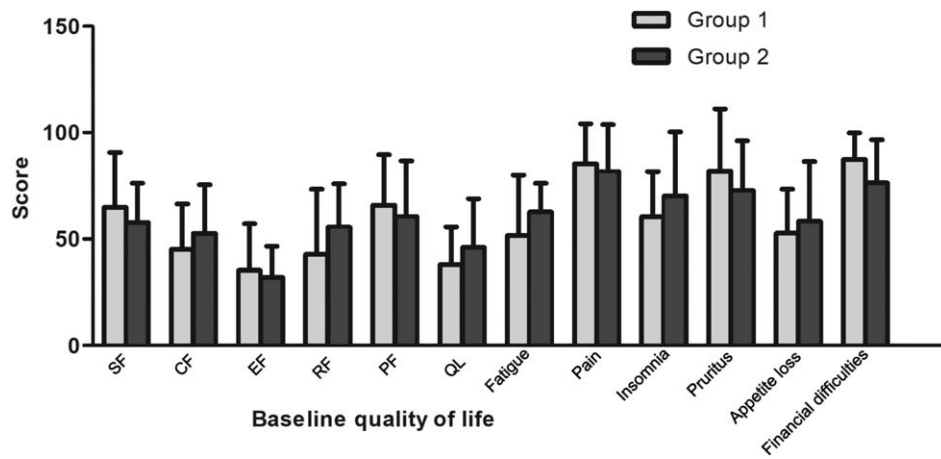


Figure 3. Baseline quality of life for the 2 groups (group 1, n=69; group 2, n=187) in patients with HZ ($P > .05$). CF=cognitive function, EF=emotional function, PF=physical function, QL=global health score, RF=role function, SF=social function.

Table 2
Health-related quality of life outcomes at 6 and 9 months after therapy.

	Follow-up at 6 months		P^*	Follow-up at 9 months		P^*
	Group 1 (n=68)	Group 2 (n=183)		Group 1 (n=64)	Group 2 (n=174)	
Age	67.3 ± 10.06	71.8 ± 9.03	.072	67.5 ± 9.46	70.4 ± 9.30	.051
Men	37 (54.4%)	83 (45.4%)	.202	34 (53.1%)	81 (46.6%)	.368
Smoking	28 (41.2%)	67 (36.6%)	.508	26 (40.6%)	65 (37.4%)	.645
Alcohol intakes	26 (38.2%)	50 (27.3%)	.094	25 (39.1%)	48 (27.6%)	.089
Functional scales						
SF	60.17 ± 26.39	51.34 ± 19.15	<.001	70.53 ± 22.72	59.43 ± 16.26	<.001
CF	58.12 ± 27.25	40.53 ± 16.73	<.001	63.47 ± 29.72	45.62 ± 20.12	<.001
EF	60.43 ± 25.47	37.13 ± 11.32	.003	53.49 ± 22.41	42.56 ± 13.29	<.001
RF	56.70 ± 21.34	45.37 ± 27.85	<.001	60.35 ± 26.22	47.26 ± 17.21	<.001
PF	64.29 ± 18.32	39.37 ± 21.35	<.001	71.38 ± 19.68	49.17 ± 11.58	.032
QL	61.42 ± 19.14	51.64 ± 23.37	<.001	72.42 ± 25.36	59.07 ± 19.76	<.001
Symptom scales						
Fatigue	37.09 ± 11.54	62.41 ± 22.57	<.001	31.62 ± 18.55	59.16 ± 25.63	<.001
Pain	57.82 ± 26.58	70.42 ± 31.52	<.001	41.36 ± 16.28	62.18 ± 29.33	<.001
Insomnia	60.37 ± 16.19	78.63 ± 35.72	<.001	34.53 ± 12.85	61.59 ± 28.62	<.001
Pruritus	65.72 ± 18.46	70.17 ± 24.32	.627	59.37 ± 21.51	66.39 ± 23.95	.437
Appetite loss	57.32 ± 29.64	71.43 ± 26.72	<.001	43.15 ± 28.47	53.82 ± 30.14	<.001
Financial difficulties	68.25 ± 18.82	75.32 ± 29.07	.517	61.59 ± 17.85	64.73 ± 24.62	.726

Scores range from 0 to 100. A higher score for functional scale or health status represents a higher level of functioning or health status, and a higher score in the symptom scale represents more severe symptoms. Values are expressed as mean ± standard deviation.

CF=cognitive function, EF=emotional function, PF=physical function, QL=global health score, RF=role function, SF=social function.

*Mann-Whitney U test.

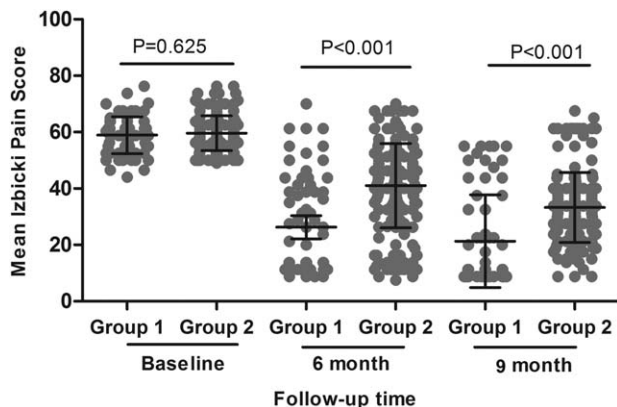


Figure 4. Izbicki pain scores at baseline, and 6 and 9 months after therapy.

infusion group than those only treated with medical therapy (26.27 ± 16.98 vs 41.03 ± 14.96 , $P < .001$). Good results in treatment of thoracic or lumbar patients with HZ with drugs and continuous epidural infusion therapy at 9 months follow-up (21.31 ± 16.45 vs 33.29 ± 12.41 , $P < .001$). For the 4 components of Izbicki pain score, no significant differences could be obtained in VAS, frequency of pain attacks, analgesic medication use, and inability to work between the 2 groups at baseline. However, the scores or the rate of patients with analgesic drugs was significantly reduced at any time point of follow-up ($P < .001$) (Fig. 5).

We also assessed the pain condition for thoracic or lumbar HZ at 1 to 3 months after rash onset (group 1, n=48; group2, n=129). At the end of follow-up, the pain score was significantly lower among patients treated with medical therapy and epidural infusion group ($P < .001$) (Table 3).

Notably, diabetes was found in 67 (26.2%) patients. Of the 67 patients, 12 required diet control, 17 required oral drugs, and 49

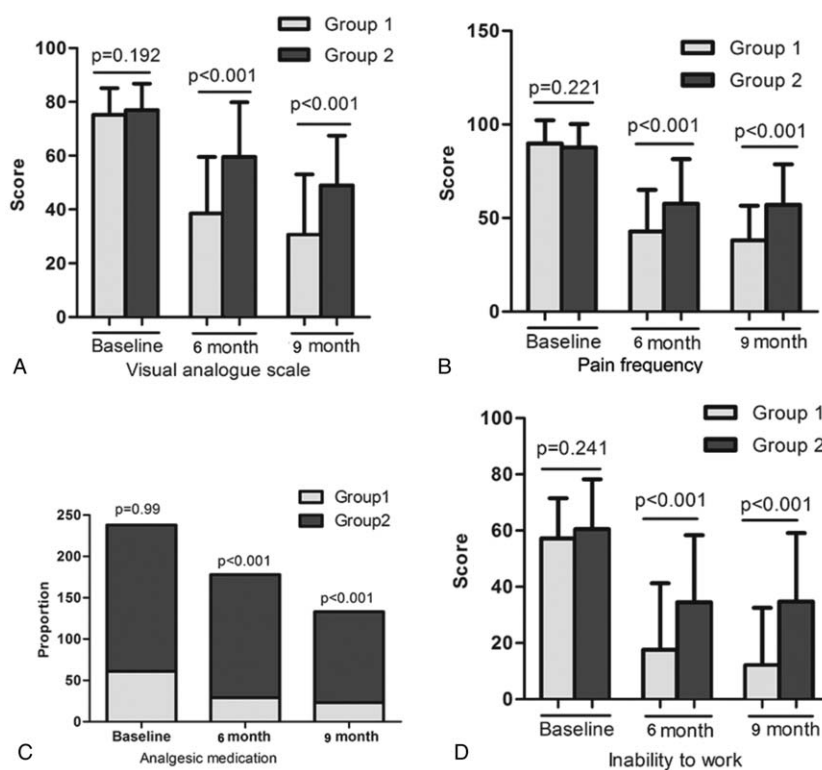


Figure 5. Follow-up results of the pain score at baseline, and 6 and 9 months after therapy. (A) Visual analog score. (B) Frequency of pain attacks. (C) Analgesic medication use. (D) Inability to work.

Table 3
Follow-up (9 months) results for the pain score in herpes zoster patients at 1 to 3 months after rash onset.

	Group 1 (n = 48)	Group 2 (n = 129)	P*
Pain VAS	38.69 ± 19.82	59.45 ± 29.06	<.001
Frequency of pain attacks	51.33 ± 28.46	63.28 ± 31.73	<.001
Pain medication	9.53 ± 11.53	18.41 ± 17.57	<.001
Inability to work	40.37 ± 15.71	60.49 ± 18.52	<.001

VAS = visual analog scale.
* Mann-Whitney U test.

required insulin therapy. During 9 months follow-up, 12 patients were found de novo diabetes. Table 4 shows the results for the pain score in HZ patients with diabetes. Scores for pain VAS, frequency of pain attacks, pain medication, and inability to work were significantly higher in thoracic or lumbar HZ patients with diabetes ($P < .001$).

Table 4
Follow-up (9 months) results for the pain score in herpes zoster patients with diabetes.

	Diabetes (n = 79)	Normal (n = 159)	P*
Pain VAS	67.35 ± 16.52	45.26 ± 21.15	<.001
Frequency of pain attacks	58.62 ± 19.27	49.32 ± 20.72	<.001
Pain medication	13.42 ± 18.63	8.37 ± 11.29	<.001
Inability to work	59.56 ± 18.32	38.26 ± 13.67	<.001

VAS = visual analog scale.
* Mann-Whitney U test.

In addition, 16 patients with PHN underwent continuous epidural infusion therapy (6 men and 10 women). For the patients with PHN, gabapentin was used in dosages of 1800 mg daily, amitriptyline in dosages of 25 mg daily, and oxycodone in dosages of 30 mg daily. All the patients did not respond to medical therapy. Even if the patients with PHN treated medical therapy, the VAS score varied from 6 to 9. Of the 16 patients, only 4 patients achieved satisfactory pain relief. Seven patients required analgesic drugs, and 6 patients still were unable to work (Fig. 6).

4. Discussion

This is the first largest retrospective study to evaluate the effect of 2% lidocaine continuous epidural infusion therapy for thoracic or lumbar HZ. This study found that combination of continuous epidural infusion and medical therapy was superior to only medical therapy in the treatment of thoracic or lumbar HZ at 1 to 3 months after rash onset. The results showed significant improvements in scores of EORTC QLQ-C30 and pain scales in patients with continuous epidural infusion therapy. However, we also found that both PHN and diabetes patients with continuous epidural infusion therapy failed to achieve sustained complete pain relief.

It is well-known that zoster-related pain is the most common disabling symptom of HZ and PHN. Although over 70% patients with HZ had satisfactory pain relief with antiviral drugs, a few have no effect on this therapy.^[11] For this group of patients, general consensus shows that opiates anti-epileptics, tricyclic antidepressants, and capsaicin may be effective to relieve pain symptoms.^[11,12] Moreover, acute zoster pain could develop to

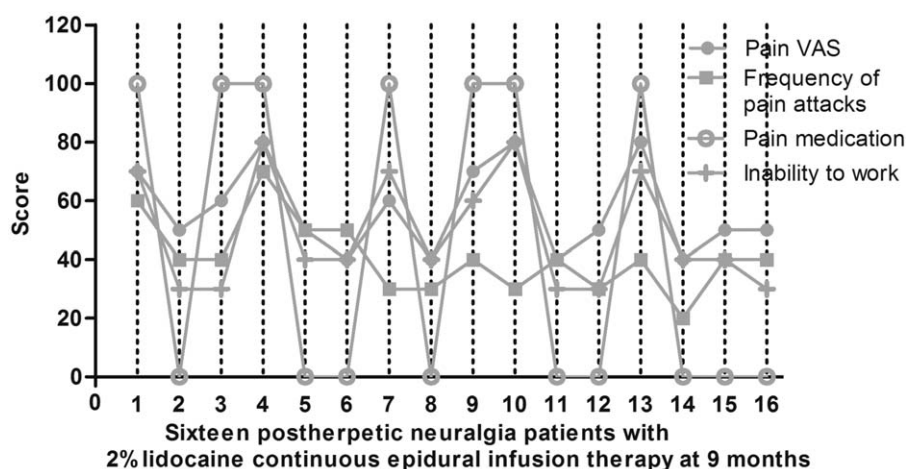


Figure 6. Results of the pain score for 16 postherpetic neuralgia patients with continuous epidural infusion therapy (pain medication: 0=no analgesic, 100=analgesic). VAS = visual analog scale.

chronic pain.^[13] According to our experience, once the patients at this phase (usually at 1–3 months after rash onset) failed to achieve complete pain relief, PHN was easily to occur. Therefore, pain control for patients with HZ at 1 to 3 months after rash onset is crucial.

Besides the medical therapy, continuous epidural infusion therapy is another treatment options existing for treatment of patients with HZ at 1 to 3 months, which can significantly improve the scores of global health status/quality of life and pain scales. One previous study has been published that continuous thoracic epidural administration successfully treated zoster-associated pain after 2 months follow-up in 2 cases.^[14] Recently, Makharita and colleagues published the results of a randomly controlled trial that compared paravertebral block using bupivacaine plus dexamethasone and paravertebral block using saline as placebo.^[15] After 3 weeks follow-up, the active group (bupivacaine plus dexamethasone) achieved significant pain relief. They showed that shorter duration of pain, herpetic eruption, and lower doses of pregabalin and acetaminophen were found in the active group. More importantly, the incidence of PHN was lower than placebo group. In our study, we found that there was a significant reduction in pain score when compared with baseline. Both at 6 and 9 months posttherapy, analgesic medication was lower to consume in continuous epidural infusion group ($P < .001$).

In addition, we were the first study which focused on the evaluation of pain control for patients with HZ at 1 to 3 months after rash onset. Most previous studies paid close attention to acute HZ or PHN. Knowledge is limited concerning the treatment of patients with HZ at 1 to 3 months after rash onset. Results of our study showed that effective pain relief was obtained for the patients with HZ with continuous epidural infusion at 1 to 3 months after rash onset ($P < .001$). Disappointingly, continuous epidural infusion therapy might be not proper for patients with PHN. In our study, 16 patients with PHN underwent this therapy. Only 4 patients achieved satisfactory pain relief. About 10/16 (62.5%) patients had readmission to our department. But the continuous epidural infusion therapy was ineffective for readmission.

Similarly, the combination of continuous epidural infusion and drugs therapy was superior to single medical therapy in terms of quality of life. Epidural lidocaine can be effective for pain relief and improve quality of life. We found that epidural lidocaine

could reduce scores on the symptom scales except for pruritus symptom. Zoster-related pain and itch can be considered as a significant negative impact on functional status and patient quality of life.^[16] However, Elkersh and colleagues published the results of a case report that high thoracic epidural infusion of bupivacaine and clonidine was beneficial in relieving neuropathic itch in acute patient with HZ.^[17] Unfortunately, we had opposite conclusion. A possible explanation is that we used lidocaine and normal saline, not bupivacaine and clonidine for continuous epidural infusion. And previous studies lacked large sample concerning zoster-related itch research.

The correlation between HZ and diabetes is unclear. In the study, we found patients with HZ with diabetes had poor pain control. Herpetic eruption pain was associated with unsatisfactory blood glucose control. Exactly why high blood glucose could lead to poor pain control needs further research.

As for the complications, spinal epidural abscesses, catheter dislodgement, infection, and leakage are detected to be related to continuous epidural infusion. Holt and colleagues reported that the incidence of infection was 4.3% in long duration patients with epidural catheter therapy.^[18] Spinal epidural abscess was found in patients with diabetes mellitus.^[19] In fact, epidural infection occurred in 6 patients (8.8%), catheter dislodgement in 4 patients (5.8%), and catheter leakage in 3 patients (4.4%). Two patients had catheter shedding, and required reoperation. There was no epidural catheter-related complication in patients with HZ with diabetes mellitus.

Like other retrospective studies, there were several limitations. First, EORTC QLQ-C30 and Izbecki pain score are subjective measurements of quality of life and pain control, which have recall, selection, coding, and response bias. Second, we did not discuss the mechanisms of continuous epidural analgesia for treatment of HZ, since the mechanisms were quite elusive and complex. And we were lack of valid measure to monitor the signs of nerve block. Third, accurately estimating the effect of pain and quality of life on outcomes was quite difficult due to a lack of multivariate measure.

5. Conclusion

In conclusion, 2% lidocaine continuous epidural infusion therapy can lead to sustained pain relief and improve the quality

of life in patients with for thoracic or lumbar HZ at 1 to 3 months after rash onset. For patients with PHN, epidural lidocaine therapy was not recommended. In addition, patients with HZ with diabetes were difficult to relieve pain. Controlling the level of glucose rationally might help to control pain.

Author contributions

Data curation: Shaojun Li.

Formal analysis: Shaojun Li.

Investigation: Shaojun Li, Dan Feng.

Methodology: Shaojun Li, Dan Feng.

Software: Shaojun Li, Dan Feng.

Writing – original draft: Shaojun Li.

Writing – review & editing: Dan Feng.

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