

INTRATHECAL METHYLPREDNISOLONE FOR INTRACTABLE POSTHERPETIC NEURALGIA

NAOKI KOTANI, M.D., TETSUYA KUSHIKATA, M.D., HIROSHI HASHIMOTO, M.D., FUTOSHI KIMURA, M.D., MASATOSHI MURAOKA, M.D., MISAKO YODONO, M.D., MIZUE ASAI, M.D., AND AKITOMO MATSUKI, M.D.

ABSTRACT

Background There is no effective treatment for intractable postherpetic neuralgia. Because there is evidence that postherpetic neuralgia has an inflammatory component, we assessed treatment with intrathecally administered methylprednisolone to reduce pain in patients with this disorder.

Methods We enrolled 277 patients who had had intractable postherpetic neuralgia for at least one year, 270 of whom were followed for two years. The patients were randomly assigned to receive intrathecal methylprednisolone and lidocaine (3 ml of 3 percent lidocaine with 60 mg of methylprednisolone acetate, 89 patients), lidocaine alone (3 ml of 3 percent lidocaine, 91 patients), or no treatment (90 patients) once per week for up to four weeks. Each weekly dose was injected into the lumbar intrathecal space. Pain was evaluated before randomization, at the end of the treatment period, and then four weeks, one year, and two years later. Samples of cerebrospinal fluid were obtained for measurement of interleukin-8 before and at the end of the treatment period.

Results There was minimal change in the degree of pain in the lidocaine-only and control groups during and after the treatment period. In the methylprednisolone-lidocaine group, the intensity and area of pain decreased, and the use of the nonsteroidal antiinflammatory drug diclofenac declined by more than 70 percent four weeks after the end of treatment. No complications related to intrathecal methylprednisolone were observed. Before treatment, the concentrations of interleukin-8 in the cerebrospinal fluid were inversely related to the duration of neuralgia in all the patients ($r = -0.49$, $P < 0.001$). In the patients who received methylprednisolone, interleukin-8 concentrations decreased by 50 percent, and this decrease correlated with the duration of neuralgia and with the extent of global pain relief ($P < 0.001$ for both comparisons).

Conclusions The results of this trial indicate that the intrathecal administration of methylprednisolone is an effective treatment for postherpetic neuralgia. (N Engl J Med 2000;343:1514-9.)

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POSTHERPETIC neuralgia is characterized by severe burning and lancinating pain. This type of neuralgia is typically accompanied by allodynia (pain from non-noxious stimuli), which can persist for years.^{1,2} Although many treatments for postherpetic neuralgia have been described, it remains difficult to treat. The effectiveness of the recommended treatments, except for antide-

pressants, has yet to be supported by appropriate clinical studies.^{1,2}

Interleukin-8 is associated with the pain induced by inflammatory reactions,³⁻⁶ and there are high concentrations of interleukin-8 in the cerebrospinal fluid of patients who have intractable postherpetic neuralgia.⁷ Furthermore, postmortem studies of patients who had prolonged postherpetic neuralgia revealed marked inflammation around the spinal cord, with massive infiltration and accumulation of lymphocytes.⁸ The inflammatory component of postherpetic neuralgia suggests that suitably timed antiinflammatory treatment may help reverse the syndrome or at least limit its progression. This theory is consistent with the report of a patient in whom the intrathecal administration of methylprednisolone acetate provided complete relief of pain for more than a year.⁹ In a small, preliminary study, we found that epidural methylprednisolone helped alleviate postherpetic neuralgia.⁷

In this randomized, controlled study, we assessed intrathecal methylprednisolone acetate as a treatment for postherpetic neuralgia affecting areas other than those innervated by the trigeminal nerve. We also investigated whether the concentration of interleukin-8 in the cerebrospinal fluid correlates with clinical variables, including the duration of postherpetic neuralgia before treatment and the efficacy of treatment.

METHODS

Study Population

This study was a randomized, blinded clinical trial with a two-year follow-up period. The study was approved by the institutional review board of the University of Hirosaki, and written informed consent was obtained from all the patients. Patients referred to the University of Hirosaki Hospital and its affiliated hospitals who had intractable postherpetic neuralgia were eligible for inclusion. We defined intractable postherpetic neuralgia as burning and lancinating pain that was accompanied by allodynia and that was restricted to the dermatomes involved in the original eruption of herpes zoster. To be included, patients had to have pain that had persisted for at least a full year after the healing of the vesicular eruptions. Patients with diabetes mellitus could be included if they did not have neuropathy.

We excluded patients with one or more of the following conditions: painful regions innervated by the trigeminal nerve, previous treatment with neurolytic nerve block for postherpetic neuralgia, polyneuropathy, or any other neurologic diseases or diseases associated with an immunocompromised state. We did not in-

From the Outcomes Research Group, Department of Anesthesiology, University of Hirosaki School of Medicine, Hirosaki, Japan. Address reprint requests to Dr. Kotani at the Department of Anesthesiology, University of Hirosaki School of Medicine, 5 Zaifu-cho, Hirosaki 036-8562, Japan.

clude patients who obtained satisfactory pain relief with conventional treatments, such as topical analgesics, physiotherapy, epidural local anesthetics, and antidepressants or anticonvulsants.

Protocol

Patients eligible for the study first received conventional treatment (antidepressants, anticonvulsants, or both; epidural local anesthetics; topical agents; or physiotherapy) for four to six weeks if any of these treatments had not been tried previously. They were then treated with diclofenac for the subsequent four weeks (the prestudy period). After the prestudy period, patients with persistent pain who chose to participate in the study were randomly assigned to receive methylprednisolone and lidocaine, lidocaine alone, or no treatment (control). Randomization was performed with the use of computer-generated codes sealed in sequentially numbered, opaque envelopes. The envelopes were opened only if the conventional treatments failed. The physicians in charge of patients' treatment were aware of the group assignments.

After randomization, the study drugs were administered once per week for four weeks. All injections were administered by the same physician. A needle was inserted into the L2–L3 intervertebral space, and 1 ml of fluid was removed for routine cytologic and biochemical tests. We then injected 3 ml of 3 percent lidocaine and 60 mg of methylprednisolone (specific gravity, 1.040; pH, 6.2 to 6.7) (in the methylprednisolone–lidocaine group) or 3 ml of 3 percent lidocaine alone (specific gravity, 1.035; pH, 6.1 to 6.5) (in the lidocaine-only group). Patients in the control group did not have lumbar puncture and received neither of these drugs during this four-week period. For patients whose pain was located in the upper thoracic or cervical area, we tilted the operating table into the head-down position immediately after the intrathecal injection to allow the injected material to spread to the upper thoracic canal and to the nerves of the involved dermatomes. Patients with abdominal or lower-body pain were kept in a horizontal position.

Patients in all three groups were permitted to take the nonsteroidal antiinflammatory drug diclofenac (50-mg tablets, up to four times daily) at any time during the study and to change the frequency as necessary. During the prestudy period, the treatment period, and the first four weeks of follow-up, patients were asked to keep a daily diary of their use of diclofenac. At the end of the first four weeks of follow-up, we collected the diaries and calculated the mean number of diclofenac tablets consumed per week. Thereafter, and for the remainder of follow-up, topical analgesics and physiotherapy, in addition to diclofenac, were permitted for temporary analgesia if unbearable pain occurred. The use of oral narcotic or non-narcotic analgesics other than diclofenac was prohibited, and no intrathecal, epidural, or neurolytic nerve blocks were administered during the entire follow-up period.

Evaluation of Pain

Pain was evaluated just before randomization, at the end of treatment, and then four weeks, one year, and two years after the end of treatment. Any conventional analgesic treatments were discontinued two weeks before each of the three follow-up evaluations, and use of diclofenac was not permitted during the 24 hours before each evaluation. Magnetic resonance imaging was performed at the four-week, one-year, and two-year evaluations by radiologists who were unaware of the patients' treatment assignments.

The severity of burning pain and lancinating pain was evaluated with use of a 10-cm visual-analogue scale (on which 0 cm represented no pain, and 10 cm the worst imaginable pain). The area of maximal pain was delineated on the skin with an ink marker, and its surface area was then calculated from a tracing of the marked region. The severity of allodynia was also evaluated with use of a 10-cm visual-analogue scale. The areas of allodynia were determined by gentle stroking of the skin with a 2-cm-wide electric toothbrush. As the skin was stroked in a direction toward the area of neuralgia, the patient was asked about changes in sensation. The border of the areas where sensation changed was defined in

eight directions and marked on the skin. The area of allodynia was calculated from a tracing of the marked region.

Global pain relief was evaluated with use of a 10-cm visual-analogue scale and the results classified as excellent (>75 percent relief), good (50 to 75 percent relief), fair (25 to 49 percent relief), or poor (<25 percent relief). All evaluations of pain were conducted by physicians who were unaware of the patients' treatment assignments.

Measurement of Interleukin-8

Five-milliliter samples of cerebrospinal fluid were obtained before randomization and at the end of the treatment period from all the patients. In addition, we obtained cerebrospinal fluid from 50 patients who had neither postherpetic neuralgia nor other neurologic disorders. The samples were centrifuged at $500 \times g$ to remove cellular elements, and the supernatant was then stored at -80°C for subsequent assay by investigators who were unaware of the patients' treatment assignments. The concentration of interleukin-8 in the supernatant was measured by an enzyme-linked immunosorbent assay (Toray-Fuji Biochemicals, Tokyo, Japan). The lower limit of detection of interleukin-8 with this assay was 3.0 pg per milliliter, and in our laboratory, the intraassay and interassay coefficients of variation were less than 5 percent and less than 8 percent, respectively.

Statistical Analysis

We evaluated differences among the study groups by one-way factorial analysis of variance and Scheffé's test. We considered P values of less than 0.01 to indicate statistically significant differences. The extent of global pain relief was evaluated with a chi-square test. Patients in each group were assigned to one of two categories: those with good or excellent (≥ 50 percent) pain relief and those with poor or fair (<50 percent) pain relief. The relation among interleukin-8 concentrations, global pain relief, and the duration of postherpetic neuralgia was evaluated by linear regression. Data are expressed as means \pm SD.

RESULTS

We screened 409 patients and enrolled 277 in the randomized portion of the study. A total of 270 patients completed the two-year follow-up: 89 in the methylprednisolone–lidocaine group, 91 in the lidocaine-only group, and 90 in the control group. The clinical and demographic characteristics of the patients before the start of the study did not differ significantly among the three groups (Table 1).

Approximately 90 percent of patients in the methylprednisolone–lidocaine group had good or excellent global pain relief at all the follow-up evaluations (Table 2). The seven patients in this group who obtained only poor or fair pain relief during follow-up had had postherpetic neuralgia for more than five years. In the lidocaine-only group, 15 percent of the patients had good or excellent pain relief at the end of treatment, but more than half of them had recurrence of pain at subsequent follow-up examinations. Fewer than 5 percent of the patients in the control group had good or excellent pain relief at any of the follow-up evaluations. Global pain relief was thus significantly better at all follow-up evaluations in the methylprednisolone–lidocaine group than in the control group ($P < 0.001$ at all evaluations) (Table 2). Magnetic resonance imaging revealed no abnormalities in the spinal cord of any of the patients in the

TABLE 1. CHARACTERISTICS OF THE PATIENTS.*

VARIABLE	METHYLPREDNISOLONE AND LIDOCAINE (N=89)	LIDOCAINE ONLY (N=91)	CONTROL (N=90)
Age (yr)	63±8	65±8	65±7
Female sex (no.)	42	47	43
Affected side (no.)			
Right	47	42	44
Left	42	49	46
Duration of neuralgia (mo)	36±19	41±20	38±19
Region of neuralgia (no.)			
Cervicothoracic	64	72	68
Lumbosacral	25	19	22
>1 Dermatome affected (no.)	57	65	62
Diabetes mellitus (no.)	21	21	18

*Plus-minus values are means ±SD. There were no significant differences in these variables among the three groups.

methylprednisolone–lidocaine group at four weeks or at one or two years after treatment. During the two-year follow-up period, none of the patients in the methylprednisolone–lidocaine group had adverse effects or recurrent pain. Routine biochemical tests on the cerebrospinal fluid to measure proteins and glucose and the number of leukocytes showed no abnormalities in the methylprednisolone–lidocaine group during the treatment period (data not shown).

In the methylprednisolone–lidocaine group, the severity of burning and lancinating pain and allodynia and the areas of maximal pain and allodynia were reduced by more than 70 percent at all post-treatment evaluations as compared with the values before treatment. In the lidocaine-only group, a significant reduction in these variables (by up to <25 percent) was noted at the end of treatment but not at subsequent follow-up evaluations. The decreases in these measures of pain were therefore significantly greater in the methylprednisolone–lidocaine group than in the other two groups ($P<0.001$) (Fig. 1 and 2).

The use of diclofenac was similar among the three groups during the prestudy period. In the methylprednisolone–lidocaine group, the use of diclofenac decreased by more than 70 percent during treatment and the subsequent four weeks. In the lidocaine-only group, diclofenac use decreased by less than 20 percent during treatment. In the control group, the use of diclofenac did not change over time. The decrease in diclofenac use was therefore significantly greater in the methylprednisolone–lidocaine group than in the other groups ($P<0.001$) (Fig. 3).

The concentration of interleukin-8 in the cerebrospinal fluid from the 50 patients without postherpetic neuralgia or other neurologic disorders was 18 ± 7 pg per milliliter, which was significantly less than the concentrations measured before randomization in the control group (35 ± 15 pg per milliliter), the lidocaine-only group (33 ± 16 pg per milliliter), and the methylprednisolone–lidocaine group (36 ± 16 pg per milliliter) ($P<0.001$ for the comparison with the values in the patients without neuralgia). The concentration of interleukin-8 measured before randomization was inversely correlated with the duration of postherpetic neuralgia ($r=-0.49$, $P<0.001$). The concentration of interleukin-8 in the cerebrospinal fluid did not change over time in either the control group or the lidocaine-only group. In the methylprednisolone–lidocaine group, however, the concentration of interleukin-8 decreased by 50 percent during treatment and to a significantly greater extent than in the other groups ($P<0.001$). The decrease in the interleukin-8 concentration in the methylprednisolone–lidocaine group correlated with the duration of neuralgia before treatment ($r=-0.53$, $P<0.001$) and with global pain relief ($r=0.40$, $P<0.001$).

DISCUSSION

In this randomized, controlled trial, intrathecal methylprednisolone provided good or excellent analgesia for the burning and lancinating pain and allodynia of postherpetic neuralgia in nearly all the pa-

TABLE 2. GLOBAL PAIN RELIEF.*

STUDY GROUP	END OF TREATMENT			4-WK FOLLOW-UP			1-YR FOLLOW-UP			2-YR FOLLOW-UP		
	GOOD OR EXCELLENT	POOR OR FAIR	P VALUE	GOOD OR EXCELLENT	POOR OR FAIR	P VALUE	GOOD OR EXCELLENT	POOR OR FAIR	P VALUE	GOOD OR EXCELLENT	POOR OR FAIR	P VALUE
	no. of patients			no. of patients			no. of patients			no. of patients		
Methylprednisolone and lidocaine (n=89)	81	8	<0.001	82	7	<0.001	82	7	<0.001	82	7	<0.001
Lidocaine only (n=91)	14	77	0.03	6	85	0.53	5	86	0.48	6	85	0.31
Control (n=90)	4	86		4	86		3	87		3	87	

*Global pain relief was categorized as good or excellent (≥ 50 percent relief) or poor or fair (< 50 percent relief). All P values are for the comparison with the control group.

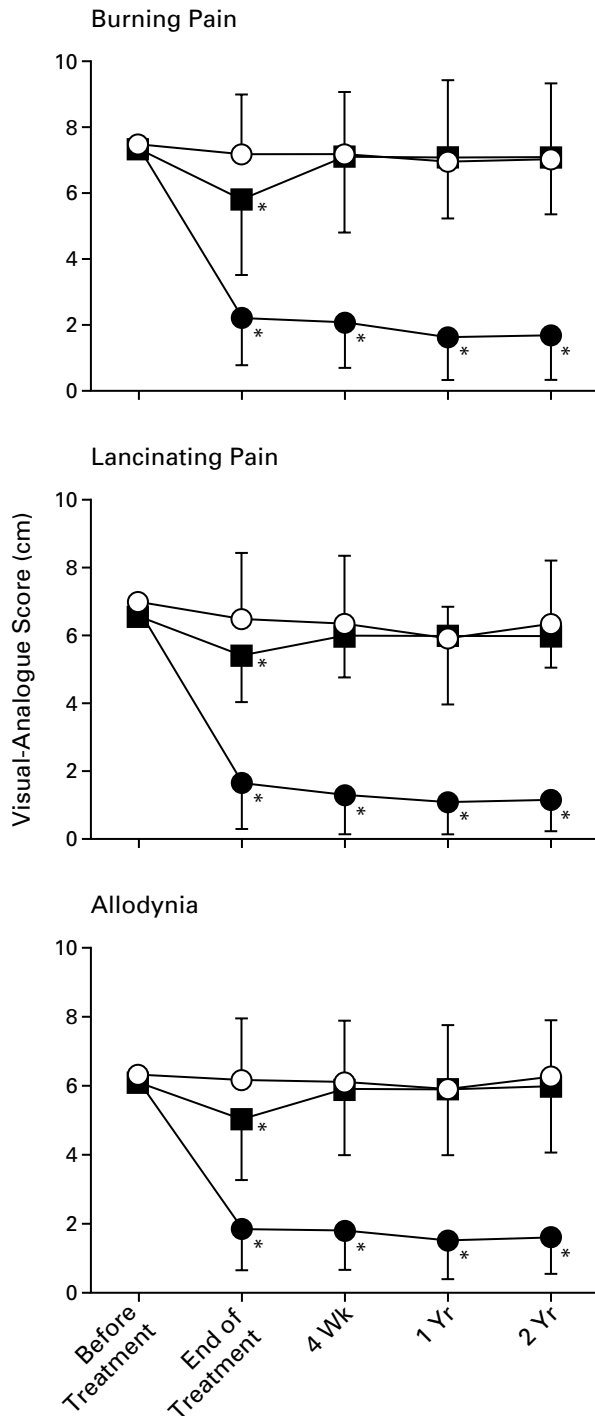


Figure 1. Mean (\pm SD) Scores on a Visual-Analogue Scale for Burning Pain, Lancinating Pain, and Allodynia in the Three Study Groups.

On this scale, 0 cm represents no pain and 10 cm the worst imaginable pain. Solid circles denote the methylprednisolone-lidocaine group (89 patients), squares the lidocaine-only group (91), and open circles the control group (90). Asterisks indicate statistically significant differences from the scores in the other groups at the same time points ($P < 0.001$).

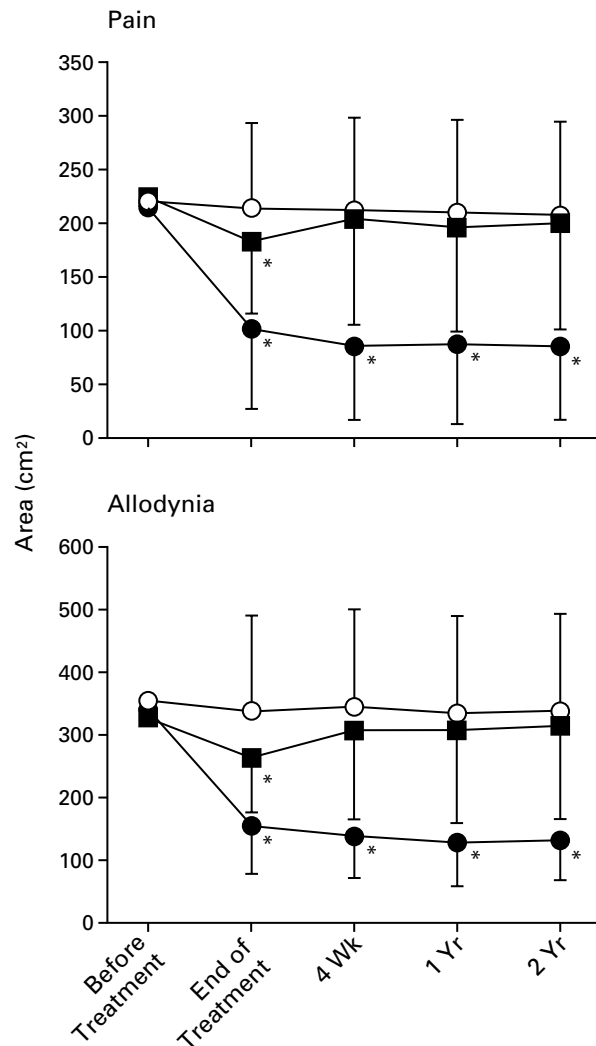


Figure 2. Mean (\pm SD) Areas of Maximal Pain and Allodynia in the Three Study Groups.

Solid circles denote the methylprednisolone-lidocaine group (89 patients), squares the lidocaine-only group (91), and open circles the control group (90). Asterisks indicate statistically significant differences from the areas in the other groups at the same time points ($P < 0.001$).

tients who received it. Furthermore, the pain relief in these patients lasted throughout the two years of follow-up and was not associated with any adverse effects. The effectiveness of methylprednisolone in providing analgesia was also evidenced by a marked decrease in the need for diclofenac in the patients in this group. Our study population was restricted to patients with long-lasting pain that was resistant to conventional treatments, including topical agents, physiotherapy, epidural local anesthetics, and antidepressants or anticonvulsants.

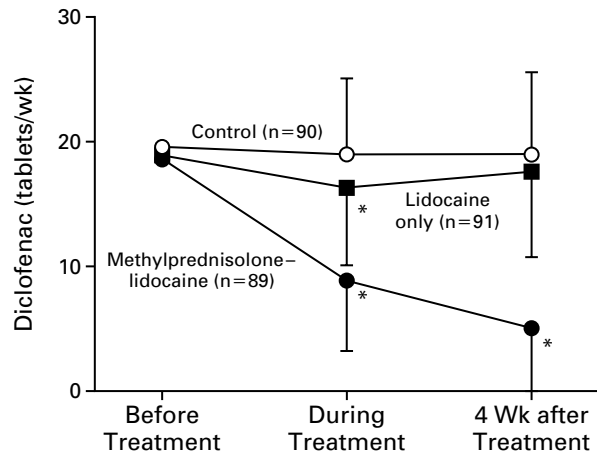


Figure 3. Mean (\pm SD) Weekly Use of Diclofenac in the Three Study Groups.

Asterisks indicate statistically significant differences from the consumption in the other groups at the same time points ($P < 0.001$).

Interleukin-8 is a potent mediator of inflammation; it is well known that high concentrations of interleukin-8 in the cerebrospinal fluid characterize spinal inflammation.^{10,11} The high concentrations of interleukin-8 we observed in the cerebrospinal fluid of our patients with postherpetic neuralgia before treatment are thus indicative of a prolonged spinal inflammatory reaction. Furthermore, the concentrations of interleukin-8 were inversely related to the duration of postherpetic neuralgia before treatment. The results of our study thus suggest that postherpetic neuralgia provokes an intense inflammatory reaction in the spinal cord and that the inflammation lasts for at least several years before gradually resolving.

The impressive pain relief that resulted from intrathecal administration of methylprednisolone is presumably mediated by the well-established antiinflammatory action of this drug. The analgesic effects of spinal corticosteroids are minimal in the absence of inflammation.¹² High interleukin-8 levels are closely related to the pain of inflammation.³⁻⁶ Studies have shown that corticosteroids inhibit the activity of interleukin-8.^{10,13} That an antiinflammatory action is the mechanism of analgesia is thus supported by the observation in our study of a methylprednisolone-induced decrease in the interleukin-8 concentration in the cerebrospinal fluid and by the finding that the decrease was significantly correlated with the degree of pain relief. Such a mechanism is also evidenced by a previous report of only poor or fair pain relief in patients who received conventional treatments for more than five years after the onset of symptoms, because it is unlikely that a massive inflammatory response persisted for more than five years.⁸

Other mechanisms by which intrathecal methylprednisolone might provide analgesia cannot be ruled out on the basis of our current data. The concentration of interleukin-8 in the cerebrospinal fluid increases during injury of the central nerve fibers from noninflammatory causes (such as stroke).^{14,15} Intrathecal methylprednisolone might also have facilitated the repair of nerve tissue by suppressing edema and cytotoxic responses. It is plausible that corticosteroids stabilize neural-cell membranes and suppress ectopic discharges of C fibers.^{16,17} Johansson and Bennett¹⁸ found in a rat model that allodynia due to sciatic mononeuropathy decreased after the administration of corticosteroids. Allodynia is due in part to increased excitation of injured C fibers. The authors thus speculated that the allodynia was eliminated because corticosteroids attenuate peripheral C-fiber activity, thereby suppressing hyperexcitability of the central nervous system.¹⁹

In our preliminary study, we used epidural corticosteroids in patients whose postherpetic neuralgia was located in the midthoracic area or lower. In the current study, we also included patients whose postherpetic neuralgia was located in the upper thoracic and cervical regions. Although we injected the corticosteroid solution into the lumbar intrathecal space, the solution was hyperbaric and spread in a cephalad direction, to the upper thoracic canal, when the operating table was tilted in a head-down position. With this technique, the degree of analgesia produced was consistent, no matter where in a given patient the postherpetic neuralgia was located, and the risks associated with cervical or thoracic intrathecal injection were avoided. An additional advantage of this approach is that we did not need to manipulate the thoracic spinal cord, which is the area in which adhesive arachnoiditis — the most serious complication of intrathecal administration of corticosteroids — is likely to develop.²⁰

Intrathecal administration of methylprednisolone produces excellent analgesia in a variety of pain-related disorders.^{12,21} This method of treatment was largely abandoned after Nelson and coworkers^{20,22,23} and others reported serious neurologic complications, including adhesive arachnoiditis and meningitis.²⁴⁻²⁶ However, these conditions were generally observed in patients receiving this treatment for multiple sclerosis.^{20,22-24} Adhesive arachnoiditis after the intrathecal administration of methylprednisolone is rare in patients with other conditions, and the percentage of patients in whom this complication occurred was not reported. Wilkinson²⁴ emphasized the possible neurotoxicity of multiple doses of intrathecal methylprednisolone. We used a maximum of four doses, regardless of the intensity of pain.

Methylprednisolone acetate has been found to be the least neurotoxic corticosteroid in both animals²⁷ and humans.²⁸ In fact, repeated intrathecal adminis-

tration of methylprednisolone in a study in animals failed to provoke neurotoxic effects.²⁹ Potential deleterious effects of methylprednisolone acetate may be related to the propylene glycol that is used as a preservative (29 mg per milliliter of drug). However, preservative-free methylprednisolone succinate can also produce serious neurotoxic effects.^{27,28} Direct injection of 100 percent propylene glycol into nerves induced nerve degeneration³⁰; however, this result does not apply to clinical situations in which direct injections into nerves are not used and it was obtained with propylene glycol concentrations 30 times as high as that in our solution. Even local anesthetics that are used clinically have considerable neurotoxic effects when injected into nerves at high concentrations.³¹ In our study we observed no clinical complications or abnormal findings on magnetic resonance imaging in the patients who received methylprednisolone, and we did not detect the pleocytosis and proteinosis that usually precede adhesive arachnoiditis.^{32,33}

The use of intrathecal methylprednisolone should be based on a careful assessment of the risk–benefit ratio. However, spontaneous remission of intractable postherpetic neuralgia is rare and would have been especially unusual in our patients, who had severe pain that had lasted more than a year and that had not been relieved by any conventional treatments. It therefore seems likely that the benefits of intrathecal methylprednisolone outweigh the risks of adhesive arachnoiditis in patients with postherpetic neuralgia — at least until the advent of alternative treatments that provide equally good long-term analgesia.

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