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

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*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.

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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

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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 $\chi^2$ 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) |