Gabapentin versus pregabalin in relieving early post-surgical neuropathic pain in patients after lumbar disc herniation surgery: a prospective clinical trial

Habibullah Dolgun, Erhan Turkoglu, Hayri Kertmen, Bora Gurer, Erdal R. Yilmaz, Selim S. Comoglu, Zeki Sekerci

Ministry of Health, Diskapi Yildirim Beyazit Education and Research Hospital, Ankara, Turkey

Objectives: The roles of gabapentin and pregabalin are well established in the management of chronic neuropathic pain. Here, we investigated the effectiveness of pregabalin and gabapentin for treating acute neuropathic pain following lumbar discectomy.

Methods: This prospective, non-randomized, and observational study included 54 patients who experienced acute neuropathic pain after lumbar discectomy. The assessments included the Leeds assessment of neuropathic symptoms and signs scale (LANSS), the Oswestry disability index (ODI), and the visual analog scale (VAS) pre-operatively and at 3 days, 6 months, and 1 year after surgery. The LANSS scores ≥ 12 suggest the presence of neuropathic pain. Those patients who reported neuropathic pain were randomly treated with gabapentin or pregabalin.

Results: In the gabapentin group, the LANSS scores increased to 14 at 3 days after surgery. The patients improved neurologically and on the LANSS, which decreased to 10 points 6 months after surgery and to 4 points at 1 year ($P < 0.001$). In the pregabalin group, the LANSS scores increased from 12 to 16 points on post-operative day 3 and then decreased to 12 and 5 at the 6-month and 1-year follow-ups, respectively (both $P < 0.001$). The ODI and VAS scores significantly improved in both groups ($P < 0.001$).

Discussion: Many patients may suffer from neuropathic pain in the early post-surgical period after lumbar discectomy. Gabapentin and pregabalin are anticonvulsant agents that may decrease perioperative central sensitization and early post-surgical neuropathic pain. Gabapentin and pregabalin effectively relieved neuropathic pain and prevented the conversion of acute pain to chronic pain at the 1-year follow-up after lumbar discectomy.

Keywords: Gabapentin, Lumbar disc herniation, Lumbar discectomy, Neuropathic pain, Pregabalin, Treatment

Introduction

The most common persistent symptoms after lumbar disc surgery are chronic neuropathic pain, motor deficits, and functional limitations.[1–5] Distinguishing whether the pain is nociceptive or neuropathic has important implications for diagnostic, lifestyle, and treatment decisions. Nociceptive pain is caused by an active illness, injury, and/or inflammatory process associated with actual or potential tissue damage. Neuropathic pain is caused by lesions or dysfunction of the nervous system and is initiated by several cellular and molecular mechanisms. Compression of neural and neurovascular structures may result in neuropathic pain. Nerve injury is reported to evoke spontaneous discharges from the cell bodies of myelinated fibers at the dorsal root ganglion (DRG) cell level.[6] The mechanism of spontaneous activity is hypothesized to be secondary to increase in the concentrations of sodium channels in areas affected by neural microinjuries, neuromas, DRGs, and areas of demyelination.[7]

The use of antiepileptic drugs (AEDs) in the treatment of neuropathic pain is based on a number of similarities in the pathophysiologic and biochemical mechanisms underlying neuropathic pain and epilepsy. Gabapentin and pregabalin are AEDs that have been studied in the treatment of a wide variety of disorders, such as neuropathic pain, epilepsy, spasticity, and anxiety.[5,6,8]

The roles of gabapentin and pregabalin are well established in the management of neuropathic pain. The primary aim of this study was to compare Leeds assessment of neuropathic symptoms and signs scale

Correspondence to: Erhan Turkoglu, Cukurambar Mah. Ogretmenler Cad., Kardelen Apt. No. 5/6, Cankaya, 06290 Ankara, Turkey. E-mail: drmet122@yahoo.com

(LANSS) scores among patients following lumbar discectomy. We also investigated a model of multimodal acute neuropathic pain management to decrease the rate of conversion from acute to chronic pain and demonstrated the effectiveness of pregabalin and gabapentin in the treatment of acute neuropathic pain following lumbar discectomy.

Materials and Methods

Study design

This prospective and observational study included 764 patients who presented with sciatica and were admitted to Ministry of Health, Diskapi Yildirim Beyazit Education and Research Hospital Neurosurgery Outpatient Clinic between January 2008 and December 2009. All the patients were assessed with conventional X-rays and magnetic resonance imaging (MRI) and diagnosed with lumbar disc herniation (LDH). Patients between 18 and 75 years old with low back pain and radiculopathy who had completed a comprehensive care program, including medical treatment, physical therapy, and bed rest for at least 6 months without success, were included in this study. Patients who had underlying degenerative disease and/or stenosis, a history of major psychopathology, spondylolisthesis, spinal fracture, infection, neoplasm, rheumatological disorders, or polyneuropathy were excluded from the study. All the patients underwent lumbar discectomy and partial medial facetectomy for LDH at Diskapi Yildirim Beyazit Education and Research Hospital Neurosurgery Clinic. The patient characteristics, including smoking status and body weight at the time of surgery, are summarized in Table 1.

Patient groups and sample size estimation

The primary aim of this study was to compare LANSS scores between groups. Sample size estimation was performed using NCSS and PASS 2000 software,[9] which revealed that group sample sizes of 25 were needed to achieve 90% power to detect a difference of 3.00 points between post-operative day 3 and month 6 in LANSS scores. All the patients were assessed with the LANSS, which is based on an analysis of sensory description and clinical examination of sensory dysfunction. The LANSS involves a simple scoring system and provides immediate information in clinical settings. Scores ≥ 12 suggest the diagnosis of neuropathic pain. We identified 54 of the 764 patients who suffered burning, shooting, or lancinating pain associated with numbness after surgery and who were diagnosed with early neuropathic pain based on their LANSS scores. These 54 patients were divided into two groups according to the treatment strategy:

Gabapentin group ($n = 27$): Gabapentin was administered to patients with LANSS scores ≥ 12 using the following initial dosing schedule: a single dose of 300 mg on the first day, 300 mg bid on the second day, and 300 mg tid on the third day. The maintenance dose was 900–1800 mg tid. For a few patients, a maintenance dose of 2400–3600 mg/day was administered for a relatively short duration and was well tolerated. The effective dose was individualized according to the response and tolerability of each patient. If adequate improvement was achieved before the standard treatment regimen was completed, early titration to cessation was possible. The maximum treatment period was the duration of the study.

Pregabalin group ($n = 27$): Pregabalin was administered to patients with LANSS scores ≥ 12 points using the following initial dosage schedule: the initial dose of pregabalin was 50 mg tid (150 mg/day) and the dose was increased to a maximum of 100 mg tid (300 mg/day) after 1 week. In cases of inadequate pain relief after 2–4 weeks of treatment at the dose of 300 mg/day, the dose was increased to 300 mg bid or 200 mg tid. The dosages were monitored and could be increased based on the tolerance and response of the patient. In cases of adequate improvement before the standard treatment regimen was completed, early titration to cessation was possible. The maximum treatment period was the duration of the study.

Surgical procedure

The surgery was performed through a standard posterior median approach to the involved segment. The primary surgeon decided the extent of surgery according to the involved levels. The involved levels are summarized in Table 2, in which the most commonly involved level was L4-L5. The operative technique for all the patients included adequate decompression of the bony elements with hemilaminectomy, partial facetectomy, foraminotomy, and discectomy under a surgical microscope. All the patients were mobilized on the day after surgery.

Follow-up

The data sources included the medical records, radiographic reviews, and pre-operative and post-operative questionnaires. The clinical and neurological status, demographic data, smoking status, duration of pre-operative symptoms, and duration of follow-up were recorded. Data entry was performed by a person who was blinded to the study protocol. The questionnaires included the LANSS, the Oswestry disability index (ODI), and the visual analog scale (VAS), which were performed pre-operatively and 3 days, 6 months, and 1 year after surgery. The main outcome was the LANSS score, which was used to determine if the radicular pain was nociceptive or neuropathic in origin (in case different treatments were needed to control pain). The LANSS has two components. The pain questionnaire asks five questions: (1) Does your pain feel like strange, unpleasant sensations?, (2) Does your pain make the skin in the

Table 1 Characteristics of the study cohort

Variables	Gabapentin (n = 27)	Pregabalin (n = 27)	P-value
Age/year	46.5 ± 9.8	44.6 ± 9.0	0.455†
Sex			
Male	8 (29.6%)	7 (25.9%)	0.761‡
Female	19 (70.4%)	20 (74.1%)	
Weight/kg	71.8 ± 10.7	67.2 ± 6.8	0.065†
Smoking	6 (22.2%)	6 (22.2%)	–

†Student's t test, ‡Pearson's Chi-square test.

painful area look different from normal?, (3) Does your pain make the affected skin abnormally sensitive to touch?, (4) Does your pain come on suddenly and in bursts for no apparent reason when you are still?, and (5) Does your pain feel as if the skin temperature in the painful area has changed abnormally? It also assesses allodynia and determines whether the patient has an altered pinprick threshold. The score scale ranges from 0 to 26, where 26 indicates the greatest likelihood that the patient is experiencing neuropathic pain. For scores $\geq$12, neuropathic mechanisms are likely to be contributing to the patient's pain. After its original validation with 100 patients, this scale has been tested and used on thousands of people, and it includes a validated self-completed epidemiological tool hypothesized to be accurate in 75–80% of cases (sensitivity 85%, specificity 80%).[10]

The ODI is a specific outcome measure for spinal disorders ranging from 0 to 100, where high scores reflect a high degree of disability. Leg and back pain were assessed by the VAS.

Statistical analysis

Data analysis was performed using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA). Whether the metric discrete variables were distributed normally or not was determined by Shapiro Wilk test. Metric discrete variables were shown as mean ± standard deviation (SD) or median (min–max), where applicable. While the mean differences between groups were compared by Student's t test, Mann Whitney U test was applied for comparisons of the median values. Nominal data were analyzed by Pearson's Chi-square test. Whether the differences in median LANSS, ODI, and VAS scores among follow-up times were statistically significant or not was evaluated by Friedman test. When the P value from Friedman test statistics is statistically significant Wilcoxon Signed Rank test was used to know which measurement time differ from which others. A P value less than 0.05 was considered statistically significant. But, for all multiple comparisons the Bonferroni adjustment was applied for controlling Type I error.

Results

The study group comprised 54 patients (39 females, 15 males). The mean age was 45.2 years, ranging from 28 to 72 years. The duration of symptoms ranged from 6 to 60 months. The patient characteristics Please consider deleting this text. are summarized in Table 1. There were no significant differences between the two groups with regard to their demographic data. Of these 54 patients, 46 (85%) underwent single-level unilateral discectomy, 5 (18.4%) underwent single-level bilateral discectomy, and 3 (11.2%) underwent two-level discectomy. There was no statistically significant difference with regard to the LANSS scores for these three types of surgeries. The most common involved level was L4–L5. The involved levels are summarized in Table 2.

The mean pre-operative LANSS score in the gabapentin group was 7 points, and on the third post-operative day, the mean LANSS scores increased to 13 points ($P < 0.001$). After gabapentin treatment, the mean LANSS score decreased to 10 points at 6 months ($P < 0.001$) and to 4 points at 1 year ($P < 0.001$). The mean pre-operative LANSS score in the pregabalin group was 8 points, which increased to 16 points on the third post-operative day ($P < 0.001$). After pregabalin treatment, the mean LANSS score decreased to 12 points at 6 months ($P < 0.001$) and to 5 points at 1 year ($P < 0.001$). The changes LANSS scores for the gabapentin and pregabalin groups are summarized in Fig. 1. There were no statistically significant differences observed between the gabapentin and pregabalin groups with regard to mean LANSS scores at any time point.

The mean pre-operative ODI for both the pregabalin and gabapentin groups was 28%, and this increased to 38 and 39% on the third post-operative day, respectively. After pregabalin and gabapentin treatment, there were statistically significant decreases in the mean ODI measured 6 months and 1 year after surgery ($P < 0.001$). Gabapentin and pregabalin were both associated with improvements in ODI for all time points except the third post-operative day (Fig. 2).

The mean pre-operative VAS values in both the pregabalin and gabapentin groups were 7 cm, and both diminished to 3 cm on the third post-operative day. The patients complained mostly of neuropathic pain after lumbar discectomy, and they reported

Table 2 The surgical levels operated between the groups

Level	Gabapentin group n/%	Pregabalin group n/%
Bilateral L4–L5	3 (11.1)	2 (7.4)
Right L1–L2	1 (3.7)	–
Right L3–L4	–	1 (3.7)
Right L4–L5, L5–S1	2 (7.4)	–
Right L4–L5	6 (22.2)	8 (29.6)
Right L5–S1	3 (11.1)	1 (3.7)
Left L3–L4, L4–L5	1 (3.7)	–
Left L3–L4	–	1 (3.7)
Left L4–L5	8 (29.6)	12 (44.4)
Left L5–S1	3 (11.1)	2 (7.4)

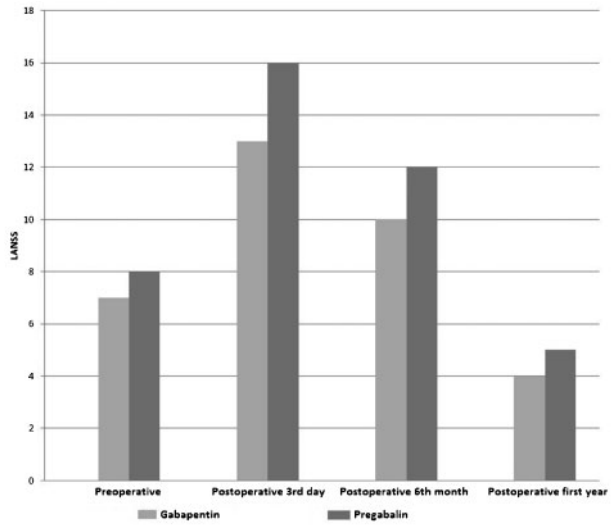

Figure 1 Bar graph showing the LANSS scores of the gabapentin and pregabalin groups.

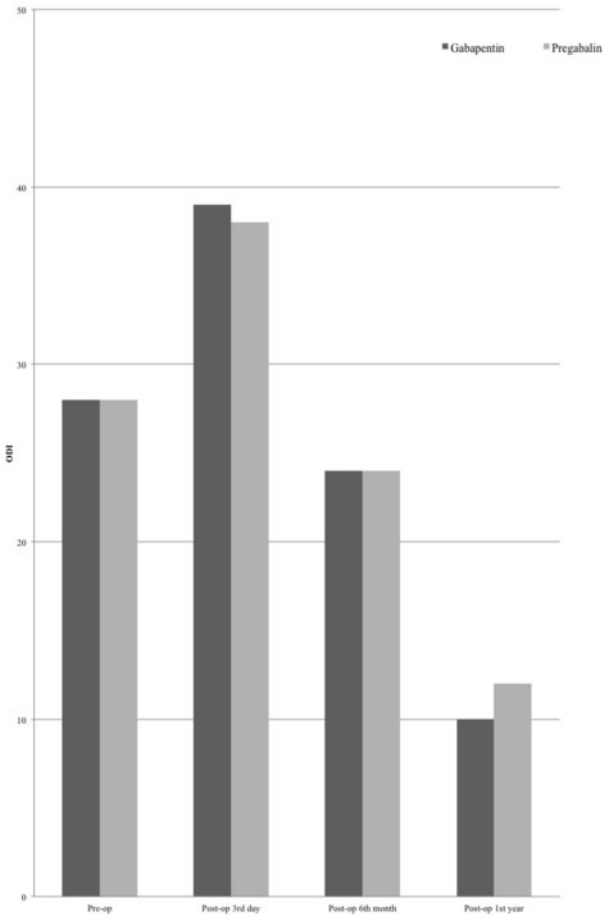

Figure 2 Bar graph showing the Oswestry disability index (ODI) of the gabapentin and pregabalin groups.

feeling mostly burning, shooting pain, and numbness rather than radicular pain. After pregabalin and gabapentin treatment, there was a statistically significant decrease for the mean VAS value 6 months and 1 year after surgery ($P < 0.001$). However, there were no statistically significant differences between the groups at any time points. The mean LANSS, ODI and VAS scores were summarized in Table 3. Also, the changes of the LANSS, ODI and VAS scores were summarized in Table 4.

Discussion

Neuropathic pain results from damage or disease affecting the somatosensory system. Compression of neural and neurovascular structures may lead to neuropathic pain. Following nerve injury caused by disc herniation and/or lumbar discectomy, normal nerve transmission may be disrupted. The receptors for inflammatory cytokines, such as tumor necrosis factor alpha (TNF-alpha) and interleukin (IL)-1 and -6, can accumulate in the injured sensory neurons and alter their function. Nerve transection can increase cytokine levels correlated with allodynia, which may be linked to glutamate release and *N*-methyl-D-aspartate (NMDA) receptor activation.[11,12] The diagnosis of neuropathic pain should be made following a detailed physical and neurological examination. Generally, patients suffer from burning, shooting, or lancinating pain associated with numbness, tingling, allodynia, and/or hyperalgesia.[6] There is no single test, symptom, or sign for diagnosis, but different studies can help to confirm impressions or rule out underlying causes.

In this study, the LANSS was used to diagnose neuropathic pain.[12] A total of 710 patients experienced

Table 3 The LANSS, ODI, and VAS scores among follow-up times

Variables	Pre-op	Post-op 3rd day	Post-op 6th month	Post-op 1st year	*P*-value[†]
LANSS					
Gabapentin	7 (0–11)[a]	13 (12–26)[a,b,c]	10 (0–24)[b,d]	4 (0–12)[c,d]	<0.001
Pregabalin	8 (0–11)[a,e]	16 (12–26)[a,b,c]	12 (3–26)[b,d,e]	5 (0–21)[c,d]	<0.001
ODI					
Gabapentin	28 (15–47)[a,e,f]	39 (20–57)[a,b,c]	24 (10–38)[b,d,e]	10 (0–14)[c,d,f]	<0.001
Pregabalin	28 (12–35)[a,f]	38 (24–46)[a,b,c]	24 (12–30)[b,d]	12 (0–28)[c,d,f]	<0.001
VAS					
Gabapentin	7 (4–10)[a,e,f]	3 (0–6)[a,b,c]	0 (0–3)[b,e]	0 (0–1)[c,f]	<0.001
Pregabalin	7 (5–9)[a,e,f]	3 (1–6)[a,b,c]	0 (0–2)[b,e]	0 (0–2)[c,f]	<0.001

LANSS: Leeds assessment of neuropathic symptoms and signs; ODI: Oswestry disability index, VAS: visual analogue scale, [†]Friedman test, [a]The difference between pre-op and post-op third day is statistically meaningful ($P < 0.001$), [b]The difference between post-op third day and post-op sixth month is statistically meaningful ($P < 0.001$), [c]The difference between post-op third day and post-op first year is statistically meaningful ($P < 0.001$), [d]The difference between post-op sixth month and post-op first year is statistically meaningful ($P < 0.001$), [e]The difference between pre-op and post-op sixth month is statistically meaningful ($P < 0.001$), [f]The difference between pre-op and post-op first year is statistically meaningful ($P < 0.001$).

Table 4 Comparisons of the differences of the LANSS, ODI, and VAS scores between groups

Variables	Gabapentin (n = 27)	Pregabalin (n = 27)	P-value[†]
LANSS			
Post-op 3rd d–pre-op	6 (0–16)	8 (5–21)	0.037
Post-op 6th m–pre-op	3 (−11 to 14)	4 (−3 to 16)	0.305
Post-op 1st y–pre-op	0 (−11 to 8)	−1 (−9 to 11)	0.721
Post-op 6th m–3rd d	−2 (−11 to 2)	−4 (−12 to 0)	0.073
Post-op 1st y–3rd d	−8 (−14 to 0)	−11 (−15 to 0)	0.011
Post-op 1st y–6th m	−5 (−12 to 0)	−5 (−12 to 0)	0.152
ODI			
Post-op 3rd d–pre-op	12 (−7 to 16)	11 (10 to 14)	0.514
Post-op 6th m–pre-op	−7 (−14 to 5)	−3 (−11 to 8)	0.038
Post-op 1st y–pre-op	−21 (−34 to −3)	−15 (−28 to −2)	<0.001
Post-op 6th m–3rd d	−17 (−27 to −2)	−14 (−22 to −4)	0.044
Post-op 1st y–3rd d	−32 (−44 to −14)	−26 (−40 to −14)	0.002
Post-op 1st y–6th m	−14 (−24 to −8)	−12 (−23 to 2)	0.005
VAS			
Post-op 3rd d–pre-op	−4 (−6 to 0)	−4 (−6 to −2)	0.666
Post-op 6th m–pre-op	−7 (−10 to −4)	−7 (−9 to −5)	0.669
Post-op 1st y–pre-op	−7 (−10 to −4)	−7 (−9 to −5)	0.689
Post-op 6th m–3rd d	−3 (−6 to 0)	−3 (−5 to −1)	0.523
Post-op 1st y–3rd d	−3 (−6 to 0)	−3 (−5 to −1)	0.406
Post-op 1st y–6th m	0 (−2 to 0)	0 (−1 to 0)	0.542

[†]Mann Whitney U test, According to the Bonferroni adjustment, $P < 0.0083$ was considered statistically significant, d: day; m: month; y: year.

symptom relief following discectomy and decompression, but the remaining 54 patients suffered burning, shooting, or lancinating pain associated with numbness and were diagnosed with neuropathic pain based on their LANSS scores.

Antiepileptic drugs have been used to treat post-herpetic neuralgia and other neuropathic pain syndromes.[13–15] Gabapentin and pregabalin were reported to produce significant pain relief as compared to placebo and achieved significant improvements in quality of life measures in patients with post-herpetic neuralgia, painful diabetic neuropathy, and post-surgical pain.[6,16–19] Randomized clinical trials (RCTs) that administered gabapentin for chronic pain reported that at daily dosages of up to 3600 mg, gabapentin significantly reduced pain compared with a placebo in patients with mixed neuropathic pain syndromes.[6,18,20] Shioe *et al.* investigated the effectiveness of gabapentin for post-operative and post-traumatic pain in thoracic surgery patients and reported a decrease in overall pain and chest wall paresthesia in 73.3 and 75% of patients, respectively.[21] Pregabalin was originally developed in the search for a compound that would maintain the biological activity of gabapentin and improve its pharmacokinetic properties. It was designed as a more potent successor to gabapentin.[5,20,22,23] Pregabalin does not bind directly to gamma-aminobutyric acid (GABA)-A or -B receptors; rather, it increases neuronal GABA levels by inducing a dose-dependent increase in glutamic acid decarboxylase activity.[24,25] Gianesello *et al.* reported that pregabalin administration reduces early post-surgical pain at rest and during movements after major spine surgeries. Patients treated with pregabalin require less opioids and exhibit improvements in their overall quality of life 3 months after surgery.[26] Randomized clinical trials have demonstrated that pregabalin is effective in pain control at a daily dose ranging from 50 to 300 mg.[26–28] Burke *et al.* reported that the patients who had been treated with pregabalin for 3 months had lower pain intensity and better overall quality of life measurements.[16] In our study, 54 consenting patients of various ages and either sex experienced early neuropathic pain following discectomy. These patients had LANSS scores $\geq$12 points and were randomly treated with gabapentin or pregabalin. Those patients who received gabapentin had significantly less pain at weeks 2–8 after surgery. We administered doses ranging from 900 to 1800 mg/day, which were usually effective for treating early post-surgical neuropathic pain. Additional doses of up to 3600 mg/day were administered in some cases, if necessary. The mean pre-operative LANSS score in the pregabalin group was 8 points, which increased to 16 points on the third post-operative day ($P < 0.001$). After pregabalin treatment, the mean LANSS score decreased to 12 points at 6 months ($P < 0.001$) and 5 points at 1 year ($P < 0.001$). A pregabalin dose of 300 mg/day (150 mg bid) was shown to be effective in controlling acute neuropathic pain, and the results revealed that gabapentin and pregabalin were effective in the treatment of post-operative neuropathic pain after lumbar discectomy.

The mean pre-operative VAS score was 7 in both groups and decreased to 3 in both groups on the third post-operative day ($P < 0.001$). The patients mostly suffered from neuropathic pain, and the nociceptive component of pain associated with disc herniation improved shortly after surgery. The VAS decreased gradually in both groups over a 6-month period ($P < 0.001$). Gianesello *et al.* reported similar VAS values and significant amelioration with pregabalin treatment.[26] In our study, this amelioration could be

explained by decompression of the nerve root itself and subsiding inflammation over time.

The mean pre-operative ODI scores were 28% in both the gabapentin and pregabalin groups. The mean ODI scores were 10 and 12% at the last follow-up in the gabapentin and pregabalin groups, respectively. ODI decreased gradually in both groups over a 6-month period.

Conclusion

Surgical procedures, such as lumbar discectomy, have an inherent risk of inducing neuropathic pain. Chronic post-surgical neuropathic pain is recognized as occurring after lumbar discectomy, but early post-surgical neuropathic pain is frequently overlooked or minimized. Identifying these types of neuropathic pain and modeling a multimodal acute neuropathic pain management plan to decrease the probability of the conversion of acute to chronic pain are important goals. Acute pain management should be a part of the multimodal treatment regimen to prevent the development of chronic pain. A continuing or partial response might be obtained using perioperative gabapentin or pregabalin therapy. We demonstrated that gabapentin and pregabalin were both effective in the treatment of early neuropathic pain following lumbar discectomy. Further studies are needed to assess the proper timing, dosage, and duration of the treatment to maximize beneficial effects.

Disclaimer Statements

Contributors Habibullah Dolgun was involved in conception and design, acquisition and data analysing, and interpretation of data; Erhan Turkoglu was involved in conception and design, acquisition and data analysing, interpretation of data, drafting of manuscript, and administrative, technical, or material support; Hayri Kertmen, Bora Gurer, and Erdal R. Yilmaz provided administrative, technical, or material support; Selim S. Comoglu was involved in supervision; and Zeki Sekerci was involved in supervision and critical revision of the manuscript for important intellectual content.

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Ethics approval All research procedures used were approved by the ethical committee of Diskapi Yildirim Beyazit Education and Research Hospital.

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