Effectiveness of continuous epidural analgesia on acute herpes zoster and postherpetic neuralgia

A retrospective study

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Abstract

Despite early treatment of herpes zoster (HZ), postherpetic neuralgia (PHN) can persist. This study was designed to compare the therapeutic and pain relief effects of continuous epidural analgesia (CEA) on the chronic phase as well as the acute phase of HZ with standard medical treatment.

Medical records of 227 patients with moderate to severe zoster-associated pain that had not responded to standard medications were retrospectively reviewed. Patients received standard treatment alone (medical group) or standard treatment plus concurrent CEA (epidural group). The acute and chronic groups were classified according to a 4-week cut-off with regard to time between the onset of the rash and the first treatment. Four groups were studied: Group A (acute/medical group); Group B (acute/epidural group); Group C (chronic/medical group); and Group D (chronic/epidural group). Pain was assessed using the visual analog scale (VAS) and measured every 2 weeks for 6 months. We compared the pain rating at 6 months after the first treatment with the initial pain rating. Response to treatment was defined as a ≥50% reduction in pain severity since the initial visit. Remission was considered complete for patients whose VAS pain score was ≤2 for >3 successive visits and who no longer needed medical support.

Patients who received a combination of standard treatment plus CEA (Groups B and D) had significantly higher response to treatment ($P = .001$) than patients receiving standard treatment alone (Groups A and C). The adjusted odds ratio (OR) for response to treatment in the epidural group versus the medical group was 5.17 (95% confidence interval [CI]: 1.75–15.23) in the acute group and 5.37 (95% CI: 1.62–17.79) in the chronic groups. The adjusted OR for complete remission in the epidural group versus the medical group was 3.05 (95% CI: 1.20–7.73) in the acute group and 4.46 (95% CI: 1.20–16.54) in the chronic group.

CEA can effectively relieve pain caused by PHN and acute HZ and increase remission rates. Combining CEA with standard medical treatment may offer a clinical advantage in the management of pain caused by PHN as well as acute HZ.

Abbreviations: CEA = continuous epidural analgesia, CI = confidence interval, HZ = Herpes zoster, OR = odds ratio, PHN = postherpetic neuralgia, VAS = visual analog scale, VZV = varicella-zoster virus.

Keywords: continuous epidural analgesia, epidural injection, herpes zoster, local anesthetics, postherpetic neuralgia

1. Introduction

Herpes zoster (HZ) results from the reactivation of a dormant varicella-zoster virus (VZV) in a sensory ganglion and usually manifests as an acutely painful vesicular rash affecting a single dermatome.[1] HZ affects 20% to 30% of individuals during their lifetimes. Owing to the age-related decline in VZV-specific

cell-mediated immunity, approximately 50% of patients are aged ≥80 years.[2] Postherpetic neuralgia (PHN), the neuropathic pain from previous VZV infection, can persist for 1 to 12 months.[3] Bouhassira et al[4] indicated that zoster-associated pain can last for 6 months in 8.5% of patients and 12 months in 6% of patients, despite early treatment with antiviral drugs.

Although HZ is not fatal, it can cause severe zoster-associated pain including both acute HZ pain and chronic PHN. Zoster-associated pain results from viral damage and increased sensitization of affected segmental sensory neuron.[5] The reactivated virus destroys affected central and peripheral nerves and leads to inflammation, immune response, and varying degrees of neuronal loss within affected spinal ganglia.[6,7] Severe zoster-associated pain often limits a patient's activities of daily living and may significantly lower functional status and quality of life.[8–10] Thus, effective treatment of zoster-associated pain is highly necessary.

There is currently no cure for zoster-associated pain and treatment is based on symptom control.[11] As zoster-associated pain may persist for a lifetime, symptom-control medications, including lidocaine patches, capsaicin cream, gabapentin, morphine, or tramadol, are often required for prolonged periods. However, long-term use of medication can burden patients and cause unintended systemic effects. Although vaccination, antiviral therapy, administration of low-dose amitriptyline, and other

treatments have been used, they do not effectively prevented PHN.[12] Therefore, more specific treatments are required to manage zoster-associated pain.

Various attempts such as sympathetic nerve blocks, epidural blocks, and spinal cord stimulation have been made to reduce zoster-associated pain.[13,14] Many researchers have focused on epidural analgesia with the administration of local anesthetics, with or without steroids, to achieve zoster-associated pain relief and prevent PHN.[15] As HZ invades with local inflammation of the dorsal root ganglion, epidural analgesia may be considered better than systemic medical treatment because it can be localized to the affected dermatome. However, previous studies were limited to patients in the acute phase of HZ and only a single dose of analgesic was injected. Additional studies are required to establish the effectiveness of epidural analgesia on PHN as well as acute HZ. This study was designed to compare the therapeutic and pain relief effects of continuous epidural analgesia (CEA) on the chronic phase as well as the acute phase of HZ with standard medical treatment.

2. Methods

2.1. Study subjects

Medical records of 332 patients with zoster-associated pain who received medical treatment and/or CEA at the pain clinic of the Korea University Guro Hospital between June 1, 2008 and June 30, 2015 were retrospectively reviewed. The acute and chronic zoster-associated pain was classified according to a 4-week cutoff with regard to time between the onset of the rash and the first treatment (acute ≤4 weeks, chronic >4 weeks).

The patients visited the pain clinic for treatment of zoster-associated pain rated ≥4 on the visual analog scale (VAS). On the VAS, 0 cm represents "no pain" and 10 cm represents "the worst pain imaginable." Patients visited the pain clinic because their pain did not subside after standard medications, including oral nonsteroidal anti-inflammatory drugs and opioids. The following patients were excluded from the study: 8 patients with immunosuppression; 73 patients with persistent zoster-associated pain for 6 months after the onset of the rash; 16 patients with a VAS pain score <4; and 8 patients with incomplete medical records. The medical records of a total of 227 patients were reviewed. Figure 1 shows the flow chart of the subjects in the study.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Korea University Guro Hospital's Institutional Review Board (approval number: MD15052). Written informed consent was obtained from all subjects.

2.2. Protocol

Data retrieved from the medical records included age, sex, time to treatment (time between rash onset and first treatment), initial pain rating (pain rating at first visit), and the pain rating for each follow-up visit. Follow-up visits occurred every 2 weeks for 6 months. Patients reported the severity of their pain by rating it on the VAS.

There were 2 treatment categories: standard treatment only (oral administration of 800 mg acyclovir once daily for 7 days if the rash had been present for less than 72 hours, and analgesics as required) and standard treatment plus concurrent CEA. Groups were classified by duration of HZ and treatment type: Group A (acute/medical group), patients with acute HZ who received only the standard treatment for HZ; Group B (acute/epidural group),
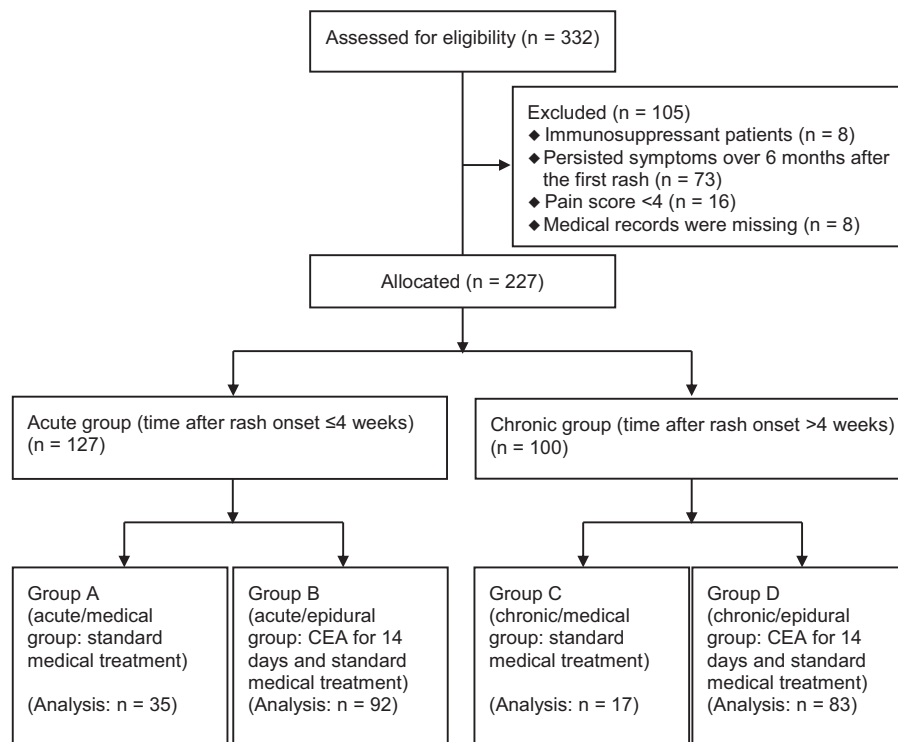
Figure 1. The flow chart of the subjects in the study. Note: CEA = continuous epidural analgesia.

patients with acute HZ who received the standard treatment for HZ plus CEA for 14 days; Group C (chronic/medical group), patients with chronic HZ who received only the standard treatment for HZ; and Group D (chronic/epidural group), patients with chronic HZ who received the standard treatment for HZ plus CEA for 14 days.

We compared the pain rating at 6 months after the first treatment with the initial pain rating. Response to treatment was defined as a ≥50% reduction in pain severity since the initial visit. Remission was considered complete for patients whose VAS pain score was ≤2 for >3 successive visits and who no longer needed medical support.

2.3. Procedures

Patients in groups B and D received CEA. Patients were asked to localize the rash and to use the VAS to quantify average pain felt in the last 24 hours. For CEA, the skin was prepped with 2% alcohol-chlorhexidine and draped in a sterile manner. For local anesthesia, 1% lidocaine was administered at the puncture site, and the epidural needle was inserted into the epidural space with the loss of resistance technique. The epidural catheter was inserted into the epidural space of the affected spinal nerve, and the catheter tip position was confirmed by C-arm images after injection of contrast media. After an initial bolus injection of ropivacaine (6 mL, 0.19%) and dexamethasone (1 mg), patients received a continuous epidural infusion of ropivacaine (275 mL, 0.095%) mixed with fentanyl (200 mcg) at a rate of 4 mL/h through a portable balloon infusion device (AutoFuser pump, ACE Medical Co., Ltd., Seoul, Korea). To minimize the risk of infection, the catheter was fixed with subcutaneous tunneling. Patients were monitored in the recovery room for 1 hour. Sensory loss in the relevant dermatome was detected 15 minutes after the bolus injection. The CEA was maintained for 14 days.

2.4. Statistical analysis

The Pearson χ^2 test, Fisher exact test, and Student t test were used to analyze patient characteristics. Logistic regression models were used to evaluate ≥50% reduction in the severity of zoster-associated pain and complete remission of zoster-associated pain. Adjusted odds ratios (ORs) were derived by logistic regression analysis with "pain reduction" or "complete remission" as the dependent variable; "group" as the independent variable; and "age, sex, time to treatment, and initial pain rating" as confounding variables. We considered the acute and chronic groups separately. We used power analysis to determine the number of subjects required to identify significant differences in pain reduction between groups. With 80% power and 2-tailed significance level set at .05 a minimum of 30 participants, 15 for each group, was required. We used sample size estimation for a 2-sample proportions test with the assumption that the proportion of control is .3 and the proportion of experiment is .8. We estimated power for a 2-sample proportions test, with a total sample size of 127 and an allocation ratio of 1:3. The estimated power was 83.3% for a pain reduction rate of 68.6% in Group A and a pain reduction rate of 91.3% in Group B. Moreover, the estimated power for a 2-sample proportions test with a total sample size of 100 was 86.8% with an allocation ratio of 1:5, Group C pain reduction rate of 41.2%, and Group D pain reduction rate of 79.5%. All statistical analyses were conducted using Stata/MP version 14.0 (StataCorp., College Station, TX). All statistical tests were 2-tailed and statistical significance was determined at P value <.05.

3. Results

3.1. General characteristics

Of the 227 patients, 127 were in the acute group and 100 were in the chronic group. Patient demographic and clinical characteristics are summarized in Table 1.

In the acute groups, 35 patients received standard treatment only (Group A) and 92 patients received standard treatment plus CEA (Group B). Compared with Group A, Group B had older patients (mean age: 60.3 ± 11.9 vs. 66.2 ± 11.1, P = .009) and a higher proportion of patients whose pain decreased by ≥50% (68.6% vs. 91.3%, P = .001). Between Groups A and B, there were no statistically significant differences in sex, time to treatment, initial pain rating, or proportion of patients who achieved complete remission.

Table 1
Characteristics of patients.

Characteristic	Acute group (n=127)			Chronic group (n=100)		
	Group A (n=35) mean±SD or number (%)	Group B (n=92) mean±SD or number (%)	P^*	Group C (n=17) mean±SD or number (%)	Group D (n=83) mean±SD or number (%)	P^*
Age, y	60.3±11.9	66.2±11.1	.009	59.8±12.5	65.5±11.9	.076
Sex			.247			.626
Men	12 (34.3)	42 (45.7)		7 (41.2)	29 (34.9)	
Women	23 (65.7)	50 (54.4)		10 (58.8)	54 (65.1)	
Time to treatment, wk	2.7±1.1	2.9±1.1	.222	13.4±5.8	11.5±5.9	.227
Initial pain rating (VAS†)	7.4±1.8	7.5±1.8	.815	5.9±1.9	7.1±1.9	.015
≥50% Decrease in pain‡	24 (68.6)	84 (91.3)	.001	7 (41.2)	66 (79.5)	.001
Complete remission§	20 (57.1)	67 (72.8)	.089	6 (35.3)	49 (59.0)	.073

SD = standard deviation, VAS = visual analog scale. Group A (acute/medical group): Patients with acute herpes zoster who received only the standard treatment for herpes zoster (oral administration of 800 mg acyclovir once daily for 7 days if the rash had been present for less than 72 hours, and analgesics as required). Group B (acute/epidural group): Patients with acute herpes zoster who received the standard treatment for herpes zoster plus continuous epidural analgesia for 14 days. Group C (chronic/medical group): Patients with chronic herpes zoster who received only the standard treatment for herpes zoster. Group D (chronic/epidural group): Patients with chronic herpes zoster who received the standard treatment for herpes zoster plus continuous epidural analgesia for 14 days.
* P value from a t test for continuous outcomes, or from a χ^2 test for normally distributed data or Fisher exact test for non-normally distributed data, comparing differences between any 2 study groups.
† Patients rated their pain by using the VAS, on which 0 is no pain and 10 is the worst pain imaginable.
‡ A rating ≥50% lower than the initial rating on the VAS was considered a ≥50% decrease in pain.
§ Complete remission was defined as pain being rated on the VAS ≤2 for 3 consecutive visits.

In the chronic group, 17 patients received standard treatment only (Group C) and 83 patients received standard treatment plus CEA (Group D). Compared with Group C, Group D had a higher average initial pain rating (VAS: 5.9 ± 1.9 vs. 7.1 ± 1.9, $P = .015$) and a higher proportion of patients whose pain decreased by $\geq 50\%$ (41.2% vs. 79.5%, $P = .001$). Between Groups C and D, there were no statistically significant differences in age, sex, time to treatment, or proportion of patients who achieved complete remission.

The location of the epidural catheter varied according to the affected dermatome level. Of the 227 patients, 128 (56.4%) had the epidural catheter inserted at the thoracic level and 99 patients (43.6%) had the catheter inserted at the cervical, lumbar, or sacral levels. None of the 175 patients who received a CEA (92 in Group B and 83 in Group D) reported complaints related to the CEA intervention. Unintended perforation of the dura mater was not reported.

Table 2 presents the unadjusted and adjusted OR between groups (Group B vs. Group A and Group D vs. Group C) associated with a $\geq 50\%$ reduction in pain severity. In the acute groups, after the adjustment for potential confounding factors including age, sex, time to treatment, and initial pain rating, the OR for pain reduction in the Group B versus Group A was 5.17 (95% confidence interval [CI]: 1.75–15.23). In the chronic groups, the adjusted OR for pain reduction in Group D versus Group C was 5.37 (95% CI: 1.62–17.79).

Table 3 presents the OR between groups associated with complete remission of zoster-associated pain. The adjusted ORs for complete remission in the epidural group versus the medical group were 3.05 (95% CI: 1.20–7.73) for the acute group and 4.46 (95% CI: 1.20–16.54) for the chronic group.

4. Discussion

CEA for 14 days combined with standard medical treatment reduced zoster-associated pain effectively in both the acute and chronic groups. Among patients with moderate to severe zoster-associated pain (initial rating ≥ 4) that did not subside after standard treatment, the rates of pain reduction and complete remission were higher in the epidural groups regardless of the time to treatment. This suggests that CEA is effective not only to prevent PHN but also for treatment of patients with PHN that persists ≥ 30 days after the onset of the rash.

There are many definitions and courses of HZ in the literature, and no definition is standard or widely accepted.[16] The definition of PHN also varies widely, but it is often defined as pain that persists for 30 to 120 days or more.[12,17] We used the generally accepted definition of PHN as pain that persisted for ≥ 30 days after the onset of the rash. In clinical care, it is necessary to focus on the early treatment of PHN.

Various treatments have been attempted to prevent PHN. However, the effects are unclear. There are many reports on the

Table 2

Comparison of pain relief for patients with acute herpes zoster and postherpetic neuralgia treated with standard treatment plus continuous epidural analgesia to patients receiving standard treatment alone.

		Unadjusted		Adjusted*	
		OR	(95% CI)	OR	(95% CI)
Acute group	Group A		Reference		Reference
	Group B	4.81	(1.74–13.31)	5.17	(1.75–15.23)
Chronic group	Group C		Reference		Reference
	Group D	5.54	(1.84–16.72)	5.37	(1.62–17.79)

CI = confidence interval, OR = odds ratio. Pain reduction was defined as a $\geq 50\%$ decrease in the rating on the VAS with respect to the initial rating. Group A (acute/medical group): Patients with acute herpes zoster who received only the standard treatment for herpes zoster (oral administration of 800 mg acyclovir once daily for 7 days if the rash had been present for <72 hours, and analgesics as required). Group B (acute/epidural group): Patients with acute herpes zoster who received the standard treatment for herpes zoster plus continuous epidural analgesia for 14 days. Group C (chronic/medical group): Patients with chronic herpes zoster who received only the standard treatment for herpes zoster. Group D (chronic/epidural group): Patients with chronic herpes zoster who received the standard treatment for herpes zoster plus continuous epidural analgesia for 14 days.
* Adjusted for age, sex, time to treatment, and initial rating on visual analog scale.

Table 3

Comparison of complete remission for patients with acute herpes zoster and postherpetic neuralgia treated with standard treatment plus continuous epidural analgesia to patients receiving standard treatment alone.

		Unadjusted		Adjusted*	
		OR	(95% CI)	OR	(95% CI)
Acute group	Group A		Reference		Reference
	Group B	2.01	(0.89–4.53)	3.05	(1.20–7.73)
Chronic group	Group C		Reference		Reference
	Group D	2.64	(0.89–7.83)	4.46	(1.20–16.54)

CI = confidence interval, OR = odds ratio. Complete remission was defined as pain being rated ≤ 2 for 3 consecutive visits. Group A (acute/medical group): Patients with acute herpes zoster who received only the standard treatment for herpes zoster (oral administration of 800 mg acyclovir once daily for 7 days if the rash had been present for <72 hours, and analgesics as required). Group B (acute/epidural group): Patients with acute herpes zoster who received the standard treatment for herpes zoster plus continuous epidural analgesia for 14 days.
Group C (chronic/medical group): Patients with chronic herpes zoster who received only the standard treatment for herpes zoster. Group D (chronic/epidural group): Patients with chronic herpes zoster who received the standard treatment for herpes zoster plus continuous epidural analgesia for 14 days.
* Adjusted for age, sex, time to treatment, and initial rating on visual analog scale.

effectiveness of antiviral therapy on HZ.[18–20] However, high-quality evidence demonstrates that oral acyclovir does not significantly reduce the incidence of PHN.[21] Although numerous treatments have been investigated for PHN, there is no consensus on their effectiveness, and prevention and treatment for PHN are difficult.[22–24] Recent individual case reports of ultrasound-guided serratus plane block[25] and superficial cervical plexus block[26] had positive results for the treatment of HZ. Although promising, these methods need to be confirmed in randomized controlled studies.

For the prevention and treatment of PHN, we focused on HZ-induced neural damage. HZ develops from the reactivation of VZV in sensory ganglion, then spreads to the affected dermatome, induces an inflammatory reaction, and causes neural damage. PHN can develop when the initial neural damage is severe or when damaged neurons are unable to recover normal neural function.[27]

The pathophysiology of PHN remains unclear. However, pathologic studies have demonstrated damage to the sensory nerves, sensory dorsal root ganglia, and dorsal horns of the spinal cord.[28] These injuries cause peripheral and central neural damage.[13] One theory is that the excitability of ganglionic or spinal cord neurons is altered; another is that a persistent, low-grade viral infection exists in the ganglia.[29] We focused on the theory that PHN is the chronic active state of VZV infection. The persistence of the virus in the ganglia causes ganglionitis and clinical-virological correlations suggest that this may cause PHN.[30] Furthermore, the detection of VZV-specific DNA in blood mononuclear cells and cerebrospinal fluid of patients with PHN many years after an HZ infection supports this hypothesis.[31,32]

Because epidural analgesia affects the distal portion of the spinal cord, such as the dorsal root ganglia, spinal nerve roots, and peripheral regions of the spinal cord, it can be used to treat localized neuropathic pain. The mechanism of action of the drugs in CEA is 2-fold: steroids reduce deafferentation by inhibiting inflammation and concomitant swelling-induced neural ischemia, whereas a low concentration of local anesthetics provides analgesia, reducing the pain at the affected dermatome.[27] Because of the nerve-specific characteristics of zoster-associated pain, epidural analgesia is one of the most effective therapeutic options.

Previous studies have confirmed the effectiveness of epidural analgesia on the acute phase of HZ.[11,33–36] Two studies showed that a single epidural injection of methylprednisolone plus bupivacaine significantly reduced acute HZ pain.[11,36] Although it was ineffective at preventing PHN,[11] it reduced the incidence of PHN significantly more than the intravenous administration of acyclovir and prednisolone did.[36] Two other studies have shown that CEA reduces zoster-associated pain,[34,35] but studies were limited to patients with acute phase of HZ. A recent review concluded that nerve blocks during the acute phase of HZ reduced the duration of zoster-related pain and the incidence of PHN.[37] Our study included patients who had chronic zoster-associated pain for up to 6 months, providing a basis to evaluate the efficacy of epidural analgesia on PHN as well as acute HZ.

Although age, pain severity, and rash severity appear to be correlated with the incidence of PHN, accurate predictors for PHN have not been defined.[13] Therefore, it is difficult to predict prognosis and select the appropriate treatment option. Treatment of zoster-associated pain should be initiated earlier for better effectiveness.[1,12] However, the present study suggests that aggressive treatment further shortened the duration of neuropathic pain, even in patients who already had been diagnosed with PHN. Our study is worthy of attention because it included

patients with PHN, in contrast to earlier studies that limited patients to those in the acute phase of HZ.

An epidural catheter was maintained for 14 days in all patients who received CEA in our study. During this period, no adverse effects were reported. Both hospitalized patients and outpatients were observed daily, and daily dressing was performed by well-trained doctors. If managed carefully, CEA is an effective and safe treatment. In this study, CEA for 14 days effectively reduced zoster-associated pain.

The limitations of our retrospective study are selection bias and information bias. Patients tend to visit a dermatologist initially and a pain specialist after treatment failure. Furthermore, we assumed that patients who had severe zoster-associated pain wanted to receive intensive treatments; there were baseline differences between the medical and epidural groups with respect to pain severity and time to treatment. However, our results show that epidural treatment was more effective in both the unadjusted and adjusted models, and that the unadjusted and adjusted ORs were similar. This suggests that pain severity had little effect on the results, and that CEA is effective even in cases of severe zoster-associated pain.

5. Conclusion

CEA can effectively relieve pain caused by PHN and acute HZ. In addition, it can increase the remission rates for both conditions. Furthermore, in this study, CEA was not associated with side effects or complications. Combining CEA with standard medical treatment can be a safe and effective treatment for patients whose zoster-associated pain rated ≥4 on the VAS, and patients whose pain had not subsided after taking standard medication such as oral nonsteroidal anti-inflammatory drugs and opioids.

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