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ORIGINAL RESEARCH

Pre-emptive analgesia with preoperative oral gabapentin and pregabalin in lumbar narrow canal surgery

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Abstract

The success of pre-emption depends on the strategy pertaining to the choice of agent and when and how, to use. This study was aimed to evaluate the efficacy of pre-emptive analgesia regarding the postoperative pain management in lumbar spinal stenosis surgery. The oral gabapentin 800 mg or pregabalin 225 mg or placebo were administered 1 h before surgery. The pain and sedation scores were measured through Visual Analogue Scale (VAS) and Ramsay Sedation Scale (RSS). Three groups of 30 patients each were included in the study. Group 1 was administered with gabapentin 800 mg, Group 2 with pregabalin 225 mg, and Group 3 with placebo 1 hour before the surgery. VAS scores at the 1st, 2nd, 4th, 6th, 8th, 10th, 12th, 14th, 16th, 18th, 20th, 22nd and 24th hours of surgery, and RSS scores and analgesic drug usage in the 1st to 24 hours of surgery were recorded. There were statistically significant differences between the 1st, 2nd and 4th hour VAS score averages. RSS scores changed among the three groups in postoperative period. The total analgesics employed in gabapentin and pregabalin groups were lower than those in placebo group. Pre-emptive analgesia of oral pregabalin or gabapentin minimized the postoperative pain in patients undergoing lumbar stenosis surgery.

Keywords

Postoperative pain; Pre-emptive analgesia; Spinal surgery; Pregabalin; Gabapentin; Gabapentinoids; Narrow lumbar canal surgery

1. Introduction

The spinal column degenerative process unfolds in four primary stages: dysfunction, dehydration, instability and collapsing. In dysfunction stage, a potential of axial and circumferential tears in the annulus exists which is coupled with localized synovitis in facet joints to elevate the risk of developing herniated disc in affected individual. These circumferential tears lead to back pain and spinal instability and can result in leaking of the disc's gel-like material, *i.e.*, nucleus pulposus which irritates the surrounding tissues including facet joints which are the small joints for providing stability and allow movement between individual vertebrae. Facet joint synovitis refers to the inflammation of synovial membrane that lines the facet joints.

The subsequent dehydration stage is marked by progressive resorption of inner disc and facet joint degeneration which lead to ongoing shifts and changes in spine curvature. The third stage of instability relates with spine's attempt to self-stabilize amidst structural alterations, and causes heightened pain and spinal deformation. Hypertrophic bone formation around facet joints and discs occurs to foster stiff and potentially ankylosing spine. The final stage of collapsing signifies irreversible degeneration of spinal discs to cause substantial mobility loss [1–3].

Lumbar spinal stenosis (LSS) relates to the gradual narrowing of spinal canal which causes discomfort in walking. Globally, an estimated 103 million elderly individuals are affected by lumbar stenosis [4]. LSS depicts the clinical symptoms such as back and leg pain, numbness, disruptions in lower limb motor and sensory function, and intermittent claudication. They have detrimental impact on individual's daily activities, and thus diminish overall life quality. Radiological assessments of the spinal canal reveal reduced space for neural structures in the canal and neuroforamina.

The pathophysiology of LSS comprehends intervertebral disc degeneration, the degenerative hypertrophy of facet joint, and thickening of ligamentum flavum. These factors contribute to the diminished volume of neural foramina and restrict the space for spinal nerve root as it exits spinal canal through each foramen. The cauda equina syndrome can occur in severe stenosis cases with the symptoms such as bowel and bladder incontinence. These symptoms originate from the compression and ischemia of nerve roots, elevated intrathecal pressure, and nerve root inflammation due to the narrowing of canal [5, 6].

The lumbar stenosis is classified based on its origin and specific location. Anatomically, stenosis is categorized as central, lateral or a combination of both as determined by the radiography. This classification is applicable to any spine region like cervical, thoracic or lumbar. A precise anatomic classification refines the identification of stenotic site for specifying its occurrence in the central canal, lateral recess, and/or neural foramen. This is the most pragmatic method for discerning nature and extent of required surgical interventions.

The origins of lumbar stenosis were initially documented by Sarpyener in children born with dysraphic abnormalities. It is classified into two main types: developmental or congenital and acquired. Congenital stenosis arises from diffuse skeletal dysplasias, such as achondroplastic dwarfism or spondyloepiphyseal dysplasia. Degenerative spondylolisthesis is also known as pseudospondylolisthesis, which is a complication of lumbar spondylosis and results in the anterior subluxation of upper vertebra without any association with spondylolysis. The postsurgical stenosis may occur after the application of bone grafts to lamina and facets during arthrodesis. The acquired lumbar stenosis can be attributed to diverse disease processes. Beside the prevalent degenerative changes, the factors including trauma (*e.g.*, lumbar burst fracture), infections (*e.g.*, discitis, osteomyelitis, Pott's disease), and skeletal conditions such as Paget's disease, diffuse idiopathic skeletal hyperostosis, ankylosing spondylitis and rheumatoid arthritis can contribute to its occurrence. Furthermore, bone or soft tissue infiltration by tumors like prostate carcinoma, and metabolic and endocrine abnormalities such as acromegaly, pseudogout, hypoparathyroidism, renal osteodystrophy and Cushing's disease with epidural lipomatosis can cause lumbar stenosis [7].

The lumbar canal stenosis is treated by conservative and surgical approaches. Conservative treatment focuses on lifestyle modifications including weight reduction, smoking cessation, regular exercise and overall lifestyle adjustments. Additionally, oral medications or epidural and block therapies such as facet injections are administered for pain relief [8].

Pharmaceutical alternatives also exist for the LSS treatment such as non-steroidal anti-inflammatory drugs (NSAIDs), opioids, serotonin-noradrenaline reuptake inhibitors (SNRIs), pregabalin/mirogabalin, prostaglandin E1 analogs (PGE1), acetaminophen, mecobalamin, neurotropin and others.

In a recent study, the degenerative lumbar spinal disorders including LSS were linked to polypharmacy in elderly individuals with degenerative musculoskeletal disorders. LSS patients facing neuropathic pain and multiple comorbidities receive higher number of prescribed medications. Moreover, psychological factors affect the postoperative number of drugs in LSS patients undergoing lumbar surgery. It was revealed in a report that 72% LSS patients were prescribed at least one pain relief drug, while 17% relied on three or more. Among 28% LSS patients not using pain relief medication before surgery, it was likely that NSAIDs, pregabalin, and opioids were preoperatively discontinued because of their ineffectiveness.

NSAIDs have been identified as the inappropriate medications for pain relief. Moreover, the NSAIDs usage can contribute to increased medication count, as the patients may require additional drugs to mitigate the gastrointestinal bleeding risk. NSAIDs utilization from polypharmacy perspective should be discouraged wherever possible.

Lumbar spinal surgery has been effective in addressing pain, motor function, fall risk, social well-being, psychological aspects and healthy life expectancy in LSS patients. The reduction in polypharmacy among elderly patients *via* the lumbar spinal surgery has socioeconomic impact. The surgical interventions concurrently contribute to the increased medical expenses. The data indicated that some LSS patients undergoing surgery experienced postoperative reduction of three or more drugs, while others had an increase. An analysis considering various factors discerned whether preoperative conditions could predict these variations. It was highlighted that patients with a decrease of three or more drugs after the surgery had favorable psychological conditions. The mental health status had been a risk factor for polypharmacy. LSS patients with good psychological conditions might respond to the impact of surgical pain relief and thus influence the number of used drugs [9].

In this study, American Society of Anesthesiologists (ASA 1) patients who had no disease other than LSS were enrolled. They ceased all medication intake prior to the surgery and premedicated with pregabalin or gabapentin. The control group received a placebo. This approach established a homogeneous patient group with standardized conditions. The sedation and analgesia states of participants were monitored in the early postoperative period.

The surgical intervention becomes imperative to alleviate compression of neural structures, particularly the nerve roots in the case of neurological deficit, intense pain or unsuccessful outcomes from conservative treatment. This involves discectomy or foraminotomy along with the additional support through lumbar spinal fusion, especially if foraminotomy is necessary.

The predominant symptom in pre- and postoperative scenarios of LSS is pain, which impacts the sleep and life quality [10].

Patients in 80% LSS surgeries experience moderate to intense pain attributed to tissue trauma caused by surgical instruments like tissue retractors, surgical implants, prolonged surgery duration or inflammation from direct nerve injury. Acute postoperative pain can persist and transit into chronic pain if not addressed in the early stages. The postoperative pain management should commence in the preoperative period by considering cognitive, psychological and social factors. The primary postoperative pain alleviators are NSAID analgesics and physical exercises combined with opioid therapy if necessary. Anticonvulsants have also been employed in managing pre- and postoperative pains [11].

Studies have indicated a correlation between the chronic pain after spinal surgery and the utilization of preoperative analgesics. Opioids as the traditional analgesics have greater potency compared to NSAIDs. However, their long-term usage is linked with issues such as tolerance, dependence, drug flooding, withdrawal and nociceptive sensitization reactions leading to heightened pain. These factors are challenging for the clinicians to manage patients' pain, and underscore the importance of identifying alternative, effective and safe analgesics.

NSAIDs function by inhibiting cyclooxygenase (COX) isoenzyme, blocking prostaglandins production, and exerting anti-inflammatory and analgesic effects. In the spinal surgery context, non-steroidal anti-inflammatory drugs are categorized as non-opioids, with widespread applications as preoperative analgesia in surgeries including colorectal surgery and radical cystectomy. Clinicians in spine surgery are recognizing the NSAIDs potential. Several studies have reported the enhanced postoperative analgesia with perioperative NSAID administration compared to a placebo alone [12].

The pre-emptive and preventive NSAIDs can reduce pain and morphine consumption, however this effect may not be consistent in all pain and morphine consumption outcomes. Such differences are not clinically significant as there is no evidence of reduction in adverse effects by opioid usage, despite some studies report on these outcomes. Only one study has reported on clinically significant adverse events from preoperative NSAIDs. There is limited data assessing the safety of pre-emptive or preventive NSAID usage [13].

The neurological symptoms linked with LSS stem from the compression and ischemia of nerve roots compressed from direct mechanical pressure or increased intrathecal pressure by canal narrowing. Nerve roots inflammation is also a contributing factor. The prevalent causes of chronic pain include fibromyalgia, diabetic peripheral neuropathy, postherpetic neuralgia (nerve damage following shingles) and neuropathic pain associated with spinal cord injury [14].

The neuropathic pain describes any acute or chronic pain syndrome arising from abnormal processing of somatosensory pain in the central or peripheral nervous system. The symptoms of neuropathic pain include burning or electric shock sensation, hyperalgesia (increased pain sensitivity), hyperpathia (exaggerated response to painful stimuli), dysesthesia (abnormal sensation), allodynia (pain by non-painful stimuli) and paresthesia (tingling or prickling sensation) [15].

Motor and sensory deficits occur with nociceptive or neuropathic pain after spinal cord injury. The neuropathic pain can manifest at above or below the level of spinal cord injury. It may result from the damage to nerve root which is the actual site of spinal cord injury or pathophysiological changes affecting neurons in the pain transduction pathway [16].

Studies demonstrate that gabapentinoids facilitate the sprouting and regeneration of corticospinal axons in mice after the spinal cord injury [17].

Human studies reveal pronounced anti-nociceptive effect of single acute dose of pregabalin administered before surgery. A dosage of 75–150 mg alleviates the post-operative pain in surgical procedures including orthopedic surgery [18], lumbar discectomy [19], septoplasty [20], thyroidectomy [21] and hysterectomy [22]. These clinical findings support the mechanism of pregabalin efficacy. However, the variability in factors such as the surgery invasiveness, duration of post-operative follow-ups, and limited statistics hinders in evaluating these studies through meta-analysis [23].

Gabapentin and pregabalin are collectively known as gabapentinoids. They were originally developed for the epilepsy treatment. They mimic GABA (Gamma-aminobutyric acid) action and modulate GABA metabolism. However, these drugs have high affinity for $\alpha 2$-δ subunits-1 and 2 of voltage-activated calcium channels. The binding of gabapentinoids to these subunits inhibits cellular calcium influx for attenuating the neurotransmission. This occurs through the same hypothesized molecular mechanism and controls the neuronal hyperexcitability.

Gabapentinoids are efficient in pain management and act as first line treatment for neuropathic pain syndromes regardless of their underlying causes. These drugs have similar action mechanism wherein they inhibit calcium influx and release excitatory neurotransmitters. They manage neuropathic pain by binding to voltage-gated calcium channels in the central nervous system (CNS) and specifically targeting the alpha-2-delta protein. This binding reduces neurotransmitter release in the CNS by diminishing calcium influx from the gated channels.

Pregabalin and gabapentin have minimal drug-drug interactions. They are not affected by cytochrome P450 enzyme because of no significant drug metabolism, *i.e.*, $<1\%$ [24, 25].

The American Society of Anesthesiologists (ASA) recommends to initiate multimodal analgesia in the preoperative period. Pre-emptive analgesia has been more effective than postoperative analgesia. The non-adequately addressed acute postoperative pain at the early stages can persist and transit into chronic pain. The postoperative pain management should thus commence before the surgery by considering the cognitive, psychological and social factors. Pain is commonly alleviated by using NSAIDs and physical exercises along with opioid therapy if necessary. Anticonvulsants are also given for pre- and post-operative pain management. The emphasis on multimodal analgesia by the ASA underscores its importance through various strategies and interventions [26–29].

2. Materials and methods

The study was conducted at the Neurosurgical and Anesthesiology departments of Tekirdağ Namık Kemal University Hospital from 01 February to 01 August 2021.

The study included 90 patients of 18–65 years old with 50–90 kg weight, belonging to ASA 1 group, and undergoing lumbar surgery for lumbar canal stenosis. Patients of <1 h and >3 h operations were excluded from the study. Patients underwent blood analysis, bleeding profile and biochemical examination prior to the surgery. The chest radiographs and electrocardiograms (ECG) were also analyzed for each patient.

The study enrolled ASA 1 patients with no disease other than LSS. Participants in this category stopped all medication before the surgery and were premedicated with pregabalin or gabapentin. The control group received a placebo. This approach standardized the patients to ensure a homogeneous group for analysis.

The sedation and analgesia states of patients were monitored in the early postoperative period. The study was designed as randomized, double-blind and placebo-controlled trial. Thirty patients were placed in each group. Prior to the surgery, all participants underwent overnight fasting and received gabapentin 800 mg or pregabalin 225 mg or placebo 1 hour before surgery. Patients were continuously monitored during the surgery for parameters including ECG, SpO_2 (oxygen saturation), blood pressure, respiratory rate and $ETCO_2$ (end-tidal carbon diox-

ide). An 18 G intravenous cannula was also inserted.

The anesthesia was induced using 2–2.5 mg propofol, 1–2 mcg/kg fentanyl and 0.6 mg rocuronium bromide. The double-blindness of study ensured that patients and researchers were unaware of administered premedication which eliminated the potential biases in study outcomes. The patients were laid in prone position after intubation using Macintosh blades. Anesthesia was sustained with a mixture of 50% O_2, 50% N_2O and 1–2% sevoflurane. Patients diagnosed with LSS underwent surgery after the clinical and radiological assessments.

The procedure included spinal cord decompression by posterior midline approach, stabilization of spine by posterior transpedicular screws, and the posterolateral interbody fusion surgery by autogenous bone graft. The incision length varied based on the required number of laminectomies. The bony spinous process, lamina and the thickened ligamentum flavum connecting the adjacent vertebrae were removed by a drill. The procedure was repeated for each affected vertebra. The protective sac covering the spinal cord and nerve roots were retracted to address bone spurs and thickened ligaments. The facet joints over nerve roots were trimmed to widen the neural foramen.

For posterolateral fusion, the two vertebrae were joined using pedicle screws to naturally fuse over time with the help of bone graft harvested from iliac crest autograft present at the pelvic bone rim. This bone graft contained cells, proteins and scaffolding to promote bone healing. Fusion did not occur immediately, rather the bone graft supported bone growth over months after the surgical procedure. The spinal fusion united the two spinal bones (vertebrae) to form single solid bone for restoring spinal stability and alignment. Autograft bone had no risk of disease transmission as it was originated from the patient's own body. This familiarity provided optimal conditions for the healthy bone fusion, immobilized the painful vertebral segment, and enhanced spinal stability while relieving the nerve compression.

Patients were brought in supine position on the completion of surgery, administered with 0.5 mg atropine and 2 mg neostigmine, and extubated. Stable patients were transferred to the ward and monitored for 24 hours postoperatively. Their pain levels were assessed using VAS and sedation status *via* RSS score.

Intravenous 1 g/100 mL paracetamol was administered as rescue analgesia in cases of patients experiencing pain. Additional 75 mg diclofenac sodium was intramuscularly given if pain persisted. Time till the first analgesic, and the total post-operatively administered analgesic dosages were documented for the subsequent comparisons.

RSS score being a widely accepted tool in anesthesiology was employed to gauge sedation levels in medical patients. It was introduced in 1974. The scale was comprised of six levels ranging from level one (minimal sedation) to level six (deep sedation). The scale had two parts: levels 1–3 assessed waking, while 4–6 evaluated sleeping. Level 4 denoted light sedation where patients still responded to stimulus. Level 5 was a sluggish response, and level 6 indicated complete sedation where patients were unresponsive to stimulus.

3. Statistics

The collected data were analysed using "Statistical Package for the Social Sciences-PC version 17.0 program (SPSS Statistics for Windows, IBM, Chicago, IL, USA)". The sample size was determined using G*Power 3.1.9.2 version (Allgemeine Psychologie und Arbeitspsychologie, Heinrich-Heine-Universitsat, Dusseldorf, Germany) [30]. The one-way analysis of variance (ANOVA) test was conducted with alpha set at 0.05, effect size (d) at 0.34, and power at 0.80. The calculated sample size was 87.A total of 90 patients were placed in three groups each with 30 participants.

Descriptive statistics including frequency, percentage, mean and standard deviation were applied. Kolmogorov-Smirnov test assessed the data to find if it followed parametric distribution. Internal consistency analysis was conducted *via* Cronbach alpha coefficients. ANOVA analysis compared more than three dependent and non-dependent groups. A *post-hoc* Tukey test was applied if significant difference was observed. A t-test was employed in cases with less than three groups. A p-value < 0.05 was considered statistically significant.

4. Results

The patients'mean age was 54.13 ± 1.22 with 72.2% women and 27.8% men. Group I (n = 30) orally received gabapentin 800 mg, Group II (n = 30) received pregabalin 225 mg, and Group III (n = 30) received placebo 1 hour before the operation. Group I had 76.6% women and 23.4% men. Group II had 76.6% women and 23.4% men. Group III had 63.3% women, and 36.7% men. There was no significant difference in the gender distribution of groups ($p = 0.421$) (Table 1).

TABLE 1. Demographic characteristics of the patients.

Demographic characteristics	n	%
Age (Mean ± SD)	54.3 ± 1.22	
Gender (F/M)		
Female (F)	65	72.2
Male (M)	25	27.8
Groups		
Group I (n:30)	30	33.3
Female	23	76.6
Male	7	23.4
Group II (n:30)	30	33.3
Female	23	76.6
Male	7	23.4
Group III (n:30)	30	33.3
Female	19	63.3
Male	11	36.7

SD: standard deviation.

A statistically significant decrease in the Visual Analog Scale (VAS) score was observed ($p < 0.05$). VAS score was higher in women compared to men ($p = 0.012 < 0.05$) (Table 2). Differences in the VAS scores were found among the groups during the 1st hour ($p < 0.05$), 2nd hour ($p = 0.04 < 0.05$) and 4th hour ($p = 0.039 < 0.05$) of surgery. VAS score in Group III (placebo control) was higher compared to the other two groups. A difference was evident between the placebo group and the groups receiving gabapentin or pregabalin (Table 3).

A difference in VAS score was found between Group III and Group I ($p = 0.022$), as well as Group III and Group II ($p = 0.049$). VAS score in Group I was higher compared to Groups II and III. The placebo control group exhibited higher VAS score than the other two groups to indicate that the preoperative administration of gabapentinoids reduced the postoperative analgesic requirements (Table 4).

In 1st hour of surgery, 68.9% patients were awake and tranquil, and increased to 98.9% in 2nd and 6th hours. All patients were awake and tranquil by the 8th hour. No signifi-

TABLE 2. Postoperative hourly VAS scores in gender difference.

Postoperative period	VAS Score in gender			Statistical analysis
	Female	Male	Total	
	Mean ± SD	Mean ± SD	Mean ± SD	*p*
1st. h VAS score	6.89 ± 1.96	5.88 ± 2.06	6.61 ± 2.03	
2nd. h VAS score	5.49 ± 1.93	4.40 ± 2.17	5.18 ± 2.05	
4th. h VAS score	4.67 ± 2.19	3.52 ± 2.12	4.35 ± 2.22	
6th. h VAS score	4.38 ± 1.86	3.20 ± 2.23	4.05 ± 2.03	
8th. h VAS score	3.98 ± 1.71	2.88 ± 1.90	3.67 ± 1.82	
10th. h VAS score	3.60 ± 1.59	2.68 ± 1.62	3.34 ± 1.65	
12th. h VAS score	3.32 ± 1.68	2.52 ± 1.47	3.10 ± 1.66	0.012*
14th. h VAS score	3.09 ± 1.65	2.28 ± 1.17	2.86 ± 1.57	
16th. h VAS score	2.89 ± 1.67	2.20 ± 1.19	2.70 ± 1.58	
18th. h VAS score	2.56 ± 1.47	2.12 ± 1.20	2.44 ± 1.45	
20th. h VAS score	2.46 ± 1.44	2.08 ± 1.11	2.35 ± 1.36	
22nd. h VAS score	2.40 ± 1.38	1.96 ± 1.05	2.27 ± 1.31	
24th. h VAS score	2.30 ± 1.29	1.88 ± 1.09	2.18 ± 1.25	
VAS score change				<0.001

**p < 0.05; VAS: Visual Analogue Scale; SD: Standard deviation.*

TABLE 3. Postoperative hourly VAS scores in different groups.

Postoperative period	Groups			Statistical analysis	
	Group I (n:30)	Group II (n:30)	Group III (n:30)		
	Mean ± SD	Mean ± SD	Mean ± SD	*F*	*p*
1st. h VAS score	6.23 ± 1.59	6.36 ± 2.65	7.23 ± 1.59	10.213	<0.001*
2nd. h VAS score	4.80 ± 1.74	4.60 ± 2.34	6.16 ± 1.70	3.245	0.044*
4th. h VAS score	3.80 ± 2.02	3.83 ± 2.54	5.43 ± 1.67	3.371	0.039*
6th. h VAS score	3.80 ± 2.17	3.63 ± 2.28	4.73 ± 1.43	2.248	0.112
8th. h VAS score	3.40 ± 2.01	3.40 ± 1.92	4.23 ± 1.43	1.376	0.258
10th. h VAS score	2.90 ± 1.76	3.30 ± 1.82	3.83 ± 1.20	3.034	0.053
12th. h VAS score	2.70 ± 1.64	2.96 ± 1.97	3.63 ± 1.18	2.338	0.103
14th. h VAS score	2.63 ± 1.69	2.60 ± 1.75	3.36 ± 1.12	1.298	0.278
16th. h VAS score	2.46 ± 1.81	2.53 ± 1.73	3.10 ± 1.06	1.781	0.175
18th. h VAS score	2.10 ± 1.53	2.26 ± 1.50	2.96 ± 1.03	0.566	0.570
20th. h VAS score	2.00 ± 1.43	2.30 ± 1.60	2.76 ± 0.89	1.187	0.310
22nd. h VAS score	1.93 ± 1.28	2.20 ± 1.58	2.70 ± 0.91	0.639	0.530
24th. h VAS score	1.90 ± 1.26	2.00 ± 1.46	2.66 ± 0.84	0.328	0.721

**p < 0.05; VAS: Visual Analogue Scale; SD: Standard deviation.*

TABLE 4. Postoperative total VAS scores in different groups.

VAS score	*p*
Group I (n:30)	
Group II (n:30)	1.000
Group III (n:30)	0.022*
Group II (n:30)	
Group I (n:30)	1.000
Group III (n:30)	0.049*
Group III (n:30)	
Group I (n:30)	0.022*
Group II (n:30)	0.049*

**p < 0.05; VAS: Visual Analogue Scale.*

cant difference was found in the RSS score ($p = 0.331 > 0.05$) among different points in time (Table 5).

A total of 76.7% patients in Group I, 60% in Group II, and 63.3% in Group III did not show change in the RSS score in first postoperative 24 hours. Furthermore, 20% in Group I, 33.3% in Group II, and 36.7% in Group III showed increase from level 1 (awake, alert, anxious and agitated) to level 2 (awake, tranquil, oriented and cooperative). Additionally, 3.3% in Group I, and 6.7% in Group II depicted decrease from level 2 to level 1. Group III had no such decrease. Moreover, 53.8% women (and no man) did not show change in the RSS score in postoperative 24 hours. A total of 41.5% women showing change had increase from level 1 to level 2, and 4.6% had decrease from level 2 to level 1. There was no significant difference in the changes of RSS score between the groups, however a difference was found based on the gender ($p < 0.05$) (Table 6).

In this study, changes in the RSS score were assessed in groups I, II and III. In Group I, 85.7% patients exhibited changes in RSS score during the postoperative 2nd h, and 14.3% in the 6th h. In Group II, 83.3% patients experienced changes in the 2nd hour, 8.3% in 4th hour, and 8.3% in 6th hour. In Group III, all the patients displayed changes in the 2nd hour. However, the differences between groups were not statistically significant ($p > 0.05$). Changes in the RSS score were significant based on the gender. Specifically, 90% women exhibited changes in the 2nd hour, 6.6% in 6th hour and 3.3% in 4th hour (Table 7).

The statistical correlation between the changes in RSS score and gender was confirmed ($p < 0.05$) (Table 8).

No statistically significant difference was found between men and women regarding postoperative analgesic need ($p = 0.660 > 0.05$). The mean analgesic need in women was 2.43 ± 0.181, and in men was 2.28 ± 0.319 in 1st postoperative 24 hours.

There was statistically significant difference between the groups ($p < 0.05$). Group I had 1.47 ± 0.178, Group II had 1.77 ± 0.190, and Group III had 3.93 ± 0 as the mean analgesic need (Table 9). The postoperative analgesic need in Groups I and II was statistically lower than in Group III ($p < 0.05$) (Table 10).

The postoperative analgesic regimen did not exhibit significant difference in postoperative hours ($p = 0.553 > 0.05$). The total analgesic need was lower in Groups I and II compared to Group III, though no statistically significant difference was found between Groups I and II ($p = 1.000 > 0.05$). Group 3 was the placebo group, and indicated that pre-emptive analgesia reduced the postoperative analgesic requirements. There was difference between pregabalin and gabapentin groups, however not statistically significant (Table 11).

5. Discussion

The primary preoperative and postoperative symptom in lumbar stenosis patients was pain where 70% patients experienced postoperative pain [31]. Macintyre *et al.* [32] reported that pre-emptive analgesia was more effective compared to managing postoperative interventions and therapeutics.

Wall in 1988 proposed that preoperative pre-emptive analgesia was conducive and managed through various strategies, including the analgesic injection before incision, advanced mobilization after surgery, and functional rehabilitation [33].

Preventive analgesia provided neuroprotection in addition to reducing postoperative pain. Perioperative pregabalin reduced the postoperative opioid consumption, particularly after the surgery causing severe pain [34].

A study measuring postoperative pain using Visual Analog Scale (VAS) pain rating depicted that preoperative gabapentin 600 mg and 900 mg were more effective than 300 mg. They led to the longer pain-free intervals until the first rescue analgesia, and lower total doses in the first postoperative 24 hours of laparoscopic abdominal surgeries. Patients receiving gabapentin 900 mg had higher sedation, somnolence, and dry mouth compared to other two groups. Preoperative gabapentin 300 mg administration did not reduce postoperative analgesic needs. The gabapentin 600 mg or 900 mg administered one hour before surgery was superior compared to 300 mg. Gabapentin 600 mg given one hour before surgery was as effective as gabapentin 900mg to control postoperative nausea and vomiting (PONV) and reduces VAS scores for 24-hour postoperative pain [35].

In another study, Group G received oral gabapentin 600 mg, while Group C oral placebo one hour before the surgery. The primary outcome was the severity of postoperative pain on VAS that ranged from 0 to 10 cm at 0, 6th and 12th hours. Secondary outcomes included the time for first analgesic request, frequency of rescue analgesia in the first 12 hours, and postoperative sedation assessed by the RSS score at 0, 6th and 12th hours. Gabapentin group (G) exhibited lower VAS scores at 6th and 12th hours compared to the control group (C). Group G also had a longer analgesia duration and delayed analgesic rescue compared to the control. RSS score showed insignificant differences between the two groups at 0, 6th and 12th hours of surgery. The conclusion was that single preoperative gabapentin dose was effective in reducing postoperative pain, prolonging analgesia duration and decreasing total opioid consumption, with no complications [36].

In another study, a preoperative gabapentin 900 mg had neuroprotection, and reduced opioid needs in inguinal hernia surgery, with no effect on sedation score [37].

In a meta-analysis, the preoperative gabapentin and prega-

TABLE 5. Postoperative hourly Ramsey scores of the patients.

Post-operative period	Awake, agitated, and/or crying		Awake, tranquil, observe surroundings		RAMSEY Sedation Scale score	Statistical analysis
	n	%	n	%	Mean ± SD	*p*
1st. h	28	31.1	62	68.9	1.68 ± 0.46	
2nd. h	1	1.1	89	98.9	1.98 ± 0.10	
4th. h	2	2.2	88	97.8	1.97 ± 0.14	
6th. h	1	1.1	89	98.9	1.98 ± 0.10	
8th. h	0	0	90	100.0	2.00 ± 0.00	
10th. h	0	0	90	100.0	2.00 ± 0.00	
12th. h	0	0	90	100.0	2.00 ± 0.00	0.331
14th. h	0	0	90	100.0	2.00 ± 0.00	
16th. h	0	0	90	100.0	2.00 ± 0.00	
18th. h	0	0	90	100.0	2.00 ± 0.00	
20th. h	0	0	90	100.0	2.00 ± 0.00	
22nd. h	0	0	90	100.0	2.00 ± 0.00	
24th. h	0	0	90	100.0	2.00 ± 0.00	

SD: Standard deviation.

TABLE 6. Postoperative Ramsay sedation score changes between groups.

	Change in Ramsay sedation scale								Statistical analysis
	No change		Change in the score				Total change		
			From 1 up to 2		From 2 down to 1				
	n	%	n	%	n	%	n	%	
Group									
Group I (n:30)	23	76.7	6	20.0	1	3.3	30	33.3	
Group II (n:30)	18	60.0	10	33.3	2	6.7	30	33.3	
Group III (n:30)	19	63.3	11	36.7	0	0	30	33.3	$p = 0.373$
Total	60	66.7	27	30.0	3	3.3	90	100.0	

TABLE 7. Postoperative hourly changes of RAMSAY score in different groups.

	Hourly change of RAMSAY scale in the postoperative 24 hours between groups								Statistical analysis
	2. h		4. h		6. h		Total		*p*
	n	%	n	%	n	%	n	%	
Groups									
Group I (n:30)	6	85.7	0	0	1	14.3	7	23.3	
Group II (n:30)	10	83.3	1	8.3	1	8.3	12	40.0	
Group III (n:30)	11	100.0	0	0	0	0	11	36.6	0.511
Total	27	90.0	1	3.3	2	6.6	30	100.0	

*$p < 0.05$.

TABLE 8. Postoperative hourly change in Ramsay sedation scales depending of the gender.

	Hourly RAMSAY scale change in the postoperative 24 hours								Statistical analysis
	2. h		4. h		6. h		Total		*p*
	n	%	n	%	n	%	n	%	
Gender									
Female	27	90	1	3.3	2	6.6	30	100	
Male	0	0	0	0	0	0	0	0	0.001*
Total	27	90	1	33.3	2	6.6	30	100	

*$p < 0.05$.

TABLE 9. Postoperative analgesic need of the patients depending of the gender and preoperative analgesia use in different groups.

Demographic characteristics	n	Postoperative analgesic use	Statistical Analysis
		Mean ± SD	*p*
Gender			
Female	55	2.43 ± 0.181	0.660
Male	25	2.28 ± 0.319	
Preoperative analgesia			
Group I (n:30)	30	1.47 ± 0.178	
Group II (n:30)	30	1.77 ± 0.190	<0.001
Group III (n:30)	30	3.93 ± 0.185	

*SD: Standard deviation; *p < 0.05.*

TABLE 10. Comparison of the groups for postoperative rescue analgesia.

Groups	*t*	SD	*p*
Group I (n:30) Group II (n:30)	−5.900	6.571	1.000
Group I (n:30) Group III (n:30)	−41.400	6.571	<0.001*
Group II (n:30) Group III (n:30)	−35.500	6.571	<0.001*

*SD: Standard Deviation; *p < 0.05.*

TABLE 11. Postoperative hourly analgesic use of the patients.

Postoperative period	Analgesic drug use				Mean analgesic drug quantity	Statistical analysis
	Yes		No			*p*
	n	%	n	%	Mean ± SD	
1st. h	71	78.9	19	21.1	1.21 ± 0.41	
2nd. h	35	38.9	55	61.1	1.61 ± 0.49	
4th. h	13	14.4	77	85.6	1.85 ± 0.35	
6th. h	11	12.2	79	87.8	1.87 ± 0.32	
8th. h	15	16.7	75	83.3	1.83 ± 0.37	
10th. h	19	21.7	71	78.9	1.78 ± 0.41	0.553
12th. h	10	11.1	80	88.9	1.88 ± 0.31	
14th. h	14	15.6	76	84.4	1.84 ± 0.36	
16th. h	10	11.1	80	88.9	1.88 ± 0.31	
18th. h	7	7.8	83	92.2	1.92 ± 0.26	
20th. h	5	5.6	85	94.4	1.94 ± 0.23	
22nd. h	6	6.7	84	93.3	1.93 ± 0.25	
24th. h	1	1.1	89	98.9	1.98 ± 0.10	
Total analgesic quantity					2.38 ± 1.48	

SD: Standard Deviation.

balin usage before spine surgery reduced the narcotic consumption and postoperative VAS scores. Administering increased doses of gabapentin (300, 600, 900, 1200 mg) lowered VAS scores and postoperative analgesic quantity compared to placebo. VAS pain score was the lowest with gabapentin 900 mg per day, followed by its 1200 mg, 600 mg, 300 mg, and pregabalin 150 mg and 75 mg. Additionally, gabapentin 900 mg per day usage had the lowest opioid consumption among all doses of gabapentin and pregabalin with mean difference of −22.07% (95% CI, −33.22% to −10.92%) for the area under cumulative ranking curve as compared to placebo. No statistically significant difference was found in adverse events (nausea, vomiting and dizziness) of all treatments [38].

In this study, gabapentin 800 mg was administered prior

to lumbar stenosis surgery with a significant difference in postoperative pain and RSS score. Karri *et al*. [39] reported that gabapentin 600 mg reduced the postoperative analgesic need in the first 4 hours with higher RSS score compared to the placebo group [39].

Geng *et al*. [40] administered oral gabapentin 600 mg 2 hours before gynecologic laparoscopic surgery and noted lower postoperative pain score, shorter hospital stay, faster intestinal recovery, lesser opioid need, and lower C-reactive protein (CPR) values compared to placebo group.

In a prospective, randomized, comparative double blinded study, 90 patients aged 18–45 years with ASA grade I or II posted for elective surgical procedure under general anesthesia were randomly allocated to two equal groups (45 in each group) to receive either 600 mg oral gabapentin or 150 mg oral pregabalin 1 h prior to surgery and showed that Gabapentin 600 mg attenuates hemodynamic surge response better than pregabalin 150 mg during laryngoscopy and endotracheal intubation in terms of Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and rate pressure product (RPP) at 3, 5 and 10 min after intubation, while there was no significant difference between the two groups at 1 min after intubation. By using an independent sample t test, there was no statistically significant ($p > 0.05$) difference in the sedation score between the two groups. Post-extubation, 2 patients in group gabapentin and 3 patients in group pregabalin had a ramsay sedation score of $\geq$3. By using an independent sample *t*-test, the *p*-value was 0.44, which was statistically not significant [41].

Kim *et al*. [42] studied various doses of oral pregabalin in lumbar spinal fusion surgery as adjunct drug with multimodal analgesic regime and found that preoperative oral pregabalin 150 mg was the optimal dose with sufficient efficiency and minimal side effects.

Kumar *et al*. [43] observed meaningful anxiolytic effects and less postoperative analgesic need in lumbar laminectomy patients administered with preoperative pregabalin 150 mg compared to the placebo. However, higher sedation scores were observed with preoperative oral pregabalin 225 mg in this study. Buvanendran *et al.* [44] demonstrated that single preoperative dose of pregabalin 300 mg reduced the central sensitization.

Spreng *et al.* [45] found that oral pregabalin 150 mg provided lower VAS score and reduction in opioid consumption compared to the placebo. Entezary *et al*. [46] reported that preoperative pregabalin 300 mg reduced the postoperative pain in abdominal hysterectomy. Kara reported that upper extremity surgery patients receiving preoperative oral pregabalin 150 mg had less postoperative analgesic need [47].

Sattari *et al*. [48] reported that patients had less post-thoracotomy pain when administered with preoperative pregabalin 300 mg.

Sing *et al*. [49] compared preoperative pregabalin 150 mg and 300 mg in laparoscopic cholecystectomy patients.Both groups had lower scores compared to the placebo, however with no significant difference between 150 mg and 300 mg. Paech *et al*. [50] administered single dose of preoperative pregabalin 100 mg and did not find sufficient difference in postoperative pain.

Peng *et al*. [51] employed preoperative oral pregabalin 75 mg and found limited analgesic effect in postoperative pain. Zhang *et al*. [52] conducted meta-analysis to find that preoperative pregabalin reduced the opioid need in first postoperative 24 hours, however pain intensity was not changed much. In this study, pregabalin 225 mg given 1 hour prior to lumbar stenosis surgery reduced the analgesic requirements compared to placebo ($p < 0.05$), with lower VAS score ($p < 0.05$).

Omara *et al*. [53] found that preoperative oral pregabalin reduced the postoperative need in first postoperative 24 hours of orthopedic surgery. Bafna *et al*. [54] performing spinal anesthesia in gynecologic surgery compared the effect of preoperative pregabalin and gabapentin, and found less analgesic need in first postoperative 24 hours. Tobias *et al*. [55] reported *via* meta-analysis that preoperative pregabalin suppressed the postoperative pain and reduced opioid requirement. In this study, the total analgesic need with gabapentin 800 mg was lower, and much lower with pregabalin 225 mg compared to the placebo ($p < 0.05$).

Purcu *et al*. [56] used pre-emptive pregabalin 150 mg with no effect on sedation. Tunc *et al*. [57] did not find significant difference in RSS score between preoperative pregabalin 150 mg and placebo group.

The US Food and Drug Administration (FDA) granted early approval in 1990s to antiepileptic drugs gabapentin and pregabalin as the new generation of antiepileptic medications for addressing post-herpetic neuralgia. Both substances are the analogs of neurotransmitter γ-aminobutyric acid (GABA), however lack pharmacological activity on GABA receptors. They are also used in treating neuropathic pain and share commonalities with some distinctions.

Gabapentin and pregabalin do not undergo hepatic metabolism and exhibit low binding affinity to plasma proteins. They do not induce or inhibit liver microsomal enzymes and seldomly engage in interactions with other drugs. Pregabalin's analgesic effect stems from its antagonistic action on voltage-gated Ca^{2+} channels wherein it primarily targets the type I $\alpha 2$-δ subunit of voltage-dependent Ca^{2+} channels in central nervous system (CNS). Gabapentin shows analgesic effects through mechanisms such as amplifying the inhibitory input of GABA-mediated pathway, countering N-methyl-D-aspartic acid receptor (NMDA) activity, antagonizing calcium channels in CNS, and inhibiting peripheral nerve conduction. Gabapentin can also influence the type I $\alpha 2$-δ subunits of voltage-dependent Ca^{2+}channels.

Clinical studies have identified common adverse reactions associated with pregabalin, including dry mouth, drowsiness, dizziness, edema and peripheral edema when administered in combination or at elevated doses. Similarly, gabapentin encompasses common side effects of nausea, dizziness, vomiting, edema and pruritus.

Both medications may thus result in adverse effects such as dizziness, drowsiness, fatigue, weakness and somnolence [58]. In this study, no side effects were observed related to preoperative gabapentinoids, which could be attributed to the anesthesia administration following the drug intake. Another explanation could be that the patients already experienced neuropathic pain before the study.

Studies cover various doses of gabapentin 300, 600, 900 and

1200 mg, as well as pregabalin 75, 150 and 300 mg. However, gap exists in literature regarding gabapentin 800 mg and pregabalin 225 mg, despite the availability of corresponding capsules in the market.

There is a neuropathic component in lumbar stenosis pain which poses challenge for pain relief with just NSAIDs. Gabapentinoids have been proven efficient in alleviating this pain. The pain dynamics undergo complete transformation after surgery. All medications are discontinued prior to surgery, and pregabalin and gabapentin are administered as pre-emptive medication while the control group receives placebo. The goal is to achieve complete pain relief after surgery, or to mitigate the intensity of postoperative pain.

Managing postoperative pain is crucial, as the untreated pain may escalate into chronic pain, and pose challenges for resolution. Pre-emptive analgesia has thus emerged to achieve such pain relief.

6. Conclusions

Patients undergoing lumbar stenosis surgery were administered with oral gabapentin 800 mg, or pregabalin 225 mg, or a placebo one hour prior to the surgery. The results depicted no significant differences in patient characteristics, including age, gender, operation duration, concurrent diseases, and ASA classification, among the groups. There was no significant difference in analgesic count based on the gender ($p = 0.660 > 0.05$). However, the total analgesic count was lower in gabapentin and pregabalin groups compared to the placebo ($p < 0.05$).

In conclusion, the preoperative oral administration of gabapentin or pregabalin may reduce postoperative pain, delay the pain medication requirement, and decrease the overall usage of analgesics in patients undergoing lumbar canal stenosis surgery.

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AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article.

AUTHOR CONTRIBUTIONS

CM—designed the research study, and wrote the manuscript. FO, NK, IY and MCA—performed the research. MJD—analyzed the data.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Namık Kemal University Medical Faculty Ethical Committee on 12 May 2020, with reference No. 02, and The Ethical Committee of The Ministry of Health on 22 June 2020, with reference No. 66175679-514.04.01-E.146122. The participants provided written consent for the study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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