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The effect of intrathecal baclofen single injection on neuropathic pain

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Background: Baclofen is a gamma-aminobutyric acid B-receptor agonist, which is usually used for patients with spasticity or patients with nerve injury inducing both spasticity and neuropathic pain. Both oral administration and intrathecal injection via a continuous infusion pump are common treatment methods. The aim of this study was to evaluate the effectiveness of a series of three individual injections of intrathecal baclofen for neuropathic pain without spasticity.
Methods: Thirty-one patients with neuropathic pain were treated with a series of three monthly individual injections of intrathecal baclofen without pump implantation A dose of 50 μg of baclofen was used. 10-cm visual analog scale (VAS) scores of spontaneous pain, allodynia, and hyperalgesia were recorded a week after each injection. Vital signs were monitored to detect any hemodynamic changes, and a myelogram was performed to detect any undesirable cerebrospinal fluid leakage. All patients were hospitalized for at least one day following each injection for close observation and to control any adverse effects.
Results: VAS scores of spontaneous pain, allodynia, and hyperalgesia decreased significantly ($P < 0.001$). The major complications were general weakness, sleepiness, and urinary retention; most of these resolved within one day without any further serious symptoms.
Conclusions: A series of three individual intrathecal baclofen injections was effective for those patients who suffered from neuropathic pain without spasticity or dystonia; no serious complications were observed. However, the average satisfaction score recorded for spontaneous pain was lower than those for allodynia and hyperalgesia. **(Anesth Pain Med 2016; 11: 399-403)**

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Key Words: Allodynia, Baclofen, Hyperalgesia, Intrathecal injection, Spontaneous pain.

INTRODUCTION

Definitive therapy is needed for the treatment of neuropathic pain. It is important to know the specific medical history of neuropathic pain in the patient and to distinguish between neuropathic pain and nociceptive pain. Effective treatment protocols for neuropathic pain have not yet been established; more than two-thirds of patients are still suffering despite many different suggested treatments, such as: antidepressants, antiepileptic medications, opioids, and peripheral nerve stimulation. This poor response is probably due to as-yet undiscovered mechanisms of pain transmission as well as a failure to target definite pain-generating mechanisms [2].

Baclofen, a gamma-aminobutyric acid B ($GABA_B$) receptor agonist, is known as an effective drug for treating severe dystonia and spasticity. It is also a powerful muscle relaxant. Baclofen is known as an effective pain controller for neuropathic pain accompanied by dystonia or spasticity. However, there has been no clinical study to date that proves the efficacy of intrathecal baclofen (ITB) injections on neuropathic pain without dystonia or spasticity [3].

ITB injection is one of the treatments for severe spasticity; it is usually performed as a continuous infusion via a catheter, with an infusion pump implanted on the lower abdomen. Implantation of such a machine can potentially cause a number of complications, such as infection, pain, mechanical dysfunction, or other malfunction of the pump necessitating repeat surgery. Patients are usually required to undergo either general anesthesia or local anesthesia for pump implantation [4,5].

A study of the effectiveness of an individual ITB injection for induced neuropathic pain in rats reported successful pharmacological suppression of GABA-provoked symptoms

such as tactile allodynia and hyperalgesia [6].

Both ITB injection alone and ITB injection with spinal cord stimulation have been reported to show varied responses even in patients presenting with similar symptoms [7]. Some of the patients who visited our clinic previously received treatment with oral baclofen, but none of them reported satisfactory results. In general, at least 30% pain reduction is considered to be clinically significant [8].

The purpose of this study was to examine the efficacy of a series of three individual ITB injections for neuropathic pain without spasticity or dystonia. The chief goal was to avoid the possible complications resulting from continuous infusion and to minimize the financial difficulties of pump implantation for patients.

MATERIALS AND METHODS

Thirty-one patients (13 male and 18 female, age range: 31–74 years) who were treated with ITB for neuropathic pain were studied retrospectively, after Institutional Review Board approval. Every patient had all three of the following symptoms: spontaneous pain, allodynia and hyperalgesia (Table 1).

ITB injections were only administered to those patients who met the departmental requirements. The inclusion criteria for this study of ITB therapy included a previous traumatic event or disease that might have caused a nerve injury; examples include: a car accident, fall, amputation, surgery, tumor, surgery for a fracture, herpes and diabetes mellitus. Exclusion criteria were as follows: 1) pediatric patients 2) allergy to baclofen 3) pregnancy 4) cerebral disease 5) depressive disorder 6) coagulopathy 7) infection or other spinal lesions 8) patients who could not cooperate in ITB administration. Most of the patients who were involved in this clinical research study had a history of multiple fractures with multiple surgeries.

To ensure the patients' safety, 6 h of NPO (*nil per os*; withholding oral intake of food and fluids) was required. electrocardiograph, pulse oximetry, and blood pressure were monitored during the procedure. The procedure was carried out in the lateral decubitus position using a 25 G spinal needle at the L3–4 level. Baclofen was injected only once the free flow of cerebrospinal fluid was observed.

Table 1. Demographic Data

Sex (M/F)	13/18
Age (yr)	55.4 ± 11.7
Weight (kg)	63.0 ± 11.0
Height (cm)	163.9 ± 9.1

Values are mean ± SD or number.

There is no standard protocol suggesting the dosage or frequency of an individual injection of ITB. However, many studies of continuous ITB administration started their test dose with a bolus of 50–100 μg with 5 ml of normal saline. Therefore, it was decided to use a dose of 50 μg of baclofen (Lioresal® Novartis Pharma Stein AG, Switzerland) in this study. This injection was repeated once each month for three months. A 10-cm visual analog scale (VAS) was used to evaluate the pain severity of spontaneous pain, allodynia and hyperalgesia. The pin prick test was used for hyperalgesia and the brush test using a cotton bud for allodynia. Spontaneous pain was evaluated based on the patient's normal daily life. The VAS score of each symptom was recorded before the first treatment, one week after each injection and one month after each injection. Patients were hospitalized for at least one day following each of the three injections for close observation and to control any adverse effects.

Statistical analysis was performed using the Statistical Package for Social Sciences software version 18.0 (SPSS Inc., USA). A paired *t*-test was performed, with a $P < 0.001$ considered to be statistically significant.

RESULTS

Thirty-one patients were treated with an individual ITB injection once a month for 3 months. The VAS scores of spontaneous pain decreased significantly subsequent to each injection ($P < 0.001$) (Fig. 1). For allodynia and hyperalgesia, the VAS score also decreased significantly ($P < 0.001$) (Figs. 2 and 3). In most of patients, a 30% pain reduction was reported both in allodynia and hyperalgesia. However, the reduction in spontaneous pain was not clinically significant (in other words, the level of a 30% reduction in pain was not reached).

There was no significant difference in the VAS scores between patients with pain in their upper extremities and those with pain in their lower extremities after the treatment.

Many adverse effects were seen after the injections (Fig. 4); however, none of the adverse effects was life threatening. The most common adverse effect was urinary dysfunction (74.2%) followed by fatigue (64.5%). Among the 5 patients who needed a Foley catheter, two of the patients requested the insertion of a Foley catheter due to the absence of a bedside

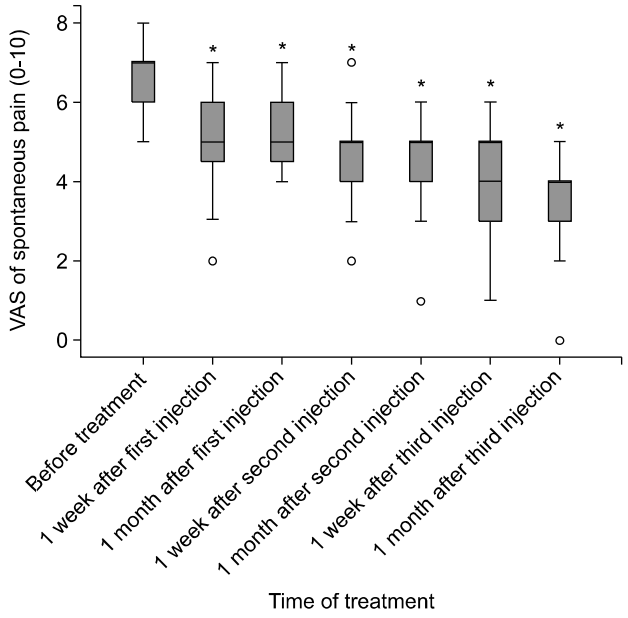

Fig. 1. Visual analog scale scores (VAS) of spontaneous pain before the treatment and each treatment. The box plot shows a statistically significant decrease of the VAS scores for each treatment. *P < 0.001 compared with initiation of treatment. VAS: visual analog scale.

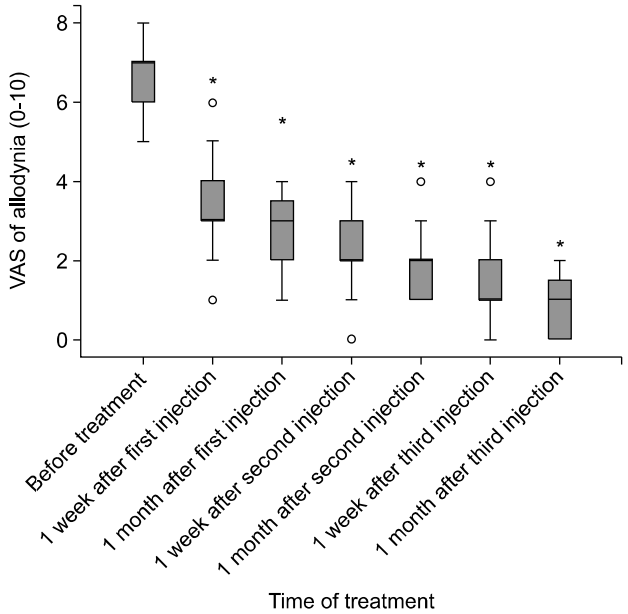

Fig. 2. Visual analog scale scores (VAS) of allodynia pain before the treatment and each treatment. The box plot shows a statistically significant decrease of the VAS scores for each treatment. *P < 0.001 compared with initiation of treatment. VAS: visual analog scale.

companion or nurse throughout the night. Therefore, the actual percentage of patients who required a Foley catheter due to voiding difficulty was 9.6%. Dizziness, sleepiness, nausea,

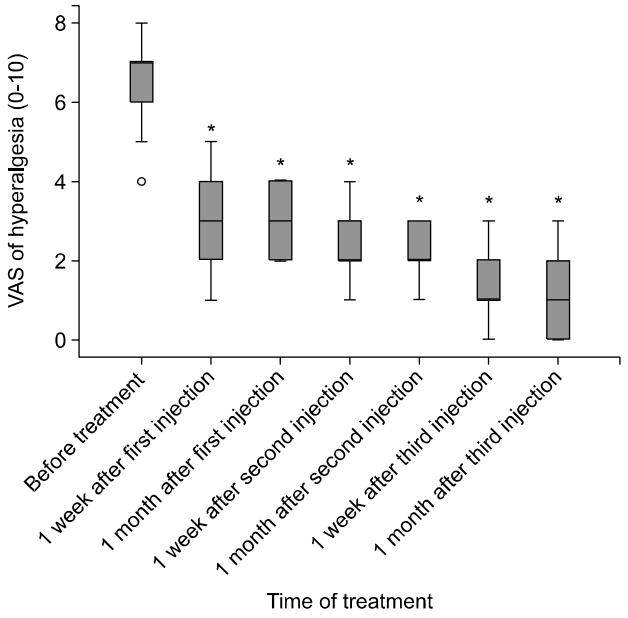

Fig. 3. Visual analog scale scores (VAS) of hyperalgesia before the treatment and each treatment. The box plot shows a statistically significant decrease of the VAS scores for each treatment. *P < 0.001 compared with initiation of treatment. VAS: visual analog scale.

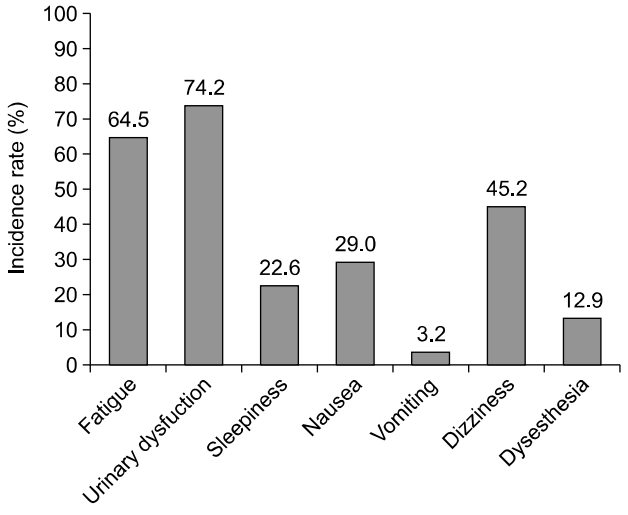

Fig. 4. The bar chart shows the incidence of adverse effects in percentages.

vomiting, dysesthesia were also reported. For fatigue, sleepiness, and dysesthesia, no special treatment was required. An antiemetic was given for those who suffered from nausea and vomiting. Most of the adverse effects disappeared within 24 h and none of them lasted more than 48 hours. No patients suffered from post-dural puncture headache (PDPH) or any other complications such as hematoma or infection.

DISCUSSION

One hypothesis of the cause of neuropathic pain is the loss of activity of the inhibitory neurotransmitter GABA in the spinal cord. There is evidence that endogenous GABA concentrations may be reduced after peripheral nerve injury. Loss of GABA-like immune-reactivity has been reported after the injury of the sciatic nerve [9].

Baclofen is a widely used agent for treating spasticity which binds to the inhibitory GABAB receptor [10].

In patients with spasticity who are treated with baclofen, the first effects occurred within 1–2 h, maximal effect was measured after 4–6 h, and the total effect lasted 6–16 h after ITB bolus administration [11]. In this study, most patients started to feel relief of their symptoms 2–6 h after the injection although some patients only reported relief after 12 h.

A high concentration of baclofen was maintained in the spinal fluid after the ITB bolus injection. Most of the baclofen initially remained in the region of the injection site during the slow, continuous infusion of ITB [11]. The slow speed of injection reduced the initial distribution of baclofen along the spinal canal [12]. Biotransformation of baclofen is low and the drug is predominantly excreted unchanged by the kidneys [13].

High oral doses (60–100 mg/day) are necessary to achieve a therapeutic effect and adequate concentration, because there is a limit of uptake of baclofen across the blood-brain barrier. It often causes such side effects as drowsiness and sleepiness when taken orally [14]. Baclofen causes few other complications at oral doses of less than 1,000 μg, but urinary retention, constipation, and hypotonia have been reported [3]. The impaired bladder function probably resulted from the depressant effects of baclofen on the spinal nerves which control urination [15]. PDPH, infection, occlusion, disconnection, and breakage of the catheter have been reported in approximately 25% of patients who used a continuous pump infusion system [3]. Although a Foley catheter is unpleasant for most patients, the routine use of a Foley catheter should nevertheless be considered because many patients exhibited urinary discomfort after the treatment, and they were required to remain in bed. Among the adverse effects that were seen in this study, a few symptoms can be prevented before they occur. For instance, nausea and vomiting can be prevented by anti-emetics; Foley catheters can be inserted to relieve urinary discomfort for all patients for a short time unless it is painful.

Discontinuation of baclofen can be associated with a withdrawal syndrome which is similar to benzodiazepine and alcohol withdrawal. Withdrawal symptoms are more likely to happen if baclofen is used via continuous infusion for more than two months, and can occur with both low and high doses. To minimize withdrawal symptoms, the drug should be discontinued gradually. Acute withdrawal symptoms can be stopped by the restart of baclofen treatment. Withdrawal symptoms include hallucinations, change of mental consciousness, agitation, delirium, insomnia, dizziness, nausea/vomiting, memory impairment, pruritus/itching, anxiety, mood disturbances, restlessness, behavioral disturbances, seizures, tremors, hyperpyrexia, and rebound spasticity [16]. However, although the treatment and study of neuropathic pain is still an ongoing process in our clinic, to date no patients have reported any withdrawal symptoms, nor have any developed a tolerance to baclofen.

Since there is no standard protocol suggesting how often to administer an individual injection of ITB, we injected all the patients once each month for three months with the same dosage. For most of the patients, the decreased VAS remained the same until the next treatment. However, a few patients visited the clinic earlier than we expected due to a recurrence of their pain. Some questions remain open. It is not clear how long the effect of an individual ITB injection could last if the patients were not injected every month. Further study is needed to evaluate the correlation between the dosage of baclofen and the length of time of symptom relief.

Statistically, baclofen was effective for all symptoms (P value < 0.001). However, less than 30% pain reduction was reported for spontaneous pain for many patients, and therefore this finding lacks clinical significance. Some patients were satisfied with this treatment although their VAS of spontaneous pain did not decrease much. We have not yet been able to explain the mechanism of this difference between the symptoms. Nevertheless, ITB injections were effective for reducing evoked pain symptoms and an improvement in the quality of life according to the patient assessments.

There were some limitations to this study. The age, sex and past medical history of the patients were not controlled for, nor were the length of time since the symptoms began or their severity. These factors should be studied in order to develop a precise therapeutic protocol.

In conclusion, a series of three individual ITB injections was effective in controlling certain pain symptoms in patients suffering from spontaneous pain, allodynia and hyperalgesia who participated in this study. Although some adverse effects

were seen during the treatment, none of the complications was serious. Urinary dysfunction should be given special consideration, however, although it was not considered to be a serious complication, since its incidence was comparably higher than other adverse effects. Further study is needed to determine the optimal dosage of baclofen to minimize adverse effects and maximize the benefits. The quality of life of our patients whose symptoms were reduced by the injection showed remarkable improvement.

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