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Efficacy of Combination Therapy With Pregabalin in Addition to NSAIDs in the Treatment of Chronic Low-Back Pain

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The efficacy and safety of the association of non-steroidal anti-inflammatory drugs (NSAIDs) and pregabalin (commonly used to control neuropathic pain), compared with the monotherapy of each, were evaluated for the treatment of chronic low back pain (CLBP), a condition known to be due to neuropathic as well as nociceptive pain mechanisms.

In the present prospective study, 71 patients received three consecutive 16-week treatment regimes, randomly assigned: NSAIDs only, pregabalin only, and NSAIDs plus pregabalin. All patients were assessed by using a visual analogue scale (VAS, 0-100 mm). The present study demonstrated that, in the patients with CLBP treated by combination therapy of pregabalin in addition to NSAIDs, the mean VAS reduction ratio was dramatically decreased compared with each monotherapy at 8, 12, and 16 weeks. That combination therapy was effective in reducing CLBP. As regards the adverse effects of each therapy, the frequency of dizziness was higher in the patients treated with pregabalin only and with the combination treatment with NSAIDs plus pregabalin. Gastrointestinal adverse effects were recognized in the NSAID treatment group, although there was not a significant difference and such adverse effects were not recognized in Group B and Group C.

In conclusion, it was demonstrated that combination therapy is more effective than monotherapy for CLBP, although the adverse effects of pregabalin, mainly dizziness and headache, need to be paid attention to.

Key words: Pregabalin, NSAIDs, Chronic low back pain, Neuropathic, Nociceptive

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INTRODUCTION

Low back pain is the most common reason for all physician visits in Japan [1, 2]. Many patients have several episodes of acute low back pain and do not seek medical care [3]. Among those who do seek medical care, pain, disability, and ability to return to work typically improve rapidly in the first month [4]. However, up to one-third of patients report persistent back pain of at least moderate intensity 1 year after an acute episode [5, 6].

Successful treatment of pain depends on the identification of the involved mechanism and use of appropriate therapeutic approaches. Woolf et al. [7] proposed that pain symptoms and syndromes should be classified into two broad mechanism-based pain categories: tissue-injury pain (nociceptive) or nervous-system-injury pain (neuropathic). CLBP has been shown to be the result of neuropathic as well as nociceptive pain mechanisms [8-11]. Based on this evidence, it has been suggested that antidepressants and/or anticonvulsants in combination with opioids, traditional nonsteroidal anti-inflammatory drugs, or muscle relaxants could be useful in the treatment of this condition [11-13].

Even if there is an increasing knowledge that different mechanisms of pain require appropriate treatments and often polypharmacotherapy and although drug combination is frequently empirically adopted in clinical practice, prospective studies concerning the relative efficacy and safety of polypharmacotherapy compared with monotherapy are still relatively few [14-20].

Among the commonly used agents to control neuropathic pain, pregabalin, which has been validated in different clinical settings, has been frequently used for patients with CLBP [14-16]. To the patients with several pain benefit from NSAIDs, which are commonly used for orthopedic diseases. Among NSAIDs, celecoxib or meloxicam are selec-

tive COX-2 inhibitors that have been shown to be effective in the treatment of different pain models that are considered to be predominantly of nociceptive origin; in addition, COX-2 inhibitors have been shown to have fewer digestive symptoms than other NSAIDs and are thus easy to administer to patients with CLBP with a lower probability of such side effects [21, 22].

The main purpose of the present examination is to compare the safety and efficacy of the association of NSAIDs, including the selective COX 2 inhibitor and pregabalin, with the monotherapy of each for the treatment of CLBP in a mixed population of patients with CLBP prospectively and then to interpret the clinical significance of the combination therapy of those drugs.

METHOD

Patients who complained of CLBP at the Nagami Clinic from July 2009 to July 2011 were invited to participate in this study. A total of 71 patients, 27 male and 44 female, completed the study. The mean age of the enrolled patients was 68.8.±6.9 years. At the beginning of this study, the objective was explained to the patients and their families, and informed consent was obtained. Furthermore, adequate care was taken to protect the privacy of the individuals participating in the study. Each patient was informed that the clinical data from the study would not be used for any purpose other than for the present study.

In the present study, the criteria were defined by Nagami Clinic as follows: Chronic low back pain (symptoms duration: >6 months) due to disc prolapse, lumbar spondylosis, and/or spinal stenosis;

1) Minimum VAS at recruitment of each patient was >40 mm;
2) Age: >50 years old, <85 years old.

Furthermore, patients were excluded from the studies if they had CLBP that was either neurological in etiology, due to recent major trauma, or due to a visceral disorder (< 6 months). Patients were also excluded if they had a history of any of the following: rheumatoid arthritis; spondyloarthropathy; spinal stenosis (associated with neurological impairment); malignancy; fibromyalgia; tumors or infections of the brain, spinal cord, or peripheral nerves; or a herniated disc associated with neurological impairment within the past 2 years. Additional exclusion criteria included patients who had had surgical intervention for CLBP or multiple spinal surgeries within 6 months prior to consideration for the present study; or active esophageal, gastric, or duodenal ulceration or bleeding within 3 months prior to the first dose of study medication. The patients who had several internal complications, such as diabetes mellitus, neurological disease, cardiovascular disease, and chronic kidney disease, were excluded from the present study. Prospective examinations were performed at the Nagami Clinic from July 2009 to July 2011, and we compared the efficacy and tolerability of the combination of anti-inflammatory drugs, NSAIDs, and the antineuropathic drug, pregabalin, to either NSAIDs or pregabalin for the treatment of CLBP as a result of prolapsed disc, lumbar spondylosis, and spinal stenosis.

Assessment

Primary outcomes were assessed by pain reduction following different treatment regimes. Secondary outcomes were assessed by the adverse effects due to the treatments under study. Safety was assessed by the monitoring of treatment emergent adverse events (AEs), serious AEs (SAEs), safety laboratory tests, concomitant medications, physical examinations, and discontinuations. Discontinuations due to specific AEs of GI or central nervous system (CNS) origin, commonly associated with NSAIDs and pregabalin treatment, were defined as permanent withdrawal due to lack of tolerability. They included abdominal pain, dyspepsia, nausea, vomiting, somnolence, dizziness, and vertigo. All observed or volunteered adverse effects were recorded regardless of the treatment group or suspected causality. The visual analogue scale was evaluated at patient recruitment and after an 8-, 12-, and 16-week treatment period of the enrolled patients (Fig. 1).

Treatment regime

After a discontinuation period of at least 10 days from any previous analgesic treatment and between treatments, each patient received the following three consecutive treatments regimes in the present study.

Three groups were divided by the used drugs (Table 1). The protocol of the present study is illustrated in Table 1.

1) NSAIDs only: Group A (n=24)

In this group, only one of three NSAID drugs (celecoxib, meloxicam, and loxoprofen sodium hydrate) was administered to the patients with CLBP. Details of the drugs are shown in Table 1.

2) Pregabalin only: Group B (n=22) (approximately 1 mg/kg/day in the first week and then approximately 1.5-2mg/kg/day).

3) NSAIDs plus pregabalin: Group C (n=25) (approximately 1 mg/kg/day in the first week and then 1.5-2mg/kg/day).

In this group, only one of the three NSAID

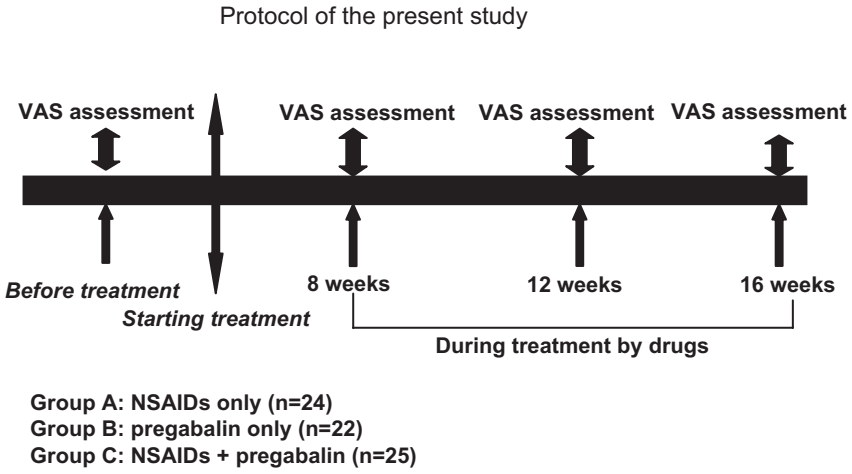

Fig. 1. The protocol of the present study is showed. VAS assessment was performed in the three groups at baseline, 8, 12, 16 weeks after treatment

Table 1. Charcteristics of the three groups
(sex, disease caused CLBP, and variety of used treatment drugs for CLBP

★Group A (n=24)	sex	male : female 8 : 16
	disease	lumbar disc herniation 9 cases
		lumbar spinal canal stenosis 8cases
		lumbar spondylosis 6cases
	Used NSAIDs drugs	
		☆celecoxib :14 cases ☆melxicam : 5cases
		☆ loxoprofen sodium hydrate : 5cases
★Group B (n=22)	sex	male : female 11 : 11
	disease	lumbar disc herniation 12 cases
		lumbar spinal cal stenosis 6cases
	Used drugs	lumbar spondylosis 4cases
		☆pregabalin only
★Group C (n=25)	sex	male : female 8 : 17
	disease	lumbar disc herniation 13cases
		lumbar spinal canal stenosis 7cases
		lumbar spondylosis 5cases
	Used NSAIDs drugs in addition to pregabalin	
		☆celecoxib : 12cases ☆meloxicam :5cases
		☆loxoprofen sodium hydrate : 8cases

drugs (celecoxib, meloxicam, and loxoprofen sodium hydrate) in addition to pregabalin was administered to the patients with CLBP. The details of the drugs are shown in Table 1.

Each treatment lasted 16 weeks. The sequence of treatments for each patient was randomly assigned as follows based on consecutive recruitment order: the first patient received only one of the three NSAIDs; the second patient received pregabalin only, and the third patient received only one of the three NSAIDs + pregabalin. Concomitant use of antidepressants and/or anticonvulsants, opioids, or muscle relaxants was not permitted during the 16-week study.

Statistical analysis

Descriptive statistics were determined by calculation of the mean and standard deviation (±SD). Statistical analysis was performed with the Student's *t* test.

Results throughout the text, tables, and figures are presented as the mean ± SD, and statistical significance was defined as $P < 0.05$.

RESULTS

Of the 71 patients initially recruited for the study, none discontinued the treatment.

However, two experienced upper gastrointestinal distress within the first two weeks of enrollment. Twenty two patients (10 taking pregabalin alone and 12 taking pregabalin + NSAIDs) suffered from the adverse effect of reported dizziness and headache characteristic of pregabalin within the first 2 weeks, but they did not give up the study. All data presented refers to the 71 patients who completed this study and were available for follow-up.

Figures 2, 3, and 4 are summaries of the mean ± standard deviation of the recorded VAS immediately prior to the beginning of each treatment regime and after the 8-, 12-, and 16-week treatment periods for groups A, B, and C. With regard to the baseline VAS, the mean values in the three groups were almost identical without significantly different values. According to the statistical analysis of data, also provided in the same table, NSAIDs alone and pregabalin alone did produce a statistically significant reduction of reported pain. In Groups A and B, the VAS scale gradually decreased from the baseline value in accordance with the period of drug administration over 16 weeks. Furthermore, the VAS scale of the combination therapy with NSAIDs plus pregabaline dramatically decreased compared with the baseline value, shown in Fig. 4. Furthermore, in evaluating the mean value of the VAS scale after treatment at 8, 12, and 16 weeks, that of Group C was significantly lower than that of the other two groups, and that of Group B was significantly lower than that of Group A. The data clearly demonstrated that the mean value of the VAS scale in each

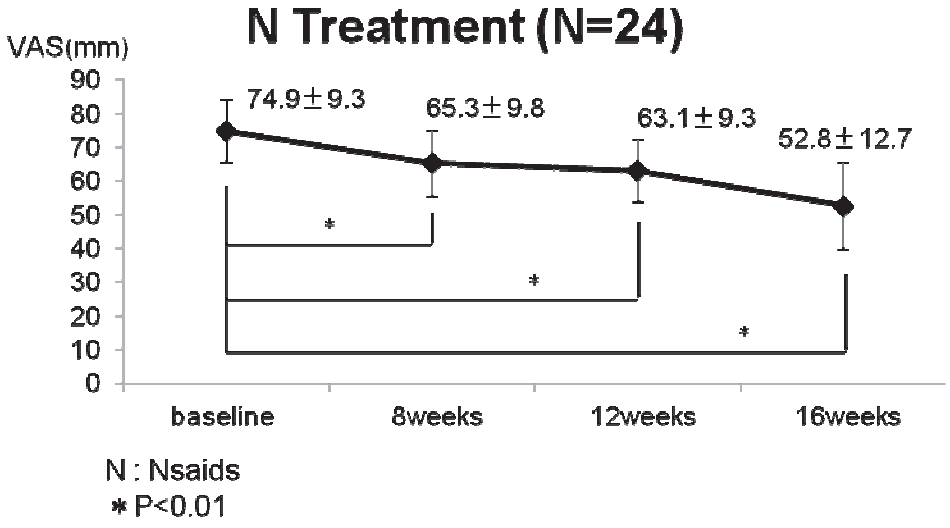

Fig. 2. Changes of VAS at baseline, 8, 12, 16 weeks in the Group A

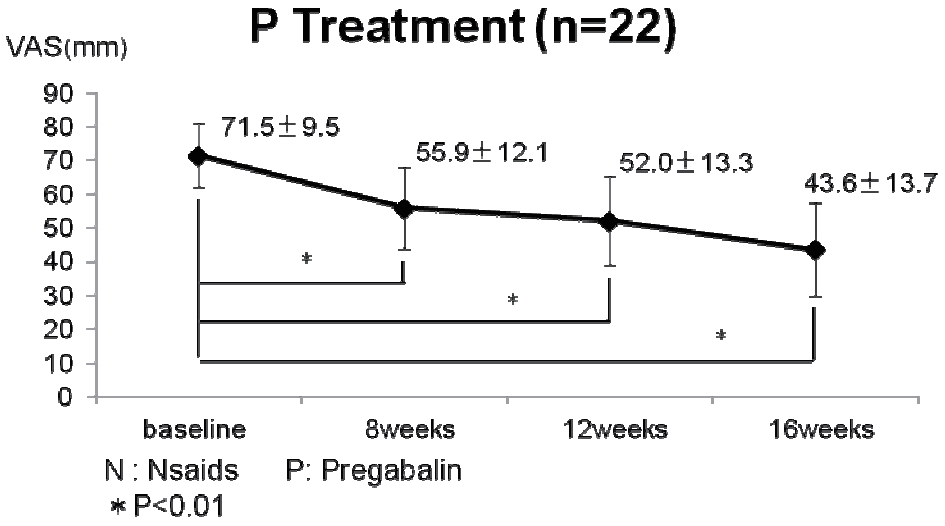

Fig. 3. Changes of VAS at baseline, 8, 12, 16 weeks in the Group B

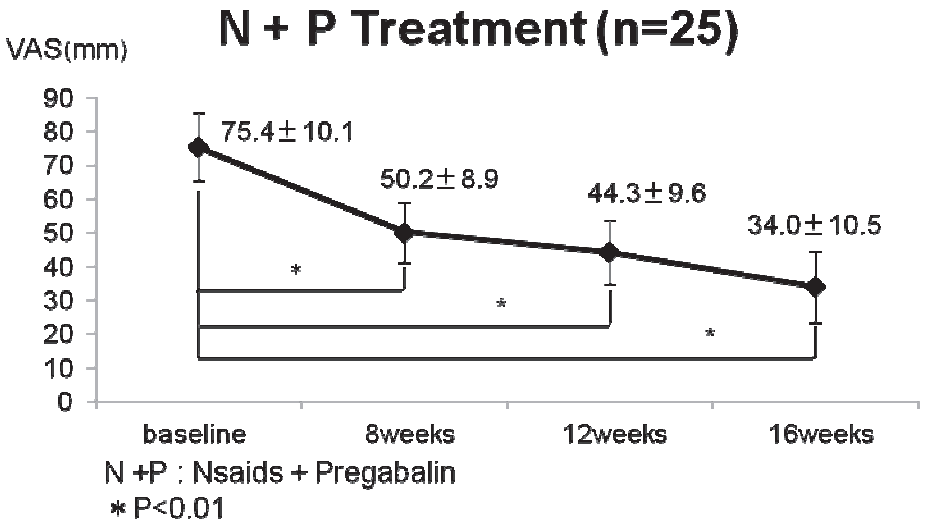

Fig. 4. Changes of VAS at baseline, 8, 12, 16 weeks in the Group C

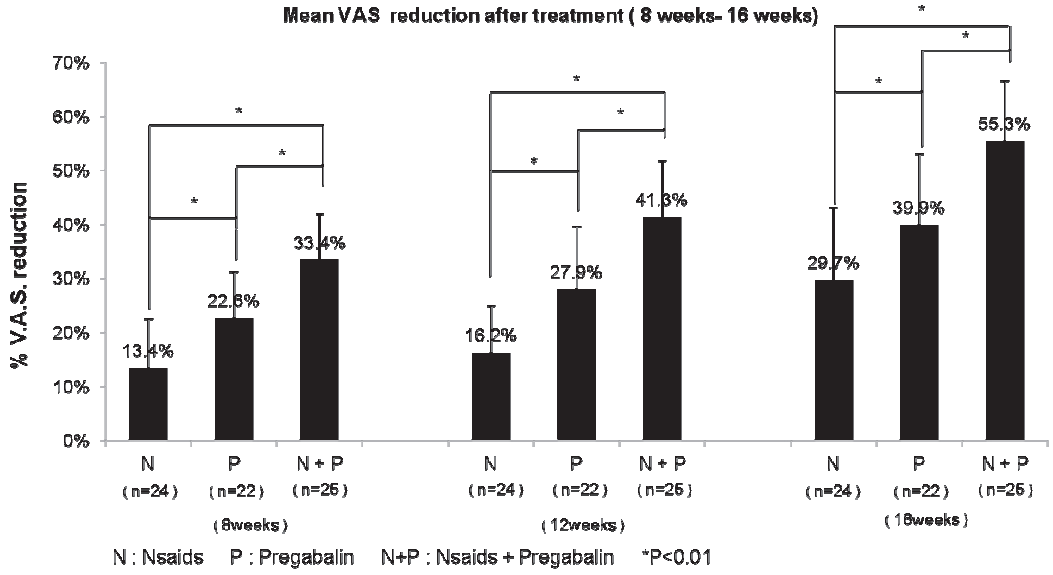

Fig. 5. Mean VAS reduction percentage after treatment in the three groups at baseline, 8, 12, 16 weeks in comparison with baseline value

Group increased in accordance with the treatment period. Among them, the tendency was prominent in Group C, which was treated by NSAIDs plus pregabalin (Fig 5).

Drug consumption

The dosage of each drug was established at the beginning of each treatment period on the basis of the weight of each patient; however, it could have been modified during the treatment course according to the pain level and side-effects reported by the patients. The overall drug consumption of each patient was tracked. In Group A, the standard dosage of NSAIDs was administered to each patient. On the other hand, the daily dosage of pregabalin in Group B was 2.26± 0.69 mg/kg, and the daily dosage of pregabalin in Group C was 2.35± 0.64 mg/kg. There was not a significant difference between the dosage of pregabalin between Groups B and C.

Adverse effects

Of the 71 patients, side-effects were recorded in 2 patients in Group A, 12 in Group B, and 19 in Group C. A total of 33 patients (46.6%) had adverse reactions to the drugs. However, discontinuation of the treatment was not necessary. Two patients in Group A had epigastralgia and nausea during therapy. Eight patients in Group B complained of dizziness, and two complained of headache. Furthermore, nine patients in Group C complained of dizziness, and three patients complained of headache. No other serious adverse effects were observed in the Group C patients (Table 2).

DISCUSSION

Neuropathic pain is caused by somatosensory injury or disease [1]. Of the pain-related diseases, the severity of neuropathic pain is particularly high, and its duration is long. Neuropathic pain also substantially reduces the quality of life (QOL) [2, 3]. The prevalence of neuropathic pain in developed countries is estimated to be from 1% to 7% [2, 4]. Neuropathic pain is associated with a variety of diseases, but many patients with neuropathic pain

Table 2. Adverse effects by administered drugs in the three groups

Adverse event preferred term	Group A (NSAIDs only : n=24)	Group B (pregabalin only : n=22)	Group C (NSAIDs+Pregabalin : n=25)
Dizziness	0	8 (36.4%)	9 (36.0%)
Somnolence	0	0	2 (8.0%)
Peripheral edema	0	0	0
Headache	0	2 (9.1%)	3 (12.0%)
Amblyopia	0	0	0
Ataxia	0	1 (4.6%)	1 (4.0%)
Confusion	0	1 (4.6%)	0
Neuropathy	0	0	1 (4.0%)
epigastralgia	1 (4.2%)	0	0
nausea or vomiting	1 (4.2%)	0	0
G-I treat bleeding	0	0	0
Diarrhea	0	0	0
Constipation	0	0	1 (4.0%)
Dry mouth	0	0	0
palpitation	0	0	0
general fatigue	0	0	0
appetite loss	0	0	0
chest pain	0	0	0
Total	2 (8.3%)	12 (54.6%)	19(76.0%)

GERD : Gastroesophageal reflux disease NERD : Nonerosive reflux disease G-I : gastro-intestinal

Values are n (%)

Adverse effects of all treatment cases

experience pain of a characteristic quality and have commonalities in their disease states. A diagnosis of neuropathic pain is made for patients with pain when the range of pain is neuroanatomically plausible, symptoms suggesting somatosensory injury or neurological disease are present, and relevant physical findings or imaging findings suggest nervous system injury or disease [7].

Although blanket recommendations cannot be practically made about the diverse pain-related diseases included under the scope of neuropathic pain and the various treatments available for these diseases, pharmacologic therapies can be used as initial treatments for neuropathic pain as a whole. Despite the growing body of knowledge about the many drugs used to treat neuropathic pain, it often must be treated in combination with other drugs because the response to the existing drugs is often inadequate. Furthermore, efficacy cannot be consistently predicted even for established drug treatments for neuropathic pain. Drugs, moreover, are slow to act and frequently produce adverse reactions.

CLBP is a significant health and socioeconomic problem and a leading cause of suffering, physical impairment, and cost to society. The lifetime incidence of CLBP is estimated to be as high as 85% for the adult population, and the condition is among the most common reasons for physician visits, hospital admission, and surgery [1-3]. For the majority of those who experience CLBP, prognosis for recovery is favorable, with most pain and disability being resolved within a few weeks. The persistence of symptoms is common. A high percentage of patients will experience additional episodes of CLBP within 1 year, and around 10% of individuals will develop CLBP in which pain persists for more than 12 weeks [5-6].

The precise pathogenesis is unclear in most cases of CLBP; it is estimated that only 10% of patients experience an identifiable disease, such as discogenic back pain, spondylolisthesis, fracture, tumor, infection, or rheumatological disease (e.g., ankylosing spondylitis), with the remaining 90% of back pain being designated as non-specific. In the majority of patients with CLBP, the cause is unknown but assumed to arise from muscle strain or ligamentous injury, whereas, in other patients, there may be evidence of degenerative disc or joint disease or vertebral fracture. Pure neuropathic causes are thought to account for 5-15% of CBLP and include herniated intravertebral disc and spinal stenosis [11-14].

NSAIDs are the most frequently prescribed medications worldwide and are widely used for patients with low back pain. Selective COX-2 inhibitors are currently available and used for patients with CLBP. A recently published systematic Cochrane review of randomized controlled trials has shown the efficacy of NSAIDs and COX-2 inhibitors in the treatment of nonspecific low back pain [12-14]. In 65 trials (total number of patients = 11, 237) statistically significant effects were found in favor of NSAIDs compared with the placebo but at the cost of more statistically significant side-effects. COX-2 NSAIDs had statistically significantly fewer side-effects than traditional NSAIDs [23].

Pregabalin suppresses the release of excitatory neurotransmitters on binding to the $\alpha^2\delta$ subunit of potential-dependent calcium channels in the central nervous system [13]. In clinical studies conducted outside Japan, pregabalin was shown to have an analgesic effect in postherpetic neuralgia [13-15], pain, and numbness associated with diabetic neuropathy [16, 17], phantom limb pain [18], Guillain-Barré syndrome, neuropathic cancer pain, post-spinal cord injury pain, and a variety of other diseases and conditions. In and outside Japan, pregabalin has been shown to have a significantly better analgesic effort than placebo in the treatment of postherpetic neuralgia, pain, and numbness associated with diabetic neuropathy. The drug also has a demonstrated analgesic effect in radiculopathy as well as post-spinal cord injury pain and post-stroke pain.

Pregabalin treatment is begun at 75mg/day as one dose before bed, 150mg/day as two doses after breakfast and supper, or 150mg/day as three doses after each meal. Even when renal function is normal, a very low dose is considered before bedtime, such as 25mg/day, for elderly patients, patients with low body weight, and others prone to adverse reactions.

Pregabalin has been widely studied for the treatment of neuropathic pain and was shown in prospective randomized clinical trials to be effective for postherpetic neuralgia and painful diabetic

peripheral neuropathy, with responder rates of approximately 50% [16].

Gilron et al. [16] first reported on the efficacy and safety of a combination of gabapentin and morphine compared with that of each as a single agent in patients with painful diabetic neuropathy or postherpetic neuralgia. The group from the Ospedale Tor Vergata in Rome more recently published the Multicenter Italian Study, which compared the efficacy, safety, and QOL of combination therapy with controlled-release (CR) oxycodone plus pregabalin versus monotherapy in patients with neuropathic pain [24]. This study, which included 409 patients, showed that the combination of CR oxycodone plus pregabalin and CR oxycodone monotherapy were both more effective for alleviating neuropathic pain than was pregabalin monotherapy. Other studies compared the efficacy of pregabalin or gabapentin in combination with different analgesic agents for postoperative pain [25, 26]. Gilron et al. [15] demonstrated, in a placebo-controlled randomized clinical trial on pain after abdominal hysterectomy, that perioperative administration of a combination of gabapentin and rofecoxib was significantly superior ($P < 0.05$) over monotherapy, with similar adverse effects, except sedation, which was more frequent with gabapentin alone. The association of gabapentin with celecoxib was found by Parsa and coworkers[18] to be significantly superior ($P < 0.001$) in reducing postoperative pain and opioid requirements than celecoxib alone in patients undergoing bilateral subpectoral breast augmentation.

Kaki et al. [11]applied the LANSS pain scale in a total of 1, 169 patients from 117 centers; 639 patients (54.7%) had scores of 12 points or more, which suggested neuropathic pain, and 530 patients (45.3%) had scores of less than 12, which suggested nociceptive pain. These authors concluded that neuropathic pain is a major contributor to CLBP.

In the present study, we also show that that the combination of NSAIDs and pregabalin was superior to either agent used alone, without any serious side effects that caused its discontinuation and a significant reduction of pain score represented by the VAS scale in patients with CLBP. In Group A with treatment by only one NSAID, the VAS scale was not significantly lower than other groups, although adverse effects were small. Meanwhile, in Group B with pregabalin treatment, the pain reduction was more significant than that in than Group A, but the frequency of dizziness was common and serious. In Group C, the mean value of the VAS scale was significantly lower than that with other monotherapy groups, although patients with adverse effects, such as dizziness and headache, were common. Discontinuation due to serious adverse effects by pregabalin did not occur. In Groups B and C, patients experienced considerable relief from severe CLBP, and their QOL improved. However, adverse effects, such as dizziness, were recognized in many patients in Groups B and C. This suggests that treatment with pregabalin in addition to NSAIDs was indeed effective for CLBP because the treatment regime reduced the degree of pain to one half that at the baseline, but care was given to prevent the adverse effects provoked by pregabalin. This was especially true with pregabalin, used for elderly patients with CLBP. Special attention was required because of the high frequency of CNS symptoms, such as dizziness. By using a combination therapy of NSAIDs and pregabalin in Group C, total drug consumption of pregabalin was reduced because simultaneous administration of some kinds of NSAIDs limited the daily dosage of pregabalin and eventually reduced the adverse effects caused by it in Group C.

The population of elderly people is currently increasing. As a result, the number of patients with CLBP is increasing. Therefore, the best method of pain relief is required. The present study indicates that a combination therapy with NSAIDs and pregabalin is very effective for CLBP patients, although some patients experienced dizziness.

In conclusion, CLBP often compromises both nociceptive and neuropathic components; therefore, a multimodal and individualized treatment approach is necessary. Combining drugs with different mechanisms of action represents a rational approach to the management of CLBP with both nociceptive and neuropathic components. The present study indicated that treatment with pregabalin in addition to NSAIDs resulted in a mean value of the VAS scale of about one-half of the baseline. Treatment with pregabalin and an NSAID is a valuable therapeutic

approach for long-term CLBP patients.

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