Effectiveness of gabapentin in the treatment of chronic post-thoracotomy pain

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Abstract

Background: Chronic post-thoracotomy pain (CPTP) consists of different types of pain. Some characteristics of CPTP are the same as those of recognized neuropathic pain syndromes. Objective: We aimed to determine the safety and efficacy of gabapentin (GP) in comparison to naproxen sodium (NS) in patients with CPTP. Methods: Forty consecutive patients with CPTP after posterolateral/lateral thoracotomy were prospectively evaluated. Twenty patients were given GP and another 20 were given NS treatment. Visual Analogue Scale (VAS) and the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scorings were performed pretreatment (day 0) and on the 15th, 30th, 45th and 60th days. Adverse events were questioned. The mean ages were 45.7 ± 14.9 and 49.8 ± 15.2 years and the mean durations of pain were 3.8 ± 0.9 and 3.8 ± 1.1 months, respectively. Results: The mean pretreatment VAS scores (VAS0) were 6.4 ± 0.6 and 6.8 ± 0.6, the mean pretreatment LANSS scores (LANSS0) were 18.85 ± 1.6 and 20.75 ± 2.6 in GP and NS groups, respectively (p > 0.05). Minor adverse events which did not mandate discontinuation of treatment were observed in seven patients (35%) in the GP and in four patients (20%) in the NS group. The number of patients with a VAS score < 3 at the latest follow-up (VAS60 < 3) was 17 (85%) and 3 (15%) in GP and NS groups, respectively (p < 0.001). Seventeen patients (85%) in the GP and 0 patients (0%) in the NS group had a LANSS score < 12 at the latest follow-up. Conclusion: Gabapentin is safe and effective in the treatment of CPTP with minimal side effects and a high patient compliance. These results should be supported with multidisciplinary studies with larger sample sizes and longer follow-ups.

Keywords: Chronic post-thoracotomy pain; Neuropathic pain; Gabapentin; Wound pain

1. Introduction

Chronic post-thoracotomy pain (CPTP) 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 following the surgical procedure’ [1]. CPTP is reported to have an incidence between 50% and 80% of patients after thoracotomy and is usually mild or moderate. However, in 5% the pain is severe and disabling [2–4]. The most likely cause is intercostal nerve damage [5,6]. The upper nerve is more likely to be damaged during rib spreading and the nerve below, by closure [5,6].

CPTP consists of different types of pain. Wallace and Wallace reported in their review both myofascial and neuropathic characteristics of CPTP pain [7]. Several studies in which patients were also asked about the characteristics and location of their pain have shown the dominance of neuropathic characteristics [7,8]. Patients with CPTP typically describe their pain as being burning, aching, electrical and/or shock-like in quality, and responding poorly to the use of opiates [9,10]. These characteristics are the same as those of recognized neuropathic pain syndromes, such as post-herpetic neuralgia [11]. The neurological mechanisms for the production of neuropathic pain, hyperaesthesia and somatic pain are well described [12,13].

CPTP is one of the most challenging conditions confronting physicians. Different strategies have been described to reduce acute and chronic post-thoracotomy pain. These have included nonsteroidal anti-inflammatory drugs, parenteral opiates, epidural and paravertebral infusions of local anesthetics, intercostal and phrenic nerve blockades, and cryotherapy [14]. However, the results were variable and no single strategy was shown to be effective in all patients.

We administered gabapentin (GP) (Neurontin, Pfizer Inc., New York, NY, USA) an anti-convulsant, to the patients with CPTP and compared its effectiveness with naproxen sodium.
does not include a standardized thoracotomy approach. But the prospective study is lacking a control group and it does not include a standardized thoracotomy approach [14,15].

2. Methods

Forty consecutive patients with CPTP were included in the study. Post-operative pain that did not respond to a conventional treatment of at least 3 months duration was regarded as chronic pain. The severity of wound pain 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’ [16]. And 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 analysis of sensory description and bedside examination of sensory dysfunction [17], simultaneously.

The patients who had a history of CPTP, a VAS score ≥ 5, and a LANSS score ≥ 12 were included in the study. At the end of the treatment, VAS score < 5 were accepted as amelioration of wound pain and LANSS score < 12 were accepted as amelioration of neuropathic pain.

The patients were divided into two groups according to the order of their presentation to the outpatient clinic. A 2 × 500 mg/day dose of NS was administered orally to one of the groups for 60 days (n = 20). GP was administered to the other group (n = 20) for 60 days with an incremental stepwise dosage protocol. The GP dosages were as follows: 300 mg/day for the first 3 days, then 900 mg/day until the 15th day, 1800 mg/day between the 15th and 30th days and finally 2400 mg/day between the 30th and 60th days. VAS and LANSS scorings were performed before the treatment (0) and on the 15th, 30th, 45th and 60th days of the treatment. Adverse events were questioned and recorded.

The patients with chest wall invasion, empyema thoracis necessitans, tumoral intercostal neural lesions, pathological costal fracture and costal resection were excluded from the study. Also the patients with the history of analgesic addiction or abuse, epilepsy, other neurologic disorders and allergy to gabapentin or NS were excluded from the study. All patients who were enrolled in the study gave informed signed consent. The study protocol was approved by our Institutional Research Ethics Committee.

Sample size was determined prospectively using data from a previous study (Transcutaneous Electric Nerve Stimulation for the Treatment of Post-thoracotomy Pain: Randomized Prospective Study) in our institution. Power analysis indicated that 17 patients per group were required to detect the efficacy of GP on VAS and LANSS (α = 0.05, β = 0.2). Assuming a potential dropout rate of 15%, we decided to recruit 20 patients per group. Statistical calculations were performed using SPSS 11.5 (SPSS, Chicago, IL, USA).

Friedman’s variance analysis was used for the evaluation of scores recorded on different post-operative days. The Mann–Whitney U-test was used for intergroup and the Wilcoxon test for intragroup evaluations. p values less than 0.05 were considered as significant.

3. Results

Patient demographics and types of operation are depicted in Table 1. Age, sex, duration of symptoms and the number of different types of surgical procedure were not different between two groups (Table 1). All 40 patients were compliant with the treatment and they completed the study.

3.1. VAS scores

The mean VAS scores before the treatment (VAS₀) were 6.4 ± 0.6 and 6.8 ± 0.6 (p > 0.05) in the GP and the NS groups, respectively. VAS₀, VAS₁₅, VAS₃₀, VAS₄₅ and VAS₆₀ scores were compared within each group to determine the decrease in wound pain. In the GP group, there was significant amelioration of wound pain (p = 0.001). However, in the NS group, although there was minimal reduction in wound pain, no amelioration was observed (p > 0.05). On the 60th day of treatment 17 (85%) patients in the GP and 3 (15%) patients in the NS group had VAS scores < 5 (p = 0.001) (Fig. 1).

3.2. LANSS scores

The mean LANSS scores (LANSS₀) were 18.85 ± 1.6 and 20.75 ± 2.6 (p > 0.05) in the GP and the NS groups, respectively. LANSS₀, LANSS₁₅, LANSS₃₀, LANSS₄₅ and LANSS₆₀ scores were compared within each group to determine the decrease in neuropathic pain (Fig. 2). There was no significant change on the 30th day regarding the neuropathic pain in each group (p > 0.05). On the 60th day of treatment...
17 (85%) patients in the GP and 0 (0%) patients in the NS group had LANSS scores \(< 12 \) \( (p = 0.001) \).

In our study, we observed that GP treatment significantly decreased both the neuropathic pain (LANSS) and the wound pain (VAS) after 45th day of treatment \((p = 0.001)\). NS was effective in the treatment of neither neuropathic pain (LANSS) nor wound pain (VAS).

### 3.3. Adverse events

Minor adverse events which did not mandate discontinuation of the treatment were observed in seven (35%) patients in the GP and four (20%) patients in the NS group. Adverse events in the GP group were nausea in three (15%), drowsiness in two (10%) and dizziness in two (10%) patients. The only adverse event observed in the NS group was stomachache in four (20%) patients.

### 4. Discussion

CPTP represents a major therapeutic challenge characterized by absence of clinical studies to guide treatment [3,4,8]. Dajczman et al. found pain present in 50% of patients at 1 year post-thoracotomy, in 73% at 2 years, in 54% at 3 years, in 50% at 4 years and in 30% of patients at 5 years post-thoracotomy. The mean pain intensity (using VAS) did not differ throughout this time [8].

The patients included in our study had wound pain scores \( \text{VAS} \geq 5 \) and neuropathic pain scores \( \text{LANSS} \geq 12 \). This corresponds to moderate or severe pain as reported in previous studies [8,14].

Various thoracic incisions have been described to decrease the incidence of post-operative 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 [5,6]. We included only the patients who had undergone posterolateral or lateral thoracotomy to our study to let the study be homogenous. Seventy five percent of the patients had posterolateral thoracotomy and 25% had lateral thoracotomy. The mean VAS scores of the patients with posterolateral or lateral thoracotomy were not different \((p > 0.05)\).

Recently, attention has focused on the potential role of anticonvulsants in post-herpetic neuralgia and other neuropathic pain syndromes [18—22]. Recent evidence shows, however, that a newer anticonvulsant, gabapentin, is efficacious in the treatment of post-herpetic neuralgia and painful diabetic neuropathy [21,23]. Gabapentin’s mechanism of action is yet to be fully elucidated. Gabapentin does not bind to \( \gamma \)-aminobutyric acid (GABA) receptors despite being a structural analogue of GABA [11]. It has been shown to bind to calcium channel subunits and to modulate high threshold calcium currents in brain neurons, implying that neuronal voltage-gated calcium channels are a possible target of gabapentin [24].

Gabapentin is recommended to be administered at doses of up to 3600 mg/day (forced titration up to this dose, which could be back titrated if the patients were unable to tolerate). In our study, GP was administered in a stepwise protocol up to 2400 mg/day, which to our belief increased patient compliance and decreased the prevalence of adverse effects. NS was found to be effective at dose of 550 mg/day in post-operative pain of moderate to severe intensity [25]. In our study, NS was administered at dose of 1000 mg/day, twice more than the dose found to be effective in post-operative pain of moderate to severe pain.

There is only one prospective clinical study about gabapentin treatment in CPTP in the literature [14]. Sihoe et al. investigated the effectiveness of gabapentin for post-operative and post-traumatic pain in thoracic surgery patients [14]. They reported that severe pain and chest wall paresthesia decreased in 73.3% and 75% of patients, respectively. We used a ten number VAS to determine the severity of chronic wound pain and LANSS to determine the severity of neuropathic pain. We compared GP with NS, a NSAID, which is used frequently as a conventional agent in the treatment of CPTP. NS decreased VAS scores below 5 only in 15% of the patients, but GP decreased VAS scores below 5 in 85% of the patients. NS was not efficacious in neuropathic pain treatment. GP was found to be efficacious in neuropathic pain treatment in CPTP decreasing the LANSS scores below 12 in 85% of patients. But there was no patient with LANSS score below 12 in the NS group.

In our study, we observed that gabapentin was safe and efficacious in the treatment of CPTP. All patients could tolerate gabapentin. Minor side effects did not cause discontinuation of the treatment, and were observed in 35% of the patients. Sihoe et al. reported the rate of minor side effects as 40% in their study [14]. In an article about gabapentin treatment in post-herpetic neuralgia with 336 patients, the incidence of dizziness, somnolence, and
diarrhea were reported as 28%, 21.4% and 5.7%, respectively, and in this study 16% of the patients quit treatment because of the side effects [20,23].

Previous trials involving gabapentin for post-herpetic neuralgia typically restricted treatment to 7 or 8 weeks course [20,23]. Sihoe et al. administered gabapentin after thoracotomy and thorax trauma for a mean duration of 21.9 weeks [14]. We administered gabapentin for 60 days. We performed VAS and LANSS scorings to evaluate different components of CPTP, VAS for wound pain and LANSS for neuropathic pain, and included a control group which made this study different from the previous study of Sihoe et al. But the major limitation of our study is that it does not report long-term follow-up results.

Intercostal nerve dysfunction is the most important reason of severe wound pain and neuropathic pain in CPTP [5,6]. This explains the low effectivity of NSAID in the treatment of CPTP as they are not effective in the treatment of neuropathic pain. In our study, although NS could provide amelioration of wound pain in a few patients according to VAS, it could not decrease LANSS scores below 12 in any patient. Gabapentin reduced both neuropathic pain and wound pain.

To our knowledge, this is the first prospective clinical study comparing the efficacy of gabapentin with naproxen sodium in a homogenous patient group with CPTP, scoring the severity of wound pain according to VAS and neuropathic pain according to LANSS.

Gabapentin seems to be safe and well tolerated in the treatment of CPTP with minor side effects. Gabapentin is effective in the treatment of chronic post-thoracotomy wound pain and neuropathic pain. However, these results must be supported with multidisciplinary studies with larger sample sizes and longer-term follow-ups.

References