The Effect of Pregabalin and Methylcobalamin Combination on the Chronic Postthoracotomy Pain Syndrome

Serda Kanbur Metin, MD, Burhan Meydan, MD, Serdar Evman, MD, Talha Dogruyol, MD, and Volkan Baysungur, MD

Departments of Thoracic Surgery, Anesthesiology and Algology, Sureyyapasa Pulmonology and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey

Background. Chronic postthoracotomy pain (CPTP) consists of different types of pain. Some characteristics of CPTP are the same as those of recognized neuropathic pain syndromes. We aimed to determine the safety and efficacy of pregabalin and methylcobalamin combination (PG-B_{12}) in comparison with diclofenac potassium (DP) in patients with CPTP.

Methods. One hundred consecutive patients with CPTP after posterolateral/lateral thoracotomy were prospectively randomly assigned and evaluated. Fifty patients were given PG-B_{12} and another 50 patients were given DP treatment. Visual Analogue Scale (VAS) and the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scorings were performed previous to the treatment (day 0) and on the 15th, 30th, 60th, and 90th days. Adverse events were questioned.

Results. The mean ages were 58.7 ± 12.2 and 54.6 ± 14.5 years, and the mean durations of pain were 4.01 ± 1.04 and 3.8 ± 1.02 months, respectively. The number of patients with a VAS score less than 5 at the latest follow-up (VAS90 < 5) was 44 (88%) and 18 (36%) in the PG-B_{12} and DP groups, respectively ($p < 0.05$). Forty-four patients (88%) in the PG-B_{12} group and 16 patients (32%) in the DP group had a LANSS score less than 12 at the latest follow-up ($p < 0.05$). Minor adverse events that did not mandate discontinuation of the treatment were observed in 14 patients (28%) in the PG-B_{12} group and 2 patients (4%) in the DP group.

Conclusions. PB-B_{12} is safe and effective in the treatment of CPTP with minimal side effects and a high patient compliance. These results should be supported by multidisciplinary studies with larger sample sizes and longer follow-ups.

(Ann Thorac Surg 2017;103:1109–13)

Chronic postthoracotomy pain (CPTP) or postthoracotomy neuralgia is defined by the International Association for the Study of Pain as pain that recurs or persists along a thoracotomy incision for at least 2 months after the surgical procedure [1]. Usually, it is a burning, dysesthetic, and aching feeling in nature, which displays many features of neuropathic pain. It occurs in approximately 50% of patients after thoracotomy; however, in 5% of patients the pain is severe and disabling. The technique of different thoracotomy incisions has been shown to have no difference in reducing the incidence of CPTP [2, 3]. The neurologic mechanisms for the production of neuropathic pain, hyperalgesia, and somatic pain are well described [4–7]. These conditions are controlled by a variety of drugs that include nonsteroidal anti-inflammatory drugs, parenteral opiates, epidurals, and paravertebral infusions of local anesthetics, narcotics, intrapleural analgesia, transcutaneous nerve stimulation, intercostal and phrenic nerve blockades, and cryotherapy [6–12]. However, the results were variable, and no single strategy was shown to be effective in all patients.

We administered pregabalin and vitamin B_{12} combination (PG-B_{12}), an anticonvulsant and methylcobalamin, to the patients with CPTP and compared its effectiveness with diclofenac potassium (DP), a nonsteroidal anti-inflammatory drug, used in conventional pain treatment. There is only one prospective study and a case report about PG-B_{12} combination treatment in CPTP.

Patients and Methods

Study Population

One hundred consecutive patients with CPTP were included in the study. After getting approval from the institutional review board, this study was conducted in the Department of Thoracic Surgery, Sureyyapasa Pulmonology and Thoracic Surgery Training and Research Hospital, on 100 consenting patients who underwent thoracotomies. Postoperative pain that did not respond to a conventional treatment of at least 3 months' duration was accepted as chronic pain. The severity of wound pain

Accepted for publication Sept 7, 2016.

Address correspondence to Dr Metin, Sureyyapasa Pulmonology and Thoracic Surgery Training and Research Hospital, Department of Thoracic Surgery, Basibuyuk, Maltepe, 34844, Istanbul, Turkey; email: serdakanbur@gmail.com.

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2016.09.031

was determined using a 10-point Visual Analogue Scale (VAS), which usually consists of a 10-cm line anchored at one end by a label such as "no pain" and at the other end by a label such as "worst pain imaginable" or "pain as bad as can be" [13, 14]. The neuropathic pain was evaluated using the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale, which helps to distinguish nociceptive and neuropathic pain and is based on the analysis of sensory description and bedside examination of sensory dysfunction [15], simultaneously. The patients who had a history of CPTP, a VAS score of 5 or greater, and a LANSS score of 12 or greater were included in the study. At the end of the treatment, VAS score less than 5 was accepted as amelioration of wound pain, and LANSS score less than 12 was accepted as amelioration of neuropathic pain. The VAS and LANSS questionnaires were assessed by a therapy-blinded algology specialist (Dr Meydan).

The closure of the thoracotomy was standard in all patients. Ribs were closed with separate absorbable sutures surrounding upper and lower ribs. No drill holes in the ribs were used. Cryotherapy or local anesthetics were not used on intercostal nerves. No epidural catheters were placed in any of the patients.

Patients with previous ipsilateral or bilateral thoracotomy, any operation for tumor which extended into the chest wall, empyema thoracis necessitans, tumoral intercostal neural lesions, or pathologic costal fracture was not included in this study. In addition, the patients with history of analgesic addiction or abuse, epilepsy, a major psychiatric disorder, other neurologic disorders, and allergy to PG-B_{12} or DP were excluded from the study. The patients who needed other medication for pain relief and did not finish the treatment or were able to come off the therapy were also not included in the study (2 patients for inadequate pain relief in the DP group and 1 patient in both groups for satisfactory resolution).

Drug Admission Protocol

The eligible patients were randomly assigned to Group A (PG-B_{12} recipients) or Group B (DP recipients). PG-B_{12} was administered (n = 50) for 90 days with an incremental stepwise dosage protocol. The PG-B_{12} dosages were as follows: 300 mg/day PG and 1 mg/day B_{12} for the first 7 days, then 600 mg/day PG and 1 mg B_{12} until the 90th day. VAS and LANSS scorings were performed before the treatment (0) and on the 15th, 30th, 60th, and 90th days of the treatment. In Group B, patients (n = 50) were managed by giving DP 50 mg three times for the first 7 days and then, on demand, as was required by the patient. Adverse events were questioned and recorded. Patients in Group A received no pain medication other than PG-B_{12}, and patients in Group B received no medication for pain relief other than DP.

The suggested duration of therapy (3 to 6 months) in the PG-B_{12} group was determined after consulting to the algology clinic. The therapy was ended in patients whom had decreased VAS and LANSS scores and with fewer complaints due to a decrease in chronic pain or neuropathic symptoms.

Statistical Analysis

The data acquired in the study were analyzed with SPSS for Windows 22.0 (Statistical Package for Social Sciences; IBM Corp., Armonk, NY). Number, percentage, mean, and standard deviation were used as descriptive statistical methods to evaluate the data. A *t* test was used to compare the quantitative pain variables between the two independent groups. The difference between intergroup repetitive pain measurements was analyzed with matched group *t* test. The relationship between the groups and categorical variables was tested with χ^2 analysis. The findings obtained were evaluated in 95% confidence interval and 5% significance level.

Results

Patient demographic characteristics and types of operation are summarized in Table 1. Age, sex, duration of symptoms, and the number of different types of surgical procedure were homogeneous between the two groups (Table 1).

Table 1. Patient Demographic Characteristics

Variable	Pregabalin-B_{12}	Diclofenac Potassium
Age, years, mean ± SD	58.7 ± 12.2	54.6 ± 14.5
Sex, n		
Male	35	36
Female	15	14
Pain duration, months, mean ± SD	4.01 ± 1.04	3.8 ± 1.02
Diagnosis, n (%)		
Lung cancer	28 (5.6)	27 (5.4)
Hydatid cyst	5 (10)	7 (14)
Bullous lung	5 (10)	6 (12)
Pulmonary nodule	4 (8)	3 (6)
Mediastinal mass	2 (4)	3 (6)
Carcinoid	2 (4)	…
Aspergilloma	4 (8)	2 (4)
Lung abscess	…	2 (4)
Incision, n (%)		
Posterolateral	40 (80)	47 (94)
Lateral	10 (20)	3 (6)
Operation, n (%)		
Pneumonectomy	5 (10)	3 (6)
Lobectomy	31 (62%)	28 (56)
Wedge	9 (18)	11 (22)
Nonresection	5 (10)	8 (16)
Complication, n (%)		
Heartburn	1 (2)	2 (4)
Dizziness	3 (6)	0
Nausea	5 (10)	0
Sedation	5 (10)	0
No complication	36 (72)	48 (96)

The mean VAS scores before the treatment (VAS0) were 6.2 ± 1.2 and 7.0 ± 1.1 ($p > 0.05$) in the PG-B_{12} and the DP groups, respectively. VAS15, VAS30, VAS60, and VAS90 reduced significantly in both groups. However, in the PG-B_{12} group the reduction in VAS scores was more than the DP group, which was statistically significant ($p < 0.05$) (Fig 1).

The mean LANSS scores (LANSS0) were 15.92 ± 2.77 and 15.20 ± 2.56 ($p > 0.05$) in the PG-B_{12} and the DP groups, respectively. LANSS15 scores in both groups had no significant reduction. However, in the PG-B_{12} group the LANSS score had more significant reduction than the DP group after 30 days ($p = 0.04$) (Fig 2). As a result, the neuropathic (LANSS) and wound pain (VAS) scores in the PG-B_{12} group were found to be significantly better than in the DP group in our study.

Minor adverse events that did not mandate discontinuation of the treatment were observed in 14 patients (28%) in the PG-B_{12} group and 2 patients (4%) in the DP group. Adverse events in the PG-B_{12} group were nausea in 5 (10%), dizziness in 3 (6%), heartburn in 1 (2%), and sedation in 5 (10%) patients. The only adverse event observed in the DP group was heartburn in 2 patients (4%) (Table 1).

Comment

CPTP is a serious and underrated condition and may influence more than 50% of all patients undergoing thoracotomy, even 4 years after operation [8]. Absence of clinical studies to guide treatment still represents a major therapeutic challenge [7, 13–16].

The first reference to CPTP was made in 1944 by United States Army surgeons who noted chronic intercostal pain in men who had undergone thoracotomy for chest trauma during the Second World War. They identified the serious problem of chronic pain and the subsequent difficulty in getting rehabilitated and returning to duty [3].

Mechanisms for chronic pain after thoracotomy are several, and no consensus exists regarding causality. The most likely cause is intercostal nerve damage. The upper nerve is more likely to be damaged during rib spreading and the nerve below by closure [4, 5]. Incision type, tumor recurrence, genetic factors, and psychosocial factors are among the other possible causes of CPTP [17, 18]. Various thoracic incisions have been described to decrease the incidence of postoperative pain. There is little evidence that any technique is superior in reducing the development of chronic pain. Both rib spreading and rib closure is the same in all these techniques. Closure and reapproximation of the ribs may be responsible for CPTP [4, 5]. We included only the patients who had undergone posterolateral or lateral thoracotomy to our study to let the study be homogenous. Eighty-seven percent of the patients had posterolateral thoracotomy and 13% had lateral thoracotomy. The mean VAS scores of the patients with posterolateral or lateral thoracotomy were not different ($p > 0.05$).

CPTP consists of different types of pain. Wallace and Wallace [6] reported in their review both myofascial and neuropathic characteristics of CPTP pain. Several studies in which patients were also asked about the characteristics and location of their pain have shown the dominance of neuropathic characteristics [6, 7]. Patients with CPTP typically describe their pain as being burning, aching, electrical, or shock-like in quality and respond poorly to the use of opiates [8, 9]. These characteristics are the same as those of recognized neuropathic pain syndromes, such as postherpetic neuralgia [10].

In contrast to traditional analgesics that are antinociceptive, gabapentinoids such as gabapentin and PG reduce the hyperexcitability of dorsal horn neurons induced by tissue damage rather than reduce the afferent input from the site of tissue injury and therefore have been recommended for perioperative administration to improve acute and chronic neuropathic pain.

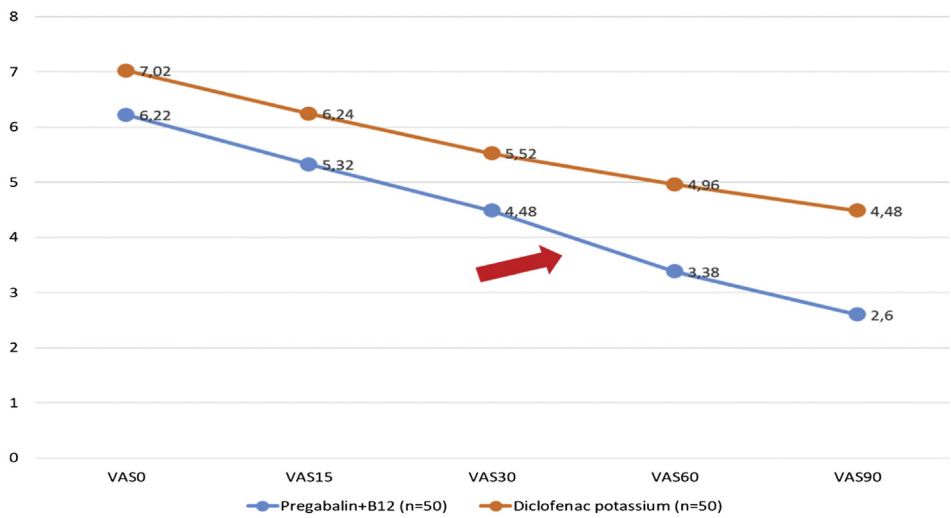

Fig 1. Visual Analogue Scale (VAS) score changes during the treatment. The red arrow indicates at what point these two curves become significantly different from each other.

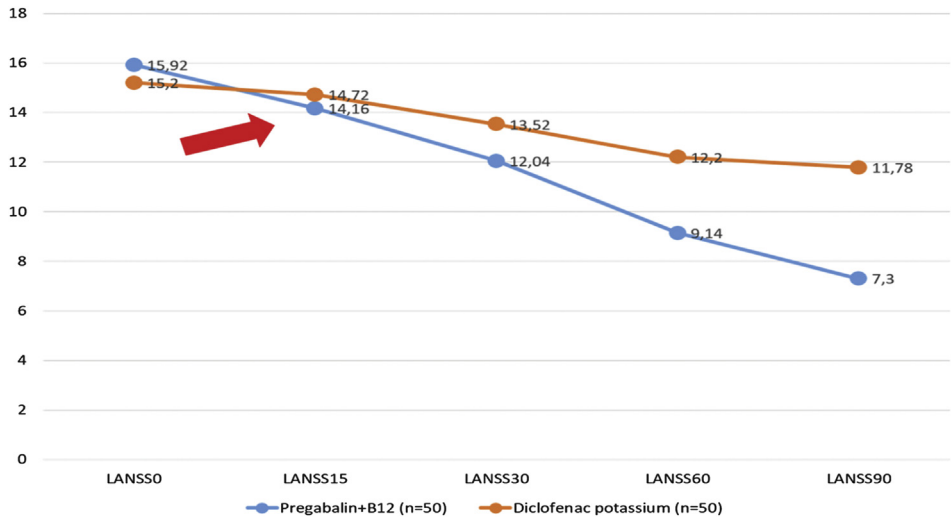

Fig 2. Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) score changes during the treatment. The red arrow indicates at what point these two curves become significantly different from each other.

Attention has focused on the potential role of anticonvulsant agents in postherpetic neuralgia and other neuropathic pain syndromes [2, 19]. In two studies that were done on painful diabetic neuropathy [20] and postherpetic neuralgia [21], gabapentinoid was reported to produce significant pain relief compared with placebo, as well as a significant improvement in measures of quality of life and mood [22–24]. PG, having the same structure and effect as gabapentin, is also a gamma-aminobutyric acid analogue, antiepileptic, analgesic, and anxiolytic drug [25–27]. It is also investigated and used in epilepsy, neuropathic pain, anxiety, and sleep disorders [27, 28]. Since 2004, it has been used in the treatment of peripheral neuropathic pain and in the combination therapy of partial epilepsy in Europe, and it is approved to be used in neuropathic pain related to diabetic neuropathy in the United States. In addition, some studies have shown vitamin B_{12} presenting neuroprotective effects, which are suggested to be related to their analgesic action in various models of neuropathic pain [29–31].

There are articles in the English literature investigating the effects of PG-B_{12} combination and PG on neuropathic pain. However, no comprehensive study on the efficacy of PG-B_{12} combination in CPTP is available. Mishra and colleagues [23] compared perioperative and postoperative PG and diclofenac sodium in a study of 50 patients. The study determined that there was a significant reduction in VAS scores in the PG group after 3 weeks [23]. Fawzi and colleagues [25] compared patients given PG before an operation with patients given a placebo for 5 days after an operation. They determined that there was less need for morphine in the early postoperative period and that LANSS scores at month 3 and 6 were significantly lower than those recorded for the patients given a placebo [25]. In this particular study, we have determined that VAS scores at day 15 and LANSS scores at day 30 are significantly lower in the PG-B_{12} group than in the DP group. However, preoperative, perioperative, and postoperative use of PG was used in those studies. In this particular study, patients with CPTP were identified 3 months after having a thoracotomy were enrolled in the trial. Early reduction in VAS and LANSS scores compared with the other studies may be associated with the fact that inflammation is less with the passing of time. The patients included in our study had wound pain scores VAS of 5 or greater and neuropathic pain scores LANSS of 12 or greater. This corresponds to moderate or severe pain as reported in previous studies [8, 32].

There are no reports on treatment with PG for pain after thoracic surgeries. A small study that was done with 4 patients by Matsutani and colleagues [33] showed significant improvement of chronic pain after taking PG after thoracotomies. A comprehensive analysis of 45 studies on the use of PG in treating perioperative pain was conducted between 2000 and 2010. Of these 45 studies, 17 of them determined that PG was effective in relieving acute postoperative pain. Whereas a reduction in the need for opioids was identified in patients using PG in 11 of the studies [26], our search only identified one study that focused on chronic pain after total knee arthroplasty. It showed that perioperative PG reduced the incidence of chronic neuropathic pain [34].

In conclusion, CPTP after thoracotomy may impair the quality of life. Nonsteroidal analgesics are often insufficient for treatment, whereas PG-B_{12} seems to be safe, effective, and well tolerated with minor side effects. However, these results must be supported with multidisciplinary studies with larger sample sizes and longer-term follow-ups.

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