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ORIGINAL ARTICLE

The effect of pregabalin treatment on balance and gait in patients with chronic low back pain: a retrospective observational study

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ABSTRACT

Background: Low back pain is the most common musculoskeletal problem, and is a major cause of loss of workforce. Chronic low back pain associated with radiculopathy often includes nociceptive and neuropathic components. While non-steroidal anti-inflammatory drugs are the first choice for the nociceptive component, pregabalin is preferred as the neuropathic component.

Materials and methods: A retrospective analysis was conducted of 48 patients (26 women, 22 men) who had chronic low back pain associated with radiculopathy. A follow-up chart was used to collect data from February 2017 to November 2017. The patients characteristics (age, gender, initial daily dose of pregabalin), neuropathic pain (DN4 scale; Douleur Neuropathique, 4 questions), and balance and gait (Tinetti Balance and Gait Test) were assessed.

Results: The DN4 scores in the fourth ($p < .001$) and 12th ($p < .001$) weeks were significantly lower in patients. The Tinetti total test scores (23.2 ± 3.9) in the first ($p > .001$) week were significantly lower. There was no significant difference between the Tinetti test scores (balance, gait, and total scores) at baseline and in the 12th week ($p > .001$).

Conclusion: Pregabalin is effective on neuropathic pain and may have adverse effects on balance at initial doses and dose increments. Tolerance develops to these effects at maintenance doses.

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Adverse drug events; balance; gait; pregabalin; radiculopathy

Introduction

One frequent major health problem in developed countries in Low Back Pain (LBP). It ranks within the first 10 conditions which are held responsible for the highest number of disability-adjusted life years worldwide[1]. LBP may affect all kinds of people from any age. Because of its global prevalence, it is considered one of the most serious pain conditions.

LBP is associated with high healthcare resource use, and it causes decreases in function and work productivity[2]. One year after an acute period, nearly one-third of the patients complain of persistent back pain with moderate intensity[3,4]. Woolf *et al.*[5] conducted a study and suggested the classification of the pain symptoms and syndromes as two broad mechanisms based on pain categories: Tissue-Injury Pain (nociceptive) or Nervous-System-Injury Pain (neuropathic). In previous studies, it has been reported that Chronic LBP is a result of neuropathic and nociceptive pain mechanisms. For this reason, it is classified as a Mixed Pain Syndrome[6,7].

Non-pharmacological treatments, such as exercise, multidisciplinary rehabilitation, acupuncture, mindfulness-based stress reduction, tai chi, yoga, motor control exercise, progressive relaxation, electromyography biofeedback, low-level laser therapy, operant therapy, cognitive behavioral therapy, or spinal manipulation, are recommended primarily for the treatment of Chronic LBP. However, medication is initiated in unresponsive cases[8].

Several medications have been suggested for the medical treatment of chronic LBP, including non-steroidal anti-inflammatory drugs (NSAIDs; acetaminophen) tricyclic antidepressants, opioids, tramadol, benzodiazepines, gabapentin, and pregabalin (for radiculopathy)[9].

Pregabalin is widely used worldwide as the first choice in the treatment of neuropathic pain, regardless of the primary cause[10].

We aimed to investigate the effects of pregabalin, which is frequently prescribed for Chronic LBP and whose most common side-effects are dizziness and somnolence, on neuropathic pain, gait, and balance at initial doses[11].

Materials and methods

This study was a single-center, retrospective study. It was conducted with 48 patients (26 women, 22 men) who were referred to our physical medicine and rehabilitation clinic between February 2017 and November 2017. All patients were selected retrospectively through follow-up charts in weeks 0, 1, 4, and 12. The study was approved by the Ethics Committee (BEAH2017/202).

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Table 1. Patients demographics.

Age ($n = 48$)	
Median, years	58.3 ± 11.3
Range, years	47–71
Gender	
Male ($n = 26$)	54.1%
Female ($n = 22$)	45.8%
Body Mass Index	28.8 ± 5.2
Duration of illness	11.3 ± 5.3
Dizziness 1st week	55%
Dizziness 12th week	4.3%
Peripheral edema 1st week	11.2%
Peripheral edema 12th week	8.7 %
Fall history (last 1 year)	3.2%
Additional drug use	57.3%

Table 2. Evaluation of changes in scores.

	M ± SD	Median
Dn4 score		
Start	7 ± 1.1	7
1st week	6.8 ± 1.1	7
4th week	5.1 ± 1.6*	6
12th week	2.9 ± 0.7*	3
VAS		
Start	6.8 ± 2.3	5
1st week	5.2 ± 1.8*	5
4th week	4.5 ± 0.9*	4
12th week	2.9 ± 1.1*	2
Tinetti gait score		
Start	11.5 ± 2	12
1st week	9.8 ± 2.4*	9
4th week	11.0 ± 1.5	11
12th week	11.7 ± 1.9	13
Tinetti balance score		
Start	15.5 ± 1.6	16
1st week	11.5 ± 2.6*	10
4th week	14.9 ± 3.8	14
12th week	14.7 ± 1.6	14
Tinetti total score		
Start	27.0 ± 2.7	28
1st week	23.2 ± 3.9*	23
4th week	25.9 ± 3.1	26
12th week	26.4 ± 2.8	27

*Intra-group change, $p < .05$ (Wilcoxon test).

Inclusion criteria for the study were as follows:

- Chronic LBP (duration of the symptoms: >6 months, mean: 13 ± 6 months) because of disc prolapse, lumbar spondylosis, and/or spinal stenosis;
- Minimum Visual Analog Scale (VAS) at recruitment: >4;
- Age: >18 years;
- DN4 (Douleur Neuropathique, 4 questions) >4; and
- Patients who began with pregabalin 75 mg (B.I.D.) and continued with pregabalin 150 mg (B.I.D.).

Exclusion criteria for the study were as follows:

- Those who underwent joint or lumbar disc herniation surgery;
- History of neurologic disease;
- Hearing and visual impairments;
- Endocrine disease (e.g. diabetes mellitus, thyroid dysfunction), uncontrolled hypertension, cardiac disease, malignancy, and rheumatologic disease;
- Major psychiatric disorder;
- Taking another medication that may affect balance (sedatives, hypnotics, antidepressants, and benzodiazepines); and
- Renal and liver dysfunction.

Age, gender, additional drug use, history of falls within the past year, dizziness, and peripheral edema were evaluated for all cases, and physical examinations were performed.

Neuropathic pain scores were assessed with the Douleur Neuropathique 4 (DN4) scale[12]. The scale was developed in France with 160 patients who complained of neuropathic or non-neuropathic pain for more than 3 months. It consists of 10 questions: seven about the symptoms (burn, painful chill, electric shock, prickling, tingling, insensitivity, and itching) and three about the results of clinical inspection (slight touch hypoesthesia, pricking hypoesthesia, and brushing allodynia). One point is given for "Yes" and 0 is given for "No". The maximum total score that may be received from the scale is 10. Patients who have scores ≥4 are defined as having neuropathic pain. The Turkish version of the DN4 was demonstrated to be valid and reliable[13].

Pregabalin plus naproxen sodium medication were administered to Chronic LBP patients having neuropathic pain detected with the DN4 scale. All patients were evaluated before treatment with the Tinetti balance and gait test. The Tinetti test assesses balance and gait in two main categories with 16 questions: The first nine questions are about balance, and the next seven questions are about gait. Scores are calculated as follows: The total score received from the first nine items indicates the balance score, the total score received from the next seven items indicates the gait score, and the sum of the scores for all items indicates the total score. The 16 items represent the totality of the movements made during daily life activities. Scoring is based on observation and defined as follows: 2 points = the specified movement is performed correctly, 1 point = the specified movement is performed with adaptations, 0 points = the inability to perform the specified movement. A total score of 18 or below shows a high risk of falling, a total score between 19 and 24 shows a moderate risk of falling, and a total score of 24 or above shows a low risk of falling[14]. The Visual Analog Scale (VAS) is a single-item, continuous scale for pain intensity assessment. It is a 10-cm line with endpoints labeled as "no pain at all" on the left and "pain as bad as it could be" on the right. The patient is asked to define his/her pain intensity by putting a mark on the line between the two endpoints. The distance between two endpoints is measured using a ruler to obtain the score. All patients had a standard home exercise program that they were instructed to follow for 30 minutes each day.

Statistical analysis

Mean, standard deviation, median (lowest and highest values), frequency, and ratio values were used in the descriptive statistics of the data. The distribution of the variables was measured by the Kolmogorov-Smirnov test. The

independent-samples *t*-test and Mann-Whitney U-test were used in the analysis of the independent quantitative data. The Wilcoxon test was used in the analysis of the dependent quantitative data. The Chi-square test was used in the analysis of the independent qualitative data. The SPSS 22.0 Program was used for statistical analysis.

Results

Patient age, gender distribution, body mass index (BMI), duration of illness, and use of additional drugs are shown in Table 1 ($p > .05$).

The DN4 scores in the 4th ($p < .001$) and 12th ($p < .001$) weeks were significantly lower in patients (Table 2).

The Tinetti Balance, gait, and total score in the 1st ($p > .001$) week were significantly lower and in the 4th and 12th ($p > .001$) weeks; there were no significant changes in all scores from baseline (Table 2).

The VAS scores showed a significant decrease compared with baseline.

Discussion

In our study, it was seen that there was a decrease in balance and gait scores in both the 1st and 4th weeks after treatment in Group 1 (pregabalin plus naproxen sodium). There was a significant improvement in the neuropathic pain scores (DN4) in the same group. There was an impairment in balance and gait scores in accordance with dose increments. However, it was observed that the balance and gait scores approached normal values in 12 weeks.

Pregabalin has been obtained synthetically as a structural derivate of the inhibitory neurotransmitter γ–aminobutyric acid (GABA). It is an α_2-δ ligand and has analgesic, anticonvulsant, anxiolytic, and sleep-modulating effects[15]. After oral intake, it is absorbed quickly and reaches peak plasma concentrations between 0.7–1.3 h. The oral bioavailability of pregabalin is nearly 90%. It is independent from dose and frequency of intake. The elimination half-life of pregabalin is nearly 6 h. The steady state occurs within 1–2 days of repeated administration. In terms of oral bioavailability, the plasma clearance of pregabalin is equal to renal clearance. This shows that it undergoes negligible non-renal elimination. Pregabalin is not bound to plasma proteins. Approximately 90% of an oral dose of pregabalin is eliminated unchanged in urine. Renal functions affect its pharmacokinetics[16].

Pregabalin affects neuropathic pain by modulating the alpha-2-delta subunits of voltage-gated calcium channels in the central nervous system. In addition, it also reduces the release of many neurotransmitters, including glutamate, noradrenaline, and substance P[17].

Freynhagen *et al.*[18] reported that the most common side-effects of pregabalin were dizziness (31.4%), somnolence (17.8%), peripheral edema (2.8%), weight increase (5.4%), and balance disorder (2.4%) in patients receiving pregabalin due to Chronic LBP. Savk[19] reported that the most common side-effect of pregabalin was dizziness. Moreover, Griffin and Brown[20] and Li *et al.*[21] reported that dizziness, fatigue, and somnolence were among the most common adverse effects of pregabalin.

Dizziness may occur due to labyrinthitis or cardiac, neurological, or psychological reasons, but may also be caused by medications.

Pregabalin may cause a gait, dizziness, and balance disorder. This situation can lead to deterioration in the quality-of-life of the patients and loss of workforce[22]. Balance disorder increases the risk of falls[23]. Gait and balance disorders, especially in elderly patients, are an important cause of morbidity and mortality, and may lead to falls that often result in admission to the emergency department and hospital[24].

In the past decades, over 20 risk factors were identified as risk factors for falls[25]. A number of commonly used drugs have been claimed to be associated with increased risk of fall and fracture[26,27]. Use of sedatives, hypnotics, antidepressants, and benzodiazepines was claimed to be an important risk factor for falls in the elderly[27]. Some other drugs (antihypertensives, diuretics, NSAIDs, and β-blockers) were also associated with increased risk of fall[26,27]. Although the NSAID given to the Control Group (naproxen sodium) is reported in the literature to affect balance, we found no significant change in the balance scores in Group 2.

There are, of course, many factors that cause the side-effects of a drug to emerge. Some of the causes may contribute to an inter-individual pharmacological response (renal/liver impairment or genetic causes, such as cytochrome P450 [CYP450]) polymorphisms. For this reason, not only the number of medications, but also the types of medications, is important in terms of possible interactions[28].

Studies have recommended that combination therapies (for treatment of nociceptive pain) rather than pregabalin monotherapy (for the neuropathic component) are used in the treatment of Chronic LBP[29]. We used naproxen sodium in addition to pregabalin for nociceptive pain in our study. Naproxen sodium has no efficacy in the treatment of neuropathic pain. We think that this is because the home exercise program contributed to this situation and the improvement in nociceptive pain had a positive effect on the DN4 scores.

In our study, the patients with Chronic LBP who received pregabalin did not report any falls, and did not need to stop taking the medicine for any reason.

Studies show that the side-effects of pregabalin are dose-dependent[30]. We think the fact that pregabalin was started at a dosage of 75 mg BID contributed to the tolerance of the medicine and, thus, protected the patients from falls that may have happened secondary to balance and gait disturbance.

Consequently, pregabalin is effective in the treatment of Chronic LBP with neuropathic pain component. Informing patients about the effects of the medicine on gait and balance during the initial dosing period and subsequent increments would be appropriate in terms of preventing possible trauma. We believe that combination therapies, including exercise, would be more effective. We think that long-term prospective randomized controlled trials including the large numbers of patients will allow us to objectively evaluate the

effects of pregabalin, which has wide indications and efficacy, on the risk of falls.

Transparency

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Declaration of financial/other relationships

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