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Efficacy of Pregabalin on Reducing Pain in Patients with Lumbosacral Radiculopathy

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ABSTRACT

Aims Pregabalin is one of the anti-seizure and analgesic drugs, which is widely used in the treatment of neuropathic pain and chronic radiculopathy in the form of monotherapy. The aim of this study was to evaluate the effectiveness of pregabalin drug therapy with common treatment (a NSAID) on reducing pain in patients with lumbosacral radiculopathy.

Materials & Methods In this clinical trial, 90 patients with lumbosacral radiculopathy referring to the clinic of Shahid Mofatteh, Yasuj, Iran in 2018, were selected using purposeful convenience sampling and divided into intervention (N=45) and control (N=45) groups. The pain severity was assessed by standard visual analog scale (VAS). In the intervention group, 100 mg celecoxib every 12 hours, plus 75 mg per day pregabalin and in control group, 100 mg celecoxib every 12 hours, plus 75 mg per day pregabalin placebo were prescribed. After 8 weeks, the severity of the pain was again assessed and compared.

Findings At the beginning of the study, the mean pain severity in the intervention and control group did not differ significantly ($p>0.05$). After the intervention, the mean pain severity between the two groups did not show a significant difference ($p>0.05$). The severity of the pain did not differ significantly between the two groups of intervention and control according to age, disease history, location of pain and body weight ($p>0.05$).

Conclusion The efficacy of pregabalin and NSAID in comparison with NSAID use in patients with lumbosacral radiculopathy is not different in reducing pain severity.

Keywords Radiculopathy; Lumbosacral Region; Pregabalin; Low Back Pain

CITATION LINKS

[1] Accuracy of physical examination for chronic lumbar ... [2] Efficacy of gabapentin for radiculopathy caused by lumbar spinal stenosis ... [3] Lumbosacral ... [4] Diagnosis and nonoperative management of lumbar ... [5] Physical examination for lumbar radiculopathy due to disc herniation in patients with ... [6] Chronic low back pain: evaluation and management ... [7] Pharmaceutical therapy for ... [8] Evaluation and treatment of low back pain: an evidence-based approach ... [9] Medications for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians ... [10] Diagnosis and treatment of low ... [11] A Randomised, placebo-controlled trial of the effects of preoperative pregabalin on pain intensity and opioid consumption following lumbar ... [12] The effects of gastroretentive gabapentin (Gralise®) on spinal stenosis patients with ... [13] The efficiency of gabapentin therapy in patients with lumbar ... [14] The effect of pregabalin on preoperative anxiety and sedation levels: a dose ... [15] Perioperative pregabalin for postoperative pain control and quality of life after major spinal ... [16] Perioperative pregabalin improves pain and functional outcomes 3 months after lumbar ... [17] PRECISE - pregabalin in addition to usual care for sciatica: study protocol for a ... [18] A randomized, placebo-controlled trial of preoperative oral pregabalin for postoperative pain relief after minor ... [19] Pregabalin and dexamethasone in combination with paracetamol for postoperative pain control ... [20] A randomized controlled trial of perioperative administration of pregabalin for pain after ... [21] Role of calcitonin gene-related peptide and substance P in different ... [22] A protocol for systematic review for perioperative ... [23] Gabapentinoids: gabapentin and pregabalin for postoperative ... [24] Recent advances in postoperative pain ... [25] Gabapentin and postoperative pain- -a systematic review of randomized ... [26] Pregabalin in patients with postoperative dental ... [27] Persistent postsurgical pain: risk factors and ...

Introduction

Lumbosacral radiculopathy is one of the most common neurological disorders. Spondyloarthropathy is the leading cause of this syndrome and increases with age [1]. The prevalence of lumbosacral radiculopathy is approximately 3% to 5% affecting both men and women. Men aged over 40 years and women aged over 50-60 years are more likely to develop lumbosacral radiculopathy [2, 3]. The most common cause of lumbosacral radiculopathy in patients under 50 years is a herniated disc. At birth, the boundary between the nucleus pulposus and the annulus fibrosus is detectable. The amount of disc collagen increases with age, whereas the amount of water of disc decreases. As a result, a gap forms in the disc, causing changes in the annular fibers, making a person more prone to nucleus pulposus herniation [4]. Acute disc herniation causes symptoms by direct pressure on the nerve roots, as well as the inflammatory and ischemic mechanisms of the nerve roots and the posterior root ganglion [5]. The most common herniated discs occur at L4-L5 and L5-S1, leading to L5 and S1 radiculopathy. This pain is characterized by a sudden onset and severity. It increases by moving, bending to one side, or bending forward, and the Valsalva maneuver and can be improved via resting. Patients frequently complain of paresthesia in the dermatome [6].

After the age of 50, the herniated disc is less likely to cause radiculopathy, and often, chronic lesions are associated with degenerative spinal cord spondyloarthritis. With age increasing, the intervertebral discs may flatten and lose their water, transferring the body's axial loading to the articular surface, leading to hypertrophy of the articular surface, the formation of osteophytes, and the thickening of the flavum ligament. These changes cause central spinal stenosis, lateral stenosis, and creating holes. Chronic radiculopathy may be due to nerve root entrapment in the lateral stenosis, the intervertebral foramen, or the central part of the spinal canal, and involve one or more nerve roots [5].

Treatment for low back pain and radiculopathy includes supportive measures, such as exercise, weight loss, physiotherapy, pain relief, and recovery. If supportive measures fail or by observing a disruption in daily activities due to severe pain, other treatments, including medication, supplementation, surgery, etc., may be used [6]. Sometimes, due to high-risk conditions, such as chronic heart failure or chronic lung disease, or even cases, like the patient's unwillingness to have surgery, the patient can only be treated through supportive and pharmacological treatments [6].

The pathway of pain is a complex cycle of peripheral and central pathways, inflammatory mediators, and receptors [7]. Medications, such as opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, antidepressants, anticonvulsants, muscle relaxants, and topical medications can affect these components and improve symptoms [7].

Different factors, such as type of medication, pain severity and duration, and pain-related activity limitations, etc. are important in prescribing the drug. There is no single drug that specifically affects radiculopathy, or a specific guideline for prescribing the drug. Therefore, the decision to start drug treatment is based on individual conditions, drug side effects, fluctuations in pain, and quality and severity of pain [8, 9]. NSAIDs, for example, appear to be effective in treating the acute phase of radiculopathy. Acetaminophen is one of the drugs commonly used to treat low back pain and radicular pain. The main feature of acetaminophen is the inhibition of prostaglandin synthesis. It is recommended to prescribe acetaminophen as the first-line therapy for low back pain, to cause the effect quickly and as a suitable treatment for mild to moderate pain [10]. Opioids are one of the most widely used and useful painkillers, especially for people with severe pain [11]. Anticonvulsants, such as carbamazepine, topiramate, lamotrigine, gabapentin, pregabalin, etc. inhibit the sodium and calcium channels and reduce the secretion of stimulating neurotransmitters (glutamine) to strength gamma-aminobutyric acid (GABA) and stabilize neuronal membrane [12, 13].

Pregabalin is a gamma-aminobutyric acid analogue that was originally developed to treat epilepsy but is now used for several purposes, including pain relief, especially neurological pain (such as headaches and low back pain). Pregabalin was approved in 1994 by the US Food and Drug Administration (FDA) for the treatment of partial epilepsy (pregabalin is used in combination with other anticonvulsant drugs). In 2002, doctors were allowed to use the drug to reduce the pain caused by shingles (herpes neuralgia). Some physicians are currently using the drug to prevent migraine headaches, treat nystagmus, and reduce neuropathic pain.

In a study, pregabalin significantly reduced pain after lumbar disc surgery [14]. It was also reported that the pain rate was significantly lower in the pregabalin group than in the placebo group 8 hours after surgery [15]. To evaluate the effect of pregabalin on improving pain and patient function after lumbar disc surgery, 300 mg of this drug was prescribed 90 min before surgery, and 150 mg 12 and 24 h after surgery. The results showed that it reduced pain and improved postoperative patient function [16]. Pregabalin has also been shown to be effective in pain and quality of life in patients with sciatica [17].

After minor gynecologist surgical procedures in hysterectomy patients, it was reported that there was no significant difference in pain reduction compared with those treated with paracetamol and pregabalin [18, 19].

In a small number of previous studies, the effectiveness of pregabalin in the treatment of

radiculopathy has only been studied. The aim of this study was to evaluate the efficacy of pregabalin in combination with conventional therapy (NSAIDs) in reducing pain in patients with lumbosacral radiculopathy.

Materials and Methods

This clinical trial was conducted in 2018 on 90 patients with radiculopathy of spinal origin due to herniated disc referring to the clinic of Shahid Mofteh, Yasuj, Iran. Eligible patients entered the study using purposeful convenience sampling. Inclusion criteria were radiculopathy of spinal origin (due to herniated disc) based on clinical examination and MRI, the age of 25-55 years, and signing the written consent form to participate in the study. Those discontinued treatments for more than three consecutive weeks and also those were found with the progression of the disease, the need for surgery and the development of mental disorders, such as depression were excluded.

The research tools included a demographic information form, including examinations and symptoms, and a standard visual analog scale (VAS).

The VAS is a 10 cm line from 0 (no pain) at the left end to 10 (unbearable pain) at the right end. The person marks the line based on the severity of pain over the last 48 h. This scale scores pain from 0 to 10: no pain (0-1), mild pain (2-3), moderate pain (4-5), severe pain (6-7), maximum pain (8-9), and unbearable pain (10).

Patients were allocated to blocks in terms of age and sex and based on allocation with random blocks of four, divided into two groups of 45 cases, including the control and intervention groups. The pain severity in both groups was first assessed using the VAS scale and the data were noted.

A group received the routine treatment, including resting, receiving celecoxib (100 mg) every 12 h, and pregabalin placebo (75 mg). Another group received celecoxib (100 mg) every 12 h and pregabalin daily (75 mg). To blind the research, the drug and the placebo were prepared by the Abidi Pharmaceutical Company with the same appearance and with two different contents. Patients' pain levels were reassessed after 8 weeks of treatment using the mentioned questionnaire and the data were collected.

The patients participated in the study after obtaining the informed consent form. No expense was imposed on patients and insurance companies. The cases were informed about voluntary participation. All ethical observations in research on humans by the Helsinki Declaration were observed. The publication ethics issues, the confidentiality of patients' information, and general publication of data were also observed.

The collected data were analyzed by SPSS 17 software using independent t-test and paired sample t-test.

Findings

Of samples, 42 cases (46.7%) were male and 48 cases (53.3%) were female. The mean age of samples was 41.34±8.58 years. The mean age of the control and intervention groups was 39.06±8.63 and 43.62±8.00 years, respectively. The mean weight in the control and intervention groups was 68.75±11.84 and 70.28±12.14 kg, respectively. The intervention and control groups did not have a significant difference in terms of mean age and weight (p>0.05).

The pain location in the majority of the participants was low back pain, and most of them were in the age group of 40-49 years, weighed more than 70 kg, and had a one-year history of the disease (Table 1).

The mean pain severity at the baseline in the intervention and control group was not significantly different (p>0.05). After the intervention, the mean pain intensity between the two groups did not show a significant difference (p>0.05).

Also, the mean pain severity in both control and intervention groups was not significantly different after the intervention compared to before the intervention (p>0.05; Table 2).

Table 1) The absolute and relative frequency of demographic variables in intervention and control groups (n=45 per group; the numbers in parentheses are percent)

Demographic variables	Intervention group	Control group
Location of pain		
Wrist	17 (37.8)	22 (48.9)
Knees	15 (33.3)	13 (28.9)
Feet	13 (28.9)	10 (22.2)
Age group (year)		
20-29	8 (17.8)	2 (4.4)
30-39	16 (35.5)	12 (26.7)
40-49	14 (31.1)	16 (35.5)
50-59	7 (15.5)	15 (33.3)
Weight (kg)		
41-50	4 (8. 9)	3 (6.7)
51-60	8 (17. 8)	10 (22.2)
61-70	17 (37.8)	13 (28.9)
Over 70	16 (35.5)	19 (42.2)
History of disease (year)		
1	3 (6.7)	18 (40.0)
2	7 (15.5)	4 (8.9)
3	6 (13.3)	2 (4.4)
4	10 (22.2)	5 (11.1)
5	8 (17.8)	6 (13.3)
6	6 (13.3)	2 (4.4)
7	1 (2.2)	5 (11.1)
8	4 (8.9)	3 (6.7)

Table 2) Intergroup (using independent t-test) and intragroup (using paired t-test) comparison of pain intensity in the intervention and control groups in the pre-test and post-test stages

Research phases	Control group	Intervention group	t. value	Inter-group p. value
Pre-test	6.68±2.42	7.15±2.01	0.99	0.32
Post-test	6.88±2.33	7.20±2.11	0.87	0.48
t. value	0.81	0.56	-	-
Intra-group p. value	0.67	0.73	-	-

The pain severity did not differ significantly between the intervention and control groups according to age, disease history, location of pain, and body weight (p>0.05; Table 3).

Table 3) Comparison of mean pain intensity in the intervention and control groups based on demographic variables

Demographic variables	Intervention group	Control group	t. value	P. value
Location of pain				
Wrist	6.88±1.76	6.42±2.58	0.61	0.54
Knees	6.80±2.00	6.91±2.27	0.14	0.88
Feet	7.92±2.25	7.30±2.40	0.62	0.53
Age group (year)				
20-29	7.87±2.32	7.50±2.22	0.21	0.83
30-39	7.12±1.98	6.00±1.12	1.26	0.21
40-49	6.64±1.34	7.06±1.84	0.53	0.59
50-59	7.42±2.12	6.73±1.79	0.64	0.52
Weight (kg)				
41-50	8.00±1.41	7.66±2.47	0. 22	0.83
51-60	7.12±2.47	5.80±2.78	1.05	0.80
61-70	7.17±1.74	6.84±2.57	0.41	0.67
Over 70	6.93±2.26	6.89±2.18	0.05	0. 95
History of disease (year)				
1	6.00±2.64	6.61±2.70	0.36	0.72
2	6.14±2.41	8.25±1.70	1.52	0.16
3	7.83±1.72	5.50±0.70	1.78	0.12
4	7.30±2.31	6.60±2.07	0.57	0.57
5	7.25±2.12	6.83±2.78	0.31	0.75
6	7.50±1.37	8.00±1.41	0.44	0.67
7	7.00±2.19	5.60±2.50	1.23	0.28
8	7.25±1.50	6.66±3.21	0.32	0.75

Discussion

The aim of this study was to evaluate the efficacy of pregabalin in combination with conventional therapy (NSAIDs) in reducing pain in patients with lumbosacral radiculopathy.

The results of this study showed that the severity of pain did not differ significantly between the two groups of intervention and control according to age, disease history, location of pain, and body weight.

Studies using non-surgical therapies have been done, in which pregabalin did not reduce acute postoperative pain. Paech *et al*. found that pregabalin (100 mg) preoperatively did not reduce pain in the minor gynecologist surgical procedures [18]. In a study by Mathiesen *et al*., pregabalin (300 mg) with paracetamol (1 g) and dexamethasone (8 mg) preoperatively was not effective in reducing pain after hysterectomy compared to paracetamol alone or pregabalin with paracetamol [19]. Jokela *et al*. also reported that pregabalin (600 mg) caused a reduction in using oxycodone; however, at a dose of 300 mg was not different from the placebo group [20].

Through environmental sensitization, mediators, such as prostaglandins, 5-hydroxytryptamine, leukotriene, and bradykinin are released. These primary mediators release peptides, such as calcitonin gene-related peptide (CGRP), substance P, and cholecystokinin [21].

Peripheral pain receptor impulses make a synaptic connection through the A-delta and C fibers in Lamina II and V. Lamina I responds to impulses transmitted from C fibers and the neurons in Lamina V respond to harmful stimulus. In Lamina V, neurotransmitters, such as glutamate and aspartate respond to synaptic transmission [22].

The N-Methyl- d-aspartate (NMD) receptor is involved in central sensitization. This receptor is a membrane protein that regulates the entry of sodium and calcium and the release of potassium from the cell. Following the entry of calcium into the cell and the increase in its intracellular level, neurochemical and neurophysiological changes occur, which are quick and independent of the firing of spinal neurons (without external stimulation). This process is called wind-up, which stimulates posterior horn neurons without stimulation, resulting in chemical hyperalgesia and central sensitization. This type of sensitization can occur in the spinal cord or supraspinal cord, as well as in areas, such as the anterior cingulate cortex, the amygdala, and rostral ventromedial medulla [22].

Neurokinin 1 (NK1) and cyclooxygenase (COX-C) are involved in central sensitization. The dynorphin gene and NK1 in the spinal cord and COX-2 in the brain are up-regulated and exacerbate pain [22].

Pregabalin was approved by the FDA in 2004. It is originally an anticonvulsant drug, but it also has analgesic and anti-anxiety effects that are easily tolerated and have few side effects [23]. The mechanism of action of pregabalin is to bind to the alpha-2-delta subunit of the voltage-dependent calcium channel, which inhibits the release of calcium and stimulating neurotransmitters, such as glutamate, CGRP, and Substance P. As a result, it limits the content of wind-up process and reduces central sensitivity in the brain and spinal cord, and also reduces acute postoperative pain and chronic pain due to central sensitization [24-26]. Other reported cases of pregabalin use include post-herpetic neuralgia, diabetic neuropathy, and other chronic neuropathies [24]. Pregabalin at a dose of 300 mg has caused analgesic effects in animal models with acceptable side effects [21, 27].

Some studies on the effectiveness of pregabalin in reducing anxiety and sedation after elective procedures [14] have reported that pregabalin reduced pain after lumbar spinal fusion and improved quality of life three months after surgery, but it did not affect the quality of life after a year [15].

One of the limitations of this study is that pain has a multifactorial nature, in which other factors, including religious beliefs, personalities, emotional factors, different cultural and social situations, and even malingering are effective make it impossible to accurately match patients.

It is suggested that the subject of this study be studied using a larger sample size so that the results can be generalized more accurately to make it possible for planning as accurately as possible in the health system more than before. It is also recommended that the pregabalin imported and marketed under the brand name lyrica be used in another study.

Conclusion

The efficacy of pregabalin in combination with celecoxib over celecoxib alone is not significantly different in patients with lumbosacral radiculopathy. Long-term, high-dose treatments for chronic pain and central sensitization appear to be required.

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References

1- Iversen T, Solberg TK, Romner B, Wilsgaard T, Nygaard Ø, Waterloo K, et al. Accuracy of physical examination for chronic lumbar radiculopathy. BMC Musculoskelet Disord. 2013;14:206.

2- Kasimcan O, Kaptan H. Efficacy of gabapentin for radiculopathy caused by lumbar spinal stenosis and lumbar disk hernia. Neurol Med Chir (Tokyo). 2010;50(12):1070-3.

3- Tarulli AW, Raynor EM. Lumbosacral radiculopathy. Neurol Clin. 2007;25(2):387-405.

4-Shahbandar L, Press J. Diagnosis and nonoperative management of lumbar disk herniation. Oper Tech Sports Med. 2005;13(2):114-21.

5- van der Windt DA, Simons E, Riphagen II, Ammendolia C, Verhagen AP, Laslett M, et al. Physical examination for lumbar radiculopathy due to disc herniation in patients with low-back pain. Cochrane Database Syst Rev. 2010;(2):CD007431.

6- Last AR, Hulbert K. Chronic low back pain: evaluation and management. Am Fam Physician. 2009;79(12):1067-74.

7- Visco CJ, Cheng DS, Kennedy DJ. Pharmaceutical therapy for radiculopathy. Phys Med Rehabil Clin N Am. 2011;22(1):127-37.

8- Atlas SJ, Nardin RA. Evaluation and treatment of low back pain: an evidence-based approach to clinical care. Muscle Nerve. 2003;27(3):265-84.

9- Chou R, Huffman LH. Medications for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. Ann Intern Med. 2007;147(7):505-14.

10- Koes BW, van Tulder MW, Thomas S. Diagnosis and treatment of low back pain. BMJ. 2006;332(7555):1430-4.

11- Hegarty DA, Shorten GD. A Randomised, placebo-controlled trial of the effects of preoperative pregabalin on pain intensity and opioid consumption following lumbar discectomy. Korean J Pain. 2011;24(1):22-30.

12- Kaye AD, Beuno FR, Katalenich B, Stell C, Liu H, Rosinia FA, et al. The effects of gastroretentive gabapentin (Gralise®) on spinal stenosis patients with radicular pain. Pain Physician. 2014;17(2):169-78.

13- Yaksi A, Ozgönenel L, Ozgönenel B. The efficiency of gabapentin therapy in patients with lumbar spinal stenosis. Spine (Phila Pa 1976). 2007;32(9):939-42.

14- White PF, Tufanogullari B, Taylor J, Klein K. The effect of pregabalin on preoperative anxiety and sedation levels: a dose-ranging study. Anesth Analg. 2009;108(4):1140-5.

15- Gianesello L, Pavoni V, Barboni E, Galeotti I, Nella A. Perioperative pregabalin for postoperative pain control and quality of life after major spinal surgery. J Neurosurg Anesthesiol. 2012;24(2):121-6.

16- Burke SM, Shorten GD. Perioperative pregabalin improves pain and functional outcomes 3 months after lumbar discectomy. Anesth Analg. 2010;110(4):1180-5.

17- Mathieson S, Maher CG, McLachlan AJ, Latimer J, Koes BW, Hancock MJ, et al. PRECISE - pregabalin in addition to usual care for sciatica: study protocol for a randomised controlled trial. Trials. 2013;14:2013.

18- Paech MJ, Goy R, Chua S, Scott K, Christmas T, Doherty DA. A randomized, placebo-controlled trial of preoperative oral pregabalin for postoperative pain relief after minor gynecological surgery. Anesth Analg. 2007;105(5):1449-53.

19- Mathiesen O, Rasmussen ML, Dierking G, Lech K, Hilsted KL, Fomsgaard JS, et al. Pregabalin and dexamethasone in combination with paracetamol for postoperative pain control after abdominal hysterectomy. A randomized clinical trial. Acta Anaesthesiol Scand. 2009;53(2):227-35.

20- Jokela R, Ahonen J, Tallgren M, Haanpää M, Korttila K. A randomized controlled trial of perioperative administration of pregabalin for pain after laparoscopic hysterectomy. Pain. 2008;134(1-2):106-12.

21- Greco R, Tassorelli C, Sandrini G, Di Bella P, Buscone S, Nappi G. Role of calcitonin gene-related peptide and substance P in different models of pain. Cephalalgia. 2008;28(2):114-26.

22- Eipe N, Penning J, Ansari M, Yazdi F, Ahmadzai N. A protocol for systematic review for perioperative pregabalin use. Syst Rev. 2012;1(40):1-7.

23- Imani F, Rahimzadeh P. Gabapentinoids: gabapentin and pregabalin for postoperative pain management. Anesth Pain Med. 2012;2(2):52-3.

24- Vadivelu N, Mitra S, Narayan D. Recent advances in postoperative pain management. Yale J Biol Med. 2010;83(1):11-25.

25- Ho KY, Gan TJ, Habib AS. Gabapentin and postoperative pain- -a systematic review of randomized controlled trials. Pain. 2006;126(1-3):91-101.

26- Hill CM, Balkenohl M, Thomas DW, Walker R, Mathé H, Murray G. Pregabalin in patients with postoperative dental pain. Eur J Pain. 2001;5(2):119-24.

27- Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006;367:1618-25.