The Effects of Epidural Blockade on the Acute Pain in Herpes Zoster

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Objective: To evaluate the relief of acute pain and possible preventive effects on postherpetic neuralgia through the use of an epidural blockade in the acute stage of herpes zoster.

Design: Prospective, nonrandomized, comparative clinical trial.

Setting: A dermatologic clinic in a university hospital.

Patients: Sixty-five consecutive patients with pain due to acute herpes zoster were treated for a 7-day hospitalization period from July 1, 1996, through June 30, 1997.

Intervention: The consecutive patients were divided into 2 groups. Group A consisted of 30 patients who were seen from July 1, 1996, through December 31, 1996, and who were treated with intravenous acyclovir (5 mg/kg) for 7 days. Group B consisted of 35 patients who were seen from January 1, 1997, through June 30, 1997, and who were treated with intravenous acyclovir (5 mg/kg) and an epidural blockade for 7 days. The changes in the intensity of pain and the total duration of pain in both groups were assessed for 12 to 18 months.

Main Outcome Measures: The number of days required for relief of pain and the total duration of pain.

Results: The mean ± SD number of days required for relief of pain, which was rated on a scale of 100 (worst pain) to 0 (no pain), was significantly fewer in group B than in group A: it took 2.6 ± 1.1 days to go from 100 to 50 on the relief-of-pain scale in group B, but 3.8 ± 1.1 days in group A (P = .03), and 12.5 ± 6.4 days to go from 100 to 10 in group B, but 20.1 ± 14.6 days in group A (P = .04). The duration of late residual pain was significantly shorter in group B (5.9 ± 5.8 days) than in group A (11.9 ± 7.5 days) (P = .03). The total duration of pain was also significantly shorter in group B (18.5 ± 9.3 days) than in group A (31.6 ± 17.6 days) (P = .04).

Conclusions: We believe that an epidural blockade combined with an antiviral agent is a very effective treatment modality for the pain of acute herpes zoster, and we recommend its use for the prevention of postherpetic neuralgia, with a view to shortening the total duration of pain, especially late residual pain.

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Postherpetic neuralgia (PHN) is the most common and feared complication of herpes zoster (HZ). Although PHN resolves spontaneously within the first year in the great majority of cases, the pain is often relentless and persists for years, or even a lifetime. Thus, PHN is difficult to manage and, unfortunately, refractory to most forms of treatment modalities. It has been demonstrated that antiviral treatment, corticosteroids, sympathetic and regional nerve blockade, and a combination of these therapies in the early stage of disease have preventive effects on PHN and reduce the duration of acute pain in HZ. Early therapeutic interventions with antiviral drugs, particularly newly developed drugs, such as valacyclovir hydrochloride and famciclovir, allowed dramatic improvements of the skin lesions of HZ and reductions in the incidence of PHN. Corticosteroid therapy has also been postulated to be beneficial by some authors, although there is controversy concerning the effectiveness of corticosteroids because of the immunosuppressive effects.

Although an epidural blockade is undeniably effective in providing relief of acute pain in HZ, the concept of its preventive action on PHN is intriguing, but unproved. Also, little information is available on the long-term efficacy of epidural blockade for the prevention of PHN. Therefore, we designed this prospective interventional study to evaluate the effectiveness of epidural blockade on acute pain in HZ and the prevention of PHN.

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PATIENTS AND METHODS

PATIENTS

Sixty-five consecutive patients with HZ were admitted to Wonju Christian Hospital, Yonsei University Wonju College of Medicine, Wonju, South Korea, from July 1, 1996, to June 30, 1997. Patients were divided into 2 groups. Group A consisted of 30 patients who were seen from July 1, 1996, through December 31, 1996, and who were treated with intravenous acyclovir (5 mg/kg three times a day) for 7 days. Group B consisted of 35 patients who were seen from January 1, 1997, through June 30, 1997, and who were treated with intravenous acyclovir (5 mg/kg three times a day) and an epidural blockade for 7 days. All patients began treatment for acute HZ within 14 days of the onset of the disease. The disease was classified as mild (<25 lesions), moderate (25-50 lesions), or severe (>50 lesions), according to the number of papules, vesicles, ulcers, and crusts within the primary dermatome. The lesions were located in the cervical through the sacral dermatomes. Patients with trigeminal nerve involvement were excluded. All supplementary treatments, including amitriptyline hydrochloride (30 mg/d), acetaminophen (960 mg/d), and wet dressing with 0.3% aluminum chloride, were provided to both groups. After 7 days of hospitalization for acyclovir therapy with or without epidural blockade, all patients were seen as outpatients. The patients continued taking amitriptyline and acetaminophen in decreasing dosages (to 20 and 480 mg/d, respectively) until the relief-of-pain score decreased to 10, and then to 0. Topical analgesic therapy (ketoprofen gel) was also continued until the patients were completely free of pain. For recurrence of pain during follow-up evaluations, the dosages of supplementary medicines were increased, and nonpharmacological physical therapy, such as a hot compress or an ice pack, was continued. Follow-up evaluations were made weekly or biweekly for 6 months; thereafter, follow-up telephone calls were made between 12 and 18 months.

ASSESSMENT OF PAIN

The changes in the intensity of pain were assessed by a self-rating relief-of-pain scale that ranged in score from 100 (worst pain) to 0 (no pain). The intensity of pain at admission and/or the worst pain within the early phase of HZ was defined as 100; then, the relief-of-pain score was recorded daily for 7 days and thereafter weekly or biweekly until the patients were completely free of pain (0). The types of pain checked were (1) a constant, deep-aching, “bruising” or burning sensation; (2) an intermittent, sharp, lancinating, shooting, or electric shock–like pain; and (3) allodynia, or a superficial, dysesthetic, or itchlike sensation. The severity of pain was graded according to Wood et al14 as mild (does not disturb sleep), moderate (causes frequent awakening), and severe (excruciating, devastating, does not allow sleep).

METHOD OF EPIDURAL BLOCKADE

An epidural catheter was placed at the epidural space of the affected spinal nerve. Following an initial bolus injection of 0.25% bupivacaine (5-7 mL) and methylprednisolone acetate (40 mg), each patient received a continuous epidural infusion of 0.125% bupivacaine with a portable balloon infusion device (Baxter Infusion; Baxter Healthcare Co, Deerfield, Ill). The rate of infusion was 2 mL/h. Epidural blockade was selected on the basis of the following inclusion and exclusion criteria: The inclusion criteria were (1) patient has HZ in the active stage (≤14 days from onset); (2) patient has uncomplicated HZ (no systemic or localized skin infection); (3) patient has no drug history (anticoagulant); and (4) patient has no disease history of coagulation pathway. The exclusion criteria were (1) patient does not consent; (2) patient has a coagulation abnormality or is taking anticoagulants; (3) patient has systemic or localized skin infection; and (4) patient is in an older age group and has cardiovascular disease (eg, hypertension, arrhythmia, or heart failure). For a sudden resurgence of pain, despite the continuous epidural infusion, additional intermittent epidural injections of 0.25% bupivacaine (5-7 mL) were administered 2 to 5 times during the hospital stay. The epidural infusion was continued until the patients were discharged from the hospital.

STATISTICAL ANALYSIS

The duration, from the initial day of treatment (pain intensity score, 100) to the day the patients evaluated the pain intensity as 50 and 10, was defined as the days required for the relief of pain (DRP) (ie, for the pain to decrease in intensity from 100 to 50 and from 100 to 10). The days required for the intensity of pain to go from 100 to 0 was defined as the total duration of pain (TDP). The days required for the intensity of pain to go from 10 to 0 were defined as the duration of late residual pain (DLRP). Therefore, the DLRP is calculated as follows: DLRP (DRP from 10 to 0) = TDP (DRP from 100 to 0) − DRP from 100 to 10.

All continuous variables are expressed as mean ± SD. Differences between and within the treatment groups were tested by 2-way analysis of variance and nonpaired t test. A value of P < .05 was considered to be statistically significant.

RESULTS

Sixty-five patients were admitted to our clinic for the study. Two patients in group B were unavailable for follow-up at 1 and 2 weeks. Follow-up telephone calls for evaluation of change or recurrence of pain at 6 months and between 12 and 18 months revealed the absence of pain in all patients. The demographic characteristics of the 65 patients are summarized in Table 1. There were no significant differences in the distribution of age, sex, and mean duration of symptoms between the 2 groups.

The types and grades of pain are shown in Table 2. Twenty-three patients (10 in group A and 13 in group B) had one or more associated systemic disorders (Table 3), which were most commonly associated with hypertension (14 of 65) and diabetes mellitus (12 of 65).

The distribution of DRP (from 100 to 50 and from 100 to 10) and TDP in both groups is shown in Figure 1.
The time required for the loss of the pain due to acute HZ was significantly less in group B than in group A (Figure 2). Twelve of the 65 patients (7 in group A; 5 in group B) reported complete relief of pain within 7 days. Nineteen (9 in group A; 10 in group B) reported complete relief of pain within 14 days. The longest TDP was 68 days in group A and 47 days in group B. All patients in both groups had complete relief of pain within 10 weeks. Differences in the therapeutic effect on pain between the 2 groups were not detectable until after 2 weeks. After 2 weeks, there was a more rapid resolution of pain in group B than in group A (Figure 2). This difference was closely related to the rapid resolution of late residual pain ($P < .05$). The DRP (from 100 to 50 and from 100 to 10) and the TDP were significantly less in group B than in group A ($P = .03$) (Table 4).

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Most investigators described regional nerve block and sympathetic blockade as effective for the relief of the acute pain of HZ.10,16-21 In 1938, Rosenak23 suggested that sympathetic blockade not only is effective for rapid relief of the acute pain of HZ but also promotes skin healing. Since then, many other investigators10,16-21 have advocated sympathetic blockade for the acute pain of HZ. Some investigators9,10,16 suggested that the nerve block not only relieves acute pain but also, if given early in the course of disease, prevents progression to postherpetic neuralgia (PHN). Data on the relief of acute pain, however, cannot be extrapolated to predict the prevention of PHN. Also, the findings of other studies suggest that sympathetic blockade is ineffective.13-15 Although sympathetic blockade is effective for the immediate, short-term relief of the acute pain of HZ, the preventive action on PHN has been a matter of controversy, and well-designed, controlled trials of its efficacy in preventing PHN have not been performed.

Although there is no completely satisfactory treatment for established PHN, current treatment approaches have given priority to preventing the development of PHN. Our findings show that an epidural blockade provides significant pain relief and shortens the duration of acute pain in patients with HZ. Epidural blockade is of particular value in shortening the DLRP and the TDP. Therefore, in the early stage of HZ, it has preventive effects on PHN. The rapid resolution of late residual pain in group B, which was observed in the younger age group, in the early-treatment group, and in patients without systemic disorders, is noteworthy. Therefore, epidural blockade may also reduce the incidence of PHN. Although many investigators10,16-21 have reported the therapeutic effects of epidural blockade on pain in patients with HZ, they actually reported the incidence of PHN after the epidural blockade. The definitions of PHN have varied, and “Assessment of Pain” and “Statistical Analysis” subsections of “Patients and Methods” section for explanation of scores; DLRP, duration of late residual pain; and TDP, total duration of pain.

Table 5. The DRP, DLRP, and TDP According to Age and Duration of Symptoms

<table>
<thead>
<tr>
<th>Age, y</th>
<th>DRP From 100 to 50</th>
<th>DRP From 100 to 10</th>
<th>DLRP</th>
<th>TDP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
<td>Group A</td>
<td>Group B</td>
</tr>
<tr>
<td>&lt;60</td>
<td>3.7 ± 2.0 (n=18)</td>
<td>2.5 ± 1.2 (n=17)</td>
<td>16.6 ± 13.1 (n=18)</td>
<td>11.5 ± 6.7 (n=18)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>3.8 ± 1.3 (n=12)</td>
<td>2.8 ± 1.2† (n=12)</td>
<td>24.1 ± 15.8 (n=12)</td>
<td>12.9 ± 5.6† (n=12)</td>
</tr>
<tr>
<td>Duration of symptoms, d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>3.9 ± 2.1 (n=7)</td>
<td>2.0 ± 1.1‡ (n=6)</td>
<td>19.9 ± 13.7 (n=6)</td>
<td>14.2 ± 5.8 (n=6)</td>
</tr>
<tr>
<td>4-7</td>
<td>3.6 ± 2.6 (n=15)</td>
<td>2.7 ± 1.4‡ (n=15)</td>
<td>16.6 ± 13.1 (n=15)</td>
<td>12.4 ± 6.1 (n=15)</td>
</tr>
<tr>
<td>&gt;7</td>
<td>3.6 ± 1.2 (n=8)</td>
<td>3.0 ± 1.1 (n=8)</td>
<td>24.6 ± 18.3 (n=8)</td>
<td>10.2 ± 6.1 (n=8)</td>
</tr>
</tbody>
</table>

*DRP indicates days required for relief of pain (see “Assessment of Pain” and “Statistical Analysis” subsections of “Patients and Methods” section for explanation of scores); DLRP, duration of late residual pain; and TDP, total duration of pain. Values are given as mean ± SD. Group A was treated with acyclovir alone; group B, with acyclovir and epidural blockade. †P<.05 compared with values in group A. ‡P<.01 compared with values in group A.
making it difficult to determine its frequency after the onset of acute HZ. In view of this, the incidence of PHN cannot be a pertinent factor in efficacy evaluation. Most pain in patients with HZ is self-limiting and gradually subsides both in quality and quantity. However, pain lasts for a considerable time in patients with moderate or severe HZ lesions, in those in the older age group (>60 years), and in those who delay treatment in the initial period. The pain exists on a spectrum from mild and unobtrusive to severe and even debilitating. Patients with HZ have stabbing or burning pain, which may be constant and deep or intermittent and lancinating. Allodynia, which is closely related to the central sensitization of the dorsal root ganglion, is the most persistent of symptoms, sometimes lasting for years. Most patients suffer from all 3 types of pain. In relation to the rapid resolution of late residual pain, there was little evidence of allodynia on the scarred skin lesions by the end of treatment in group B.

Wood et al reported that, based on the findings of a randomized, double-blind, placebo-controlled study, pain was noted in 62% of patients who received 7 days of oral acyclovir therapy at 4 weeks after skin eruption, in 24% at 12 weeks, and in 14% at 24 weeks. Surprisingly, our study showed that patients with pain accounted for 43% (28/65) (60% [18/30] in group A vs 27% [10/35] in group B) of all the patients at 4 weeks after skin eruption and for 6% (2/30) (only in group A) at 8 weeks. None of the patients in groups B and A had pain at 7 and 10 weeks, respectively. We think that there are several possible reasons why our patients responded better and reported a shorter duration of pain than the patients in previous studies. First, all our patients were treated early, within 14 days of onset; 48 (74%) of the 65 patients were treated within 7 days and 33 (51%) within 3 days. To avoid the development of PHN, all treatment modalities should be given as soon as possible after the onset of the disease. The optimal time for epidural blockade has been a matter of speculation. Most authors suggest that the response is best when the epidural blockade is administered early in the course of the disease. Second, our patients had a less severe grade of pain. Forty-six (71%) of the 65 patients had a mild to moderate grade of pain. The incidence and severity of HZ directly correlates with increased age. The disease is more severe, and the duration of pain in HZ is also longer in older patients. Also, the more severe and painful the outbreak of HZ is in older patients initially, the more likely that PHN will develop. Finally, combination therapy with acyclovir and epidural blockade was continued for 7 days. It has been demonstrated that antiviral agents, corticosteroids, sympathetic and regional nerve blockade, and a combination of these therapies in the early stage of disease have preventive effects on PHN. The combination therapy with corticosteroids and antiviral drug in patients with HZ shortens the period of analgesic drug therapy and produces an earlier return to normal activity. However, there is no study of combination therapy with antiviral agents and epidural blockade. Their combination may be more effective on the relief of the acute pain in patients with HZ and may have more preventive effects on PHN.

The pathomechanisms of preventive action of the epidural blockade on PHN is still under discussion. The primary lesion of HZ is an acute inflammatory state of the dorsal root ganglion, which may cause increased sympathetic vasoconstriction in the affected segment, followed by permanent neural damage. Most authors describe sympathetic blockade as inhibiting vasoconstriction, and thus blocking the ischemic damages of nerve. The therapeutic effects of the epidural blockade result in both sympathetic blockade and anesthetization of the distal portion of the spinal cord, such as the dorsal root ganglion, posterior spinal nerve, and periphery of the spinal cord. While the suppressive effects of the sympathetic blockade on the ischemic damage of nerve is widely known, the anesthetizing effects of the distal portion of the spinal cord has not been stressed. The anesthetizing effects of the distal portion of the spinal cord with epidural blockade induce rapid relief of acute pain in patients with HZ and block the central sensitization in the dorsal horn and dorsal root ganglion. Therefore, the succession of neurogenic inflammation is interrupted. Recently, studies have suggested that preventing the afferent stimuli generated by injured peripheral nerves from reaching the central nervous system contributes to the reduction of the duration of pain and lowers the intensity of the pain of acute tissue injury. Following peripheral tissue inflammation, repetitive C-fiber afferent stimulation produces a progressive increase in action potential discharge and a prolonged increase in excitability of neurons in the dorsal horn of the spinal cord. This noxious stimulation-induced central sensitization contributes to the development of prolonged pain that persists after the initial stimulus has abated. The central sensitization in the dorsal horn and dorsal root ganglion leads to efferent impulses that release neuropeptides from branches of the sensory nerves. A variety of neuropeptides have been described in the skin and may play a role in the neurogenic inflammation. Simultaneously, several kinds of neuropeptides activate connective tissue mast cells, releasing histamine and eicosanoids. Histamine potentiates the local inflammatory responses and also restimulates sensory receptors in the periphery to generate an axonal reflex and subsequent release of neuropeptides, augmenting the inflammatory response.

Combining anesthetics and steroids in the epidural blockade is a rational means of gaining the benefits of both drugs, while minimizing the adverse effects that are unique to each. It also provides a synergy in the relief of pain and in the interruption of central sensitization. Steroids relieve pain by reducing inflammation and by blocking transmission of the nociceptive C-fiber input. They decrease inflammation by inhibiting the action of phospholipase A2, a rate-limiting enzyme in the production of prostaglandins and leukotrienes. Prostaglandins and leukotrienes sensitize small neurons and enhance pain generation. Altered permeability in response to inflammatory mediators results in venous congestion and intraneural edema. Abnormal conduction by nerve fibers and generation of pain follow. Steroids also produce analgesia by blocking transmission of nociceptive input and have a direct membrane action that prevents the development of ectopic neural discharge.
All patients in our study were hospitalized for 7 days. During this period, the patients in group A received 5 mg of intravenous acyclovir 3 times a day, and those in group B received the same amount of intravenous acyclovir plus an epidural blockade. Patients with a sudden resurgence of pain also received intermittent 5- to 7-mL epidural injections of 0.25% bupivacaine. Manabe et al suggested that continuous epidural blockade can shorten the duration of treatment. Continuous epidural infusion of local anesthetics leads to a successful sensory and sympathetic blockade and results in less intense motor blockade and could theoretically reduce hemodynamic instability from the sympathetic blockade. Intermittent epidural blockade may lead to autonomic and motor blockade, with resultant hypotension, urinary retention, or impaired ambulation. Although health insurance systems differ between nations and between individuals, continuous epidural blockade for a 7-day hospitalization is both cost-effective and safe.

In conclusion, the therapeutic effect of epidural blockade on pain in HZ, as well as sensory blockade and suppression of ischemic damage of nerve, is an interruption of the cutaneous neurogenic inflammation, followed by rapid healing and recovery from neural damage. Epidural blockade for HZ is a very effective treatment modality, especially in combination with an antiviral agent, and it was not associated with adverse effects in this study. Our study was not blinded, but we believe that the findings show that epidural blockade carried out during the early stage of HZ has preventive effects on PHN by shortening the duration of pain, by decreasing the ischemic damage of the nerve, and by restraining cutaneous neurogenic inflammation. Combination treatment with epidural blockade and antiviral agents, such as valacyclovir hydrochloride and famciclovir, offers the potential for significant clinical advantages in improved management of acute HZ and prevention of PHN. Well-designed, randomized, double-blind, placebo-controlled trials are needed to prove the efficacy of such combination treatment in preventing PHN. However, although we found that epidural blockade combined with an antiviral agent can reduce pain in patients with HZ, the potential for serious complications due to epidural blockade and the invasiveness of the procedure, need to be given careful consideration.

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