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A Comparison Between Pregabalin and Gabapentin as Adjuvants to Opioids in Elective Lumbar Microdiscectomy to Control Postoperative Pain: A Randomized-Controlled Study

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ABSTRACT

Background: Although pregabalin and gabapentin have been used to control pain after spinal surgery, there is little evidence comparing their analgesic advantages to opioids.

Objective: The current study aimed to assess efficacy and safety of analgesia with pregabalin versus gabapentin compared to opioids in patients undergoing elective lumbar microdiscectomy.

Methods: This randomized-controlled trial included 72 patients scheduled for elective lumbar microdiscectomy. The patients were randomly allocated to three groups. Each group enrolled 24 patients who received 0.1 mg/kg of morphine intramuscularly 30 minutes before the surgery. One hour before the surgery, 150 mg of pregabalin was given orally for the pregabalin (P) group, meanwhile, in the gabapentin (G) group, 400 mg of gabapentin were given orally, and in the control (C) group, 100 micrograms of vitamin B12 were given orally. The primary outcome was the time to first rescue analgesia. The secondary outcomes were the intraoperative hemodynamics, visual analogue score, total consumption of morphine during the first postoperative 24 h, and morphine complications.

Results: Groups P and G had significantly longer time to first analgesia and significantly lower total morphine consumption during the first 24 h and visual analogue scores at 10, 12, 16, 20, and 24 hours postoperatively. All groups had comparable hemodynamic parameters and postoperative complications.

Conclusion: In elective lumbar microdiscectomy, preoperative administration of pregabalin provided longer time to first rescue analgesia with better acute pain control and lower total analgesic consumption compared to gabapentin and opioid analgesia.

Keywords: lumbar discectomy, Pregabalin, Gabapentin, Analgesia, Opioid.

INTRODUCTION

Acute postoperative pain is a common problem after spine surgery. Eighty percent of these patients rate their pain as severe [(1)]. Postoperative pain can be brought on by tissue damage, inflammatory, neuropathic, or visceral in nature. Both peripheral and central sensitization has a role in the development of pain [(2)]. Thus, preemptive analgesia aims to prevent central sensitization brought on by surgical incisional injury and other inflammatory reactions to surgery. Preemptive analgesia is a form of treatment that begins before surgery [(3)].

Morphine is the first treatment option for postsurgical pain. However, its use has been restricted because of several side effects including nausea and vomiting, respiratory depression, itching, constipation, and urine retention. Furthermore, some forms of pain do not respond well to opioids [(1)]. Thus, using a variety of pharmacologic medications could improve early ambulation, early release, and a lower incidence of pain [(4)]. Gabapentinoids are anticonvulsant drugs including pregabalin and gabapentin. Food and Drug Administration has licensed gabapentinoids to treat a number of ailments, such as partial seizures, nerve pain from spinal cord injuries, shingles, and diabetes [(5)].

Pregabalin and gabapentin have a well-established place in the treatment of neuropathic pain [(6, 7)]. In experimental research on neuropathic pain and inflammatory hyperalgesia, gabapentin and pregabalin were found to exhibit antinociceptive and antihyperalgesic characteristics. Furthermore, pregabalin decreases several neurotransmitters' (e.g., serotonin, glutamate, dopamine, and substance P) release by interacting with the calcium channel's 2-subunit [(8)].

Pregabalin is approximately 2.5 times the potency of gabapentin [(9)]. Over the past ten years, the off-label use of gabapentinoids for managing acute nociceptive pain, postoperative analgesia and to reduce opiate use has dramatically increased [(5, 10)]. However, the scientific evidence for the growing gabapentinoids use is contradictory, which may indicate clinical agnosticism instead of additional proof of clinical efficacy [(11)].

As the possibility of opioid-induced respiratory depression was raised by gabapentinoids, an increased rate of naloxone administration was linked to continued usage of chronic gabapentin after surgery [(12)]. Thus, the current study aimed to assess efficacy and safety of preoperative administration of pregabalin versus gabapentin as adjuvants to opioids for postoperative pain in elective lumbar microdiscectomy.

METHODS

Study design: This randomized trial was carried out at the Neurosurgery Unit, Kasr Al-Ainy Hospital, Egypt between September and November 2022.

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Inclusion criteria: The study enrolled 72 adults (20-60 year-old) patients, of both genders, with body mass index (BMI) ≤ 35 and ASA I or II who were scheduled for elective lumbar microdiscectomy.

Exclusion criteria: Bronchial asthma, severe coagulation disorders, disturbed consciousness level, psychological disorder, impaired renal function, and creatinine clearance less than 50 ml/min.

Randomization: We used a computer-generated, randomization chart and the sealed envelopes method [13]. Patients' allocation was concealed from the anesthesiologist assessing and enrolling participants.

Masking: Both the patients and the outcome assessors were masked. The anesthesiologist who administered the study drugs was not involved in intraoperative or postoperative monitoring and management.

Interventions

A total of 72 patients were divided into three groups (each group included 24 patients) who underwent elective lumbar microdiscectomy. Patients in the pregabalin (P) group received 150 mg of pregabalin (Lyroline®, 150 mg, Gelatin capsules, Hikma Quality, Egypt) orally one h before the surgery plus 0.1 mg/kg of morphine intramuscularly 30 minutes before the surgery. Patients in the gabapentin (G) group received 400 mg of gabapentin (Gaptin®, 400 mg, Capsules, Delta Pharmaceutical Industries, Egypt) orally one h before the surgery plus 0.1 mg/kg of morphine intramuscularly 30 minutes before the surgery. Patients in the control (C) group were given 100 mcg of vitamin B12 (Solgar®, 100 mcg, Capsules, Solgar, United States) orally one h before the surgery plus 0.1 mg/kg of morphine intramuscularly 30 minutes before the surgery. Full history taking, clinical examination, and routine laboratory investigations were performed for all participants.

Upon arrival to the operating room, the baseline vital data (heart rate [HR], oxygen saturation, and mean arterial pressure [MAP]) were recorded. A wide-bore cannula was secured, oxygen (2 L/min) was administered through a nasal cannula, and 70-80 mcg/kg of midazolam and 4 mg of ondansetron were given to all patients.

To induce general anesthesia, fentanyl (1 µg/kg), propofol (2 mg/kg) and atracrium (0.5 mg/kg) were intravenously administered. An endotracheal tube was inserted, and the lungs were mechanically ventilated to sustain a 30-35 mmHg end-tidal CO_2 level. Anesthesia was maintained with isoflurane at end-tidal 1.3% (1.2 MAC) in 50% oxygen /air mixture by controlled mechanical ventilation, keeping the end-tidal CO_2 at 30-35 mmHg with top up doses of atracurium (0.1 mg/kg) every 30 minutes. If the MAP and/or the HR increased by 20% or 25% from the preoperative baseline, further bolus doses of fentanyl 0.5 µg/kg were administered. Patient positioning (prone position) and precautions of this position were considered.

At the end of the surgery, all patients were placed in supine position and transported to the recovery room after extubation and being fully awake. The HR and MAP were recorded at 15 min from intubation, before and after the prone position, and every 30 min until the end of surgery. The intensity of pain was assessed postoperatively and every 2 h for the first 24 h by the visual analogue scale (VAS) [14]. Postoperatively, paracetamol (1 gm) infusion was given, once VAS score was equal or less than three. Paracetamol (1 gm) and ketorolac (30 mg) infusion were given, once VAS was equal to four or more until six. Morphine (3 mg) was given, once VAS was more than or equal to ten. Time to the first analgesic request and the total morphine consumption were recorded. Adverse effects including respiratory depression, pruritus, hypotension, nausea and vomiting, or bradycardia were recorded and managed according to the usual protocols.

Study outcomes

The time to first rescue analgesia was the primary outcome of this study, whereas the intraoperative hemodynamics (HR and MAP), VAS score, total morphine consumption in the first 24 h, and adverse effects of morphine (nausea, vomiting, respiratory depression, itching, constipation, urine retention) were considered as the secondary outcomes.

Sample size: We used the G*Power software to determine the sample size. The followings were considered: alpha = 0.05, power = 0.80, f = 0.40, and the sample size required was 66 patients, which was increased to 72 patients (24 patients per group) to compensate for the possible drop-out.

Ethical concerns: This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. This study obtained approval from the Ethics Committee of Kasr Al-Ainy Hospital (ms-159-2020). All participants gave informed, written consents.

Statistical analysis

The SPSS software, version 20 for Windows (IBM© Corp., Chicago, Illinois, USA) was used for statistical analysis. Shapiro-Wilk test was used to test for normality of the numerical data. Comparisons between the three groups were carried out using the one-way analysis of variance test for numerical data or Kruskal Wallis test, Mann-Whitney test, or Pearson's Chi-square test for categorical data. Significance was adopted at p-value ≤ 0.05.

RESULTS

We assessed 90 patients. A total of 18 patients were excluded because of refusal (N=10) and coagulation disorders (N=8), and 72 patients were included and randomly allocated to three groups (each comprised 24 patients).

Table (1) showed that the studied groups were comparable regarding age, gender, and ASA status.

Table 1. Patients' characteristics

	Pregabalin group (n=24)	**Gabapentin group (n=24)**	**Control group (n=24)**
Age, year, Mean ± SD	45.67 ± 11.42	45.21 ± 12.95	45.50 ± 11.03
Sex			
Female, n (%)	18 (75.0%)	15 (62.5%)	15 (62.5%)
Male, n (%)	6 (25.0%)	9 (37.5%)	9 (37.5%)
ASA			
I, n (%)	15 (62.5%)	13 (54.2%)	14 (58.3%)
II, n (%)	9 (37.5%)	11 (45.8%)	10 (41.7%)

The P and G groups had significantly longer time to the first rescue analgesia compared to the control group (15.14 ± 7.99 h and 13.17 ± 5.22 h vs 8.46 ± 4.89 h, respectively; P = 0.038). The intervention groups P and G had significantly lower total morphine consumption than group C (3 mg vs. 6 mg, P < 0.025) with no statistical difference between groups P and G. Postoperatively, the VAS scores at 10, 12, 16, and 20 h after surgery were significantly lower in the P and G groups than the corresponding times in group C (P = 0.017, P < 0.001, P < 0.001, P < 0.001, and P = 0.021, respectively). The incidence of postoperative nausea and vomiting, urine retention, constipation, respiratory depression, and itching was comparable in the three groups (Table 2).

Table 2. Postoperative analgesic consumption, postoperative visual analogue scale, and postoperative complications

Variable	**Pregabalin group (n=24)**	**Gabapentin group (n=24)**	**Control group (n=24)**	**P-value**
Time to first analgesic, h, Mean ± SD	15.14±7.9 9	13.17±5.22	8.46±4.8 9	0.038*
Total morphine consumption within the first 24 h, mg, median (range)	3 (3-6)	3 (3-6)	6 (3-6)	0.025*
VAS, median (range)				
VAS immediately postoperative	1 (0-1)	1 (0-1)	1 (0-1)	0.605
VAS after 2 h	1 (0-1)	1 (0-1)	2 (0-1)	0.857
VAS after 4 h	1 (0-1)	1 (0-1)	2 (1-1)	0.759
VAS after 6 h	1 (0-1)	2 (0-1)	2 (1-1)	0.587
VAS after 8 h	1 (0-1)	2 (0-1)	2 (1-2)	0.129
VAS after 12 h	1 (0-1)	2 (0-1)	3 (2-4)	0.017*
VAS after 14 h	2 (0-1)	3 (1-2)	4 (2-5)	<0.001**
VAS after 16 h	3 (1-4)	3 (1-4)	5 (3-6)	<0.001**
VAS after 18 h	3 (1-3)	4 (1-5)	5 (3-6)	<0.001**
VAS after 20 h	2 (0-2)	3 (1-4)	4 (2-5)	0.021*
VAS after 22 h	1 (0-1)	1 (0-1)	1 (0-1)	0.605
VAS after 24 h	1 (0-1)	1 (0-1)	2 (0-1)	0.857
Postoperative nausea/vomiting, n (%)	6 (25.0%)	4 (16.7%)	5 (20.8%)	0.777
Postoperative urine retention, n (%)	1 (4.2%)	0 (0.0%)	1 (4.2%)	0.598
Postoperative constipation, n (%)	2 (8.3%)	2 (8.3%)	0 (0.0%)	0.347
Postoperative respiratory depression, n (%)	1 (4.2%)	1 (4.2%)	0 (0.0%)	0.598
Postoperative itching, n (%)	6 (25.0%)	6 (25.0%)	4 (16.7%)	0.725

*Significant

The studied groups were comparable regarding the intraoperative and postoperative HR and MAP (Figures 1, 2, 3, and 4, all P > 0.05).

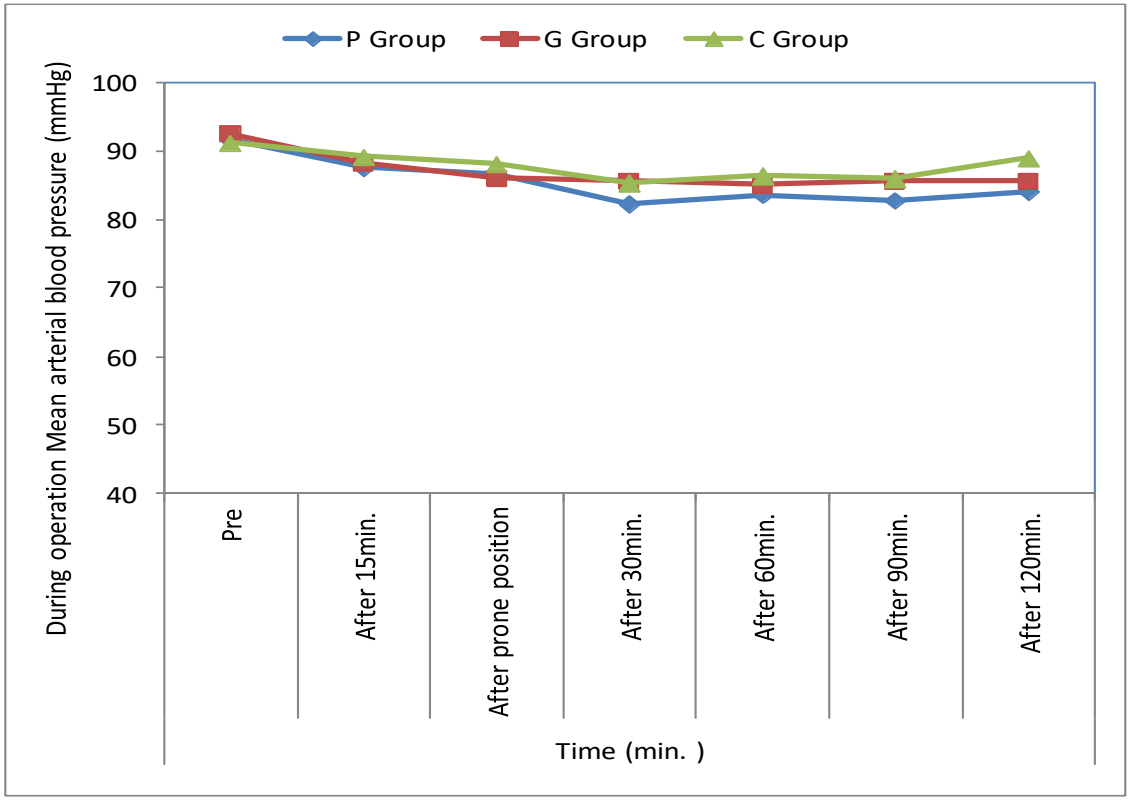

Figure 1. Intraoperative heart rate (HR, beat/min)

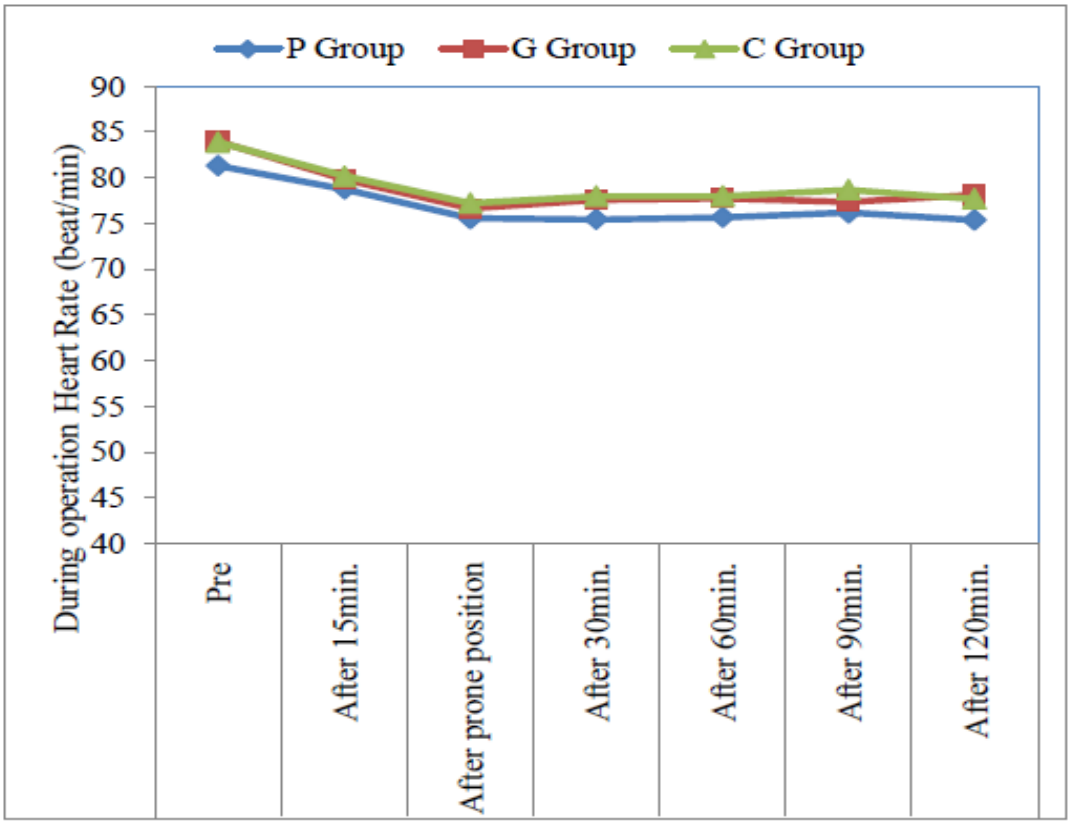

Figure 2. Intraoperative mean arterial blood pressure (MAP, mmHg)

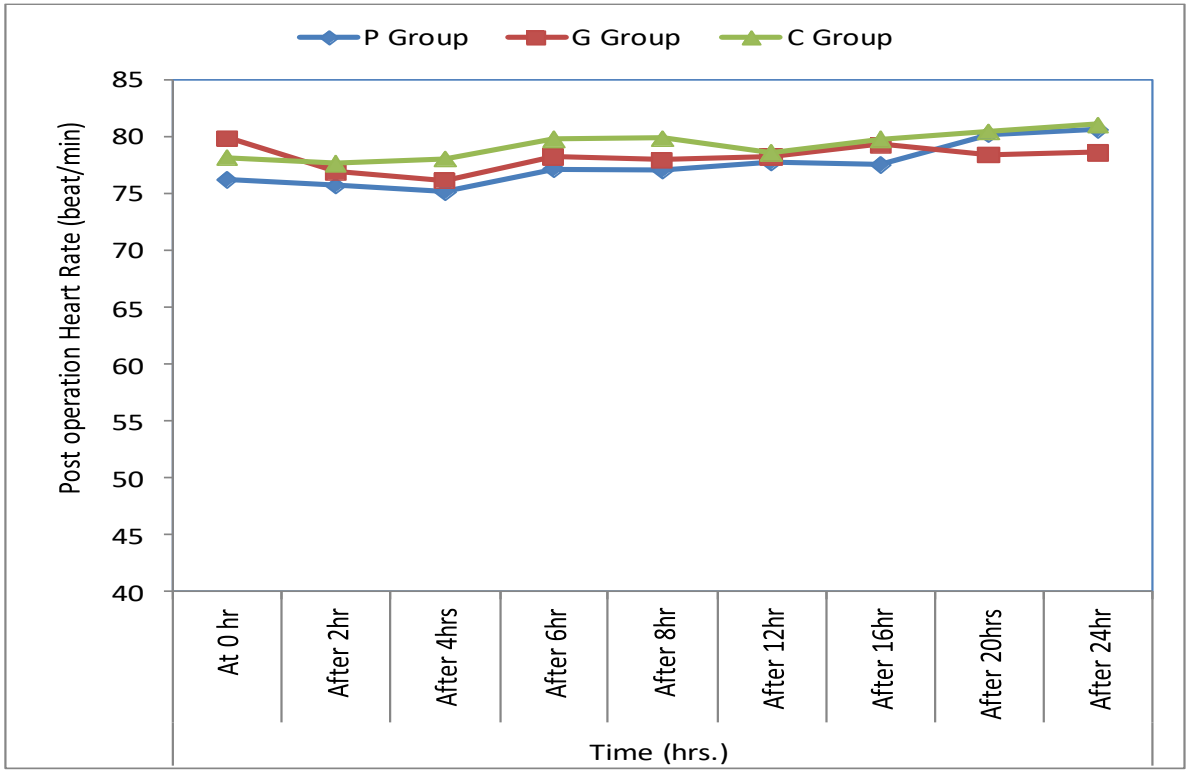

Figure 3. Postoperative heart rate (HR, beat/min)

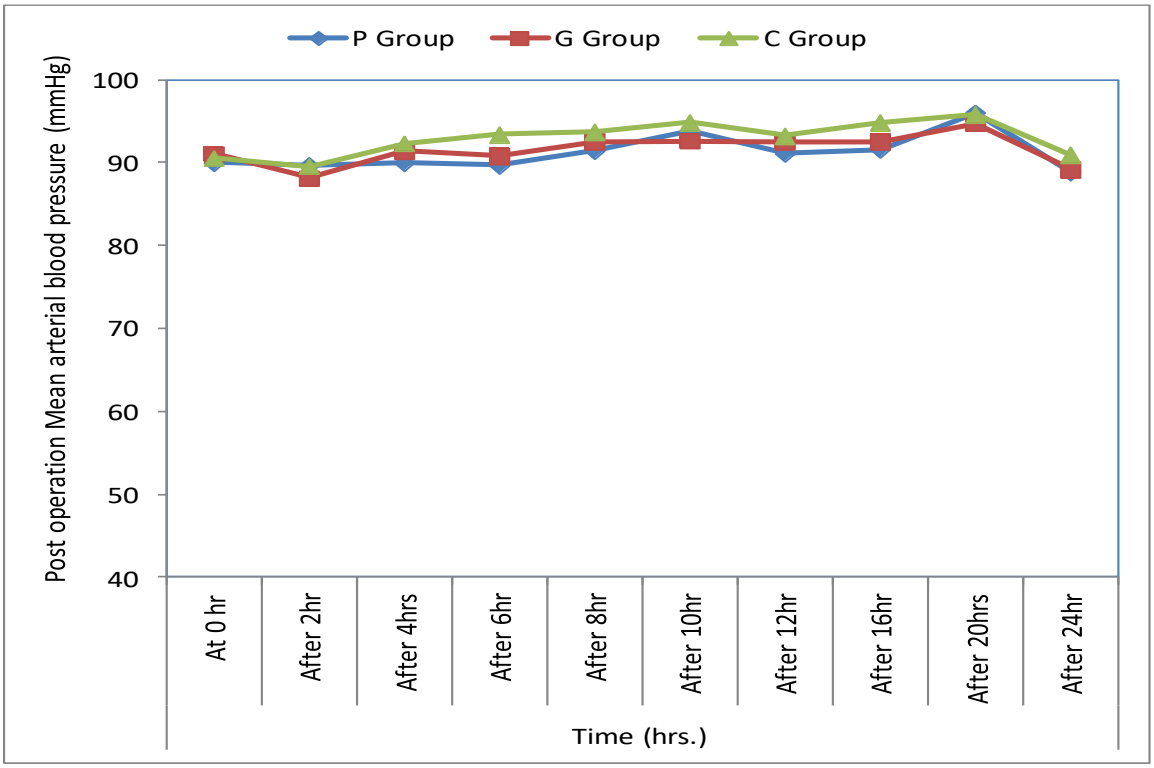

Figure 4. Postoperative mean arterial blood pressure (MAP, mmHg)

DISCUSSION

Evidence for the best postoperative pain management following neurosurgery is lacking. In addition, postoperative pain management is a continuous struggle and carries a risk of complications and adverse effects during recovery from lumbar microdiscectomy [15]. The study aimed to assess efficacy and safety of pregabalin or gabapentin as adjuvants to opioids for managing post lumbar microdiscectomy pain.

The current study showed that addition of oral preoperative pregabalin (150 mg) or gabapentin (400 mg) to opioids significantly increased the time to first analgesic demand, decreased the needs for morphine, and reduced the postoperative VAS scores at 10, 12, 16, and 20 h compared to opioids alone. Moreover, pregabalin was more effective in controlling pain than gabapentin. Several studies investigated pregabalin and gabapentin efficacy for management of postoperative pain with different doses. Pregabalin was used in doses ranging from 75 to 450 mg, and gabapentin was used in doses from 300 to 1200 mg in various clinical trials. In concordance to our findings, pregabalin (150 mg) was more effective than gabapentin (900 mg) at one h before laparoscopic cholecystectomy [16]. Furthermore, **Singh *et al.*** [17] documented that 150 mg of pregabalin exhibited greater effectiveness than a dose of 300 mg in reducing postoperative pain. Also, **Kien *et al.*** [18] found that both pregabalin (150 mg) and celecoxib given two hours before lumbar spine surgery resulted in a significantly decreased VAS scores as well as morphine consumption in the first 24 h. However, in our study we used pregabalin at one h before the surgery without nonsteroidal anti-inflammatory drugs.

In abdominal hysterectomy, **Ghai *et al.*** [19] reported that pregabalin (300 mg) 1-2 hours preoperatively produced better pain control than 900 mg gabapentin and a placebo. In lower extremity orthopedic surgery, **Montazeri *et al.*** [20] showed that the use of 300 mg of gabapentin two hours before the surgery were effective in managing pain compared to the placebo.

Khetarpal *et al.* [21] reported that both pregabalin (300 mg) and gabapentin (1200 mg) considerably minimized the need for epidural top-ups and postoperative rescue analgesia while lengthening the duration of post-spinal anesthesia. In lumbar discectomy, **Khurana *et al.*** [22] investigated oral pregabalin (75 mg) versus gabapentin (300 mg) and placebo. Pregabalin showed more reduction of pain intensity and better functional outcomes compared to gabapentin and placebo for 3 months after the surgery. Pregabalin shows superior pharmacokinetic characteristics and stronger analgesic efficacy than gabapentin. Though pregabalin therapeutic dose has a wide range, it displays extremely predictable and linear pharmacokinetics with little inter-subject variability [5].

In our study, the preemptive oral use of pregabalin and gabapentin decreased the perioperative pain. Similarly, **Khan *et al.*** [23] compared the preoperative and postoperative administration of gabapentin with different doses in lumbar laminectomy. Preoperative gabapentin administration in doses of 600, 900, and 1200 mg was effective in pain management compared to the postoperative regimen. Moreover, in elective decompressive lumbar spine surgery, **Gianesello *et al.*** [24] compared the preoperative and postoperative pregabalin intake. Preoperative pregabalin provided effective pain control and lowered the VAS scores during the first 12 h after surgery compared to the postoperative pregabalin. However, the VAS score values differed from our findings, which might be attributed to the higher dose of preoperative pregabalin (300 mg) compared to that used in our study (150 mg).

Furthermore, ketorolac and morphine were administered for 48 h postoperatively, meanwhile we used different rescue analgesic methods. Contrary to our findings, **Qadeer *et al.*** [25] compared the preoperative administration of pregabalin versus gabapentin for one week before lumbar microdiscectomy.

At lower doses, pregabalin and gabapentin showed comparable efficacy in relieving postoperative pain. In total knee arthroplasty, **Yik *et al.*** [26] compared 75 mg of pregabalin and oral tramadol to a placebo, and found that pregabalin did not reduce the total amount of opioid consumption. This may be due to the smaller dose of pregabalin (75 mg) compared to that (150 mg) used in our study. Furthermore, the preemptive use of tramadol instead of morphine was less effective compared to our findings. **Li *et al.*** [27] assessed the effects of gabapentin (600 & 300 mg) compared to placebo in reconstructive pelvic surgery. The studied groups showed comparable results as regards opioid requirements, time to leaving the recovery room, length of stay in the recovery room, and VAS scores. This discrepancy in findings is, most probably, due to the smaller sample size and different doses of gabapentin compared to our study. In addition, **Konstantatos *et al.*** [28] investigated the role of preoperative dose of 300 mg of pregabalin in the management of acute and chronic post-thoracotomy pain. Peri-operative pregabalin did not reduce pain during the nine months of postoperative period. Pregabalin was supposed to be able to stop pain from growing, although it might not be able to reduce pain from surgery alone.

The safety of both pregabalin and gabapentin as adjuvants to morphine was another aim of our study. The incidences of intraoperative and postoperative

complications were comparable in the three studied groups. **Mishra *et al*. [16]**, **Khetarpal *et al*. [21]**, **Kien *et al*. [18]** and **Singh *et al*. [17]** agree to our findings and documented safe preemptive pregabalin and gabapentin administration as adjuvants to morphine.

LIMITATIONS

We used pregabalin and gabapentin in a single dose, which may have resulted in decreased effect over time. Furthermore, the current research had a small sample size, and it was conducted in a single-center.

CONCLUSIONS

In lumbar microdiscectomy, preoperative pregabalin (150 mg) adjuvant to morphine significantly lengthened the postoperative analgesia and reduced the analgesic requirements and postoperative pain compared to 400 mg of gabapentin.

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