Comparison of Preoperative Administration of Pregabalin and Duloxetine on Cognitive Functions and Pain Management After Spinal Surgery

A Randomized, Double-blind, Placebo-controlled Study

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Study Objective: Surgical trauma is known to induce hyperalgesia, and if pain management is insufficient, it contributes to persistent pain in the postoperative period. In this study, our primary aims were to compare the effect of pregabalin and duloxetine on postoperative pain scores and cognitive functions. Our secondary aim was to determine drug-related side effects.

Design: This was a prospective, randomized, double-blind, placebo-controlled study.

Settings: The study was carried out in the setting of the operating room and the surgical ward.

Patients: Ninety-four patients, 18 to 65 years of age, ASA status I-II, scheduled for elective repair of lumbar disc herniation were enrolled in the study.

Interventions: The patients were randomly divided into 3 groups: the first group received pregabalin 75 mg orally 1 hour before the surgery and at the postoperative 12th and 24th hours. The second group received duloxetine 60 mg orally 1 hour before the surgery. At the postoperative 12th hour, they received a placebo capsule, and, at the 24th hour, they received duloxetine 60 mg again. The third group received placebo capsules orally at all timepoints.

Measurements: Postoperative pain evaluation was conducted using a Visual Analogue Scale at the postoperative first minute, 30th minute, first hour, and the 12th, 24th, and 48th hours. The preoperative and postoperative sixth hour cognitive functions were evaluated with Montreal Cognitive Assessment (MoCA) test.

Main Results: There was a significant reduction in mean MoCA scores postoperatively in all groups ($P < 0.01$). The highest MoCA score reduction was in the pregabalin group (1.83 ± 1.31 point), then in the duloxetine group (1.16 ± 0.82), and the least decrease was in the control group (0.49 ± 0.61). At all timepoints, the mean Visual Analogue Scale scores of the pregabalin and duloxetine groups were similar to each other, and they were lower than that of the control group ($P < 0.05$).

Conclusions: Preoperative use of duloxetine 60 mg can be an useful alternative to pregabalin 75 mg, as it has a similar analgesic effect on postoperative pain, with fewer incidences of drug-related negative effects on cognitive function.

Key Words: adjuvant, cognitive function, duloxetine, multimodal analgesia, postoperative pain, pregabalin

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Surgical trauma is known to induce hyperalgesia, and, if the pain management is insufficient, it contributes to persistent pain in the postoperative period.[1] Preemptive analgesia is the preventive inhibition of the pain pathway before the establishment of injury-induced hypersensitivity and can attenuate postoperative pain with different drugs and analgesic techniques.[2] Currently, opioids remain to be the analgesics of choice to treat moderate to severe pain after major surgery. Unfortunately, they are commonly associated with serious adverse effects such as respiratory depression, nausea, vomiting, pruritus, and constipation, which can inhibit rapid recovery and rehabilitation.[3] Hence, an alternative pain management approach for an opioid-sparing effect is needed in the perioperative period.

To date, several agents have been used as adjuvant therapy to general anesthesia to reduce opioid consumption in the postoperative period. Pregabalin binds to the α2-δ subunit of presynaptic, voltage-dependent calcium channels in the central and peripheral nervous system, with 6 times more affinity than gabapentin.[4] Some previous studies on pregabalin have shown a reduction effect on postoperative opioid consumption and acute postoperative pain.[5–7] However, they have reported an increased incidence of side effects such as sedation, dizziness, blurred vision, and headache related to pregabalin use.[7,8]

Recently, duloxetine, which is a potent selective serotonin and norepinephrine reuptake inhibitor, has been reported to reduce morphine requirements in the first 48 hours after knee replacement surgery.[9] Similarly, in a previous study, it was found to decrease postoperative pain scores and morphine consumption after lumbar laminectomy.[10]

Both pregabalin and duloxetine seem to be effective adjuvant analgesics to reduce postoperative pain and opioid consumption; however, studies concerning their effects on postoperative cognitive functions are limited.

The Montreal Cognitive Assessment (MoCA), which has been developed by Nasreddine et al,[11] is a screening test to assess several different components of cognitive functions, such as attention and concentration, executive functions, memory, and orientation domains. Although it was

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initially validated in Alzheimer patients with a cut-off of 26 points,[11] it has been used in several studies for detection of cognitive dysfunction after different surgeries, with different cut-off points.[12–14] MoCA has gained popularity for screening in the postoperative period, because it has a significantly higher sensitivity (90%) than the Mini Mental Test (18%) for detection of mild cognitive impairment (MCI)[11]; it is independent from demographic variables, and it takes a shorter time to administer. Turkish validity and reliability studies were completed in 2014.[15,16]

In the current study, our primary aims were to compare the effect of these 2 drugs on postoperative pain scores, as assessed by 100 mm Visual Analogue Scale (VAS), and postoperative cognitive function, as assessed using the MoCA, after preoperative administration of pregabalin 75 mg and duloxetin 60 mg orally. Our secondary aim was to determine drug-related side effects such as nausea, vomiting, and dizziness.

MATERIALS AND METHODS

After the institutional ethical committee approval (Muğla Sıtkı Koçman University Training and Research Hospital Institutional Ethics Commitee, 09.02.2017, decision number: VI), the study was conducted as a randomized, double-blind, placebo-controlled trial in an academic setting and in accordance with the Helsinki declaration. Written informed consent was obtained from each patient before enrollment. The patients between 18 and 65 years of age with ASA status I-II and scheduled for an elective repair of lumbar disc herniation were included in the study. The preoperative cognitive function levels of the patients were assessed using the 30-point MoCA, and the patients with a preoperative MoCA score under 24 were excluded from the study. The other exclusion criteria were known allergy for study drugs, history of impaired hepatic and/or renal function, chronic use of analgesics and opioids, preoperative use of duloxetine or pregabalin, alcohol and drug abuse, and body mass index over 40 mg/m^2.

The patients were randomly divided into 3 groups on the basis of a computerized randomization table created by a researcher was not involved in the study. The patients in the first group (pregabalin) received pregabalin 75 mg orally 1 hour before the surgery. The dose (75 mg) was repeated orally at the postoperative 12th and at the 24th hours. The patients in the second group (duloxetine) received duloxetine 60 mg orally 1 hour before the surgery. At the postoperative 12th hour, they received a matching microcellulose placebo capsule orally, and, at the postoperative 24th hour, they received duloxetine 60 mg again orally. The patients in the third group (placebo), received matching microcellulose placebo capsules orally at all timepoints. All of the study drugs and placebo capsules, which were prepared by the Department of Pharmacy, had the same appearance. One of the researchers who was blinded to the study groups, directly observed the patients while taking the capsules in the surgical ward.

In the operating room, all of the patients received a standard monitoring including electrocardiography, noninvasive blood pressure, peripheral oxygen saturation, and bispectral index monitoring (Datex-Ohmeda S/5 monitor M-BIS module, Helsinki, Finland). After placement of a 20 gough intravenous line, an infusion of serum physiological solution with a rate of 15 mL/kg/h was started. All of the patients received 100% oxygen by a face mask; thereafter, an anesthesiologist, who was blinded to the study groups, performed inductions with 2-3 mg/kg intravenous propofol and 1 mcg/kg intravenous fentanyl, until each patient's bispectral index monitor score decreased to a range of 40 to 60. Thereafter, 0.6 mg/kg intravenous rocuronium bromide was applied to perform endotracheal intubation. All of the patients received 4% to 6% end-tidal desflurane in the 3 L of 40% O_2 and 60% N_2O. The minimum alveolar concentration of desflurane was regulated in order to maintain a bispectral index monitor score value between 40 and 60 for each patient. When the heart rate or blood pressure of the patients increased to $>20\%$ of the basal measurements, 1 mcg/kg intravenous fentanyl was applied.

At the end of the surgery, 4 mg intravenous ondansetron was applied for postoperative nausea, and 1 mg/kg intravenous tramadol was applied for postoperative pain management to all of the participants. By the end of skin closure, the anesthesiologist stopped inhaled anesthetic agents, and administered 0.1 mg/kg of atropine and 0.5 mg/kg of neostigmine, to reverse the neuromuscular blockage. After a successful extubation, the anesthesiologist rated the postoperative pain of the patients from 0 to 10 by evaluating the expression on their faces in the operating room. The vital signs of the patients were observed for an hour in the recovery room, and then they were sent to the surgical ward. The participants received intravenous 1000 mg paracetamol every 8 hours until the end of the first postoperative day, and, when their VAS score at rest was ≥ 4, they received intramuscular 75 mg diclofenac sodium as a rescue analgesic through nurse assistance. The time for the first analgesic need and total amount of analgesic requirements in the first 24 hours were recorded. Postoperative pain evaluation of the patients was conducted by a researcher who was blinded to the study groups. At the postoperative first minute, the researcher evaluated the expression on the patients' faces and rated the postoperative pain by using a slider VAS. At the postoperative 30th minute, first hour, 12th hour, 24th hour, and 48th hour, the researcher directly asked patients to rate their pain by using 100 mm VAS. The postoperative cognitive functions of the patients were evaluated with the MoCA test at the postoperative sixth hour by the same blinded researcher.

Statistical Analyses

The sample size of the study was calculated on the basis of previous studies[17–19] in which preoperative pregabalin caused at least 10% difference in postoperative VAS scores, and, assuming α error = 0.05 (2-tailed) and β error = 0.2, and a power of 0.92, 26 participants were needed per treatment group. Considering the drop-out ratio as 10%, at least 30 patients per group were included in the study.

Number Cruncher Statistical System (NCSS) 2007 (Kaysville, UT) programme was used for statistical analysis. While the study variables were assessed, besides descriptive statistical methods (mean, median, minimum-maximum, SD, ratio), a 1-way analysis of variance was used for the comparison of parametric variables with normal distribution between ≥ 3 groups, and the Bonferroni test was used for comparison between 2 groups. The Kruskal-Wallis test was used for the comparison of parametric variables with abnormal distribution between ≥ 3 groups, and the Mann-Whitney *U* test was used for the comparison between 2 groups. Pearson χ^2 test and the Fisher-Freeman-Halton tests were used for the comparison of nonparametric variables. The paired sample *t* test was used for the comparison

of variables with normal distribution within groups. A P-value <0.05 was assessed as statistically significant.

RESULTS

A total of 105 patients were enrolled into the study. Two of the patients were excluded, as they had a preoperative MoCA score <24, and 4 of the patients declined to participate. Hence, 99 patients were randomized into 3 groups. Two patients in the duloxetine group and 3 patients in the pregabalin group were excluded during the follow-up due to delay in the postoperative MoCA assessment. Consequently, 94 patients completed the study (Fig. 1). Age, BMI, sex, distribution of comorbidities, ASA scores, preoperative pain scores, duration of surgeries, and intraoperative fentanyl consumption of the patients were similar between the groups (Table 1).

There was no statistically significant difference for the mean preoperative and mean postoperative MoCA scores between the groups ($P=0.806$, 0.073, respectively). However, there was a significant reduction in mean MoCA scores at the postoperative period when compared with the preoperative period in all of the groups ($P<0.01$).

The highest MoCA score reduction was in the pregabalin group (1.83 ± 1.31 points), and the lowest MoCA score reduction was in the control group (0.49 ± 0.61 points). When we compared mean MoCA score reduction of the groups, we found that the difference was statistically significant ($P<0.01$). The mean MoCA score reduction of the pregabalin group was higher than the duloxetine group and the control group ($P=0.040$ and 0.001, respectively).

TABLE 1. The Demographic Variables of the Patients

	Duloxetine (n = 31)	Pregabalin (n = 30)	Control (n = 33)	*P*
Age	53 ± 11	54 ± 11	54 ± 11	0.934
BMI (kg/m^2)	28 ± 3	27 ± 4	28 ± 3	0.533
Sex				
Male	11 (30.6)	13 (36.1)	12 (33.3)	0.787
Female	20 (34.6)	17 (29.3)	21 (36.2)	
Comorbidity				
No	13 (39.4)	10 (30.3)	10 (30.3)	0.603
Yes	18 (29.5)	20 (32.8)	23 (37.7)	
ASA score				
I	13 (40.6)	9 (28.1)	10 (31.3)	0.530
II	18 (29)	21(33.9)	23 (37.1)	
Fentanyl use (mcg)	95 ± 26	99 ± 29	102 ± 29	0.668
Preoperative VAS score	5 ± 1	5 ± 1	5 ± 1	0.544
Operation time (min)	90 ± 9	88 ± 11	89 ± 9	0.589

Data were detailed as mean ± SD or n (%).
BMI indicates body mass ındex; VAS, Visual Analogue Scale.

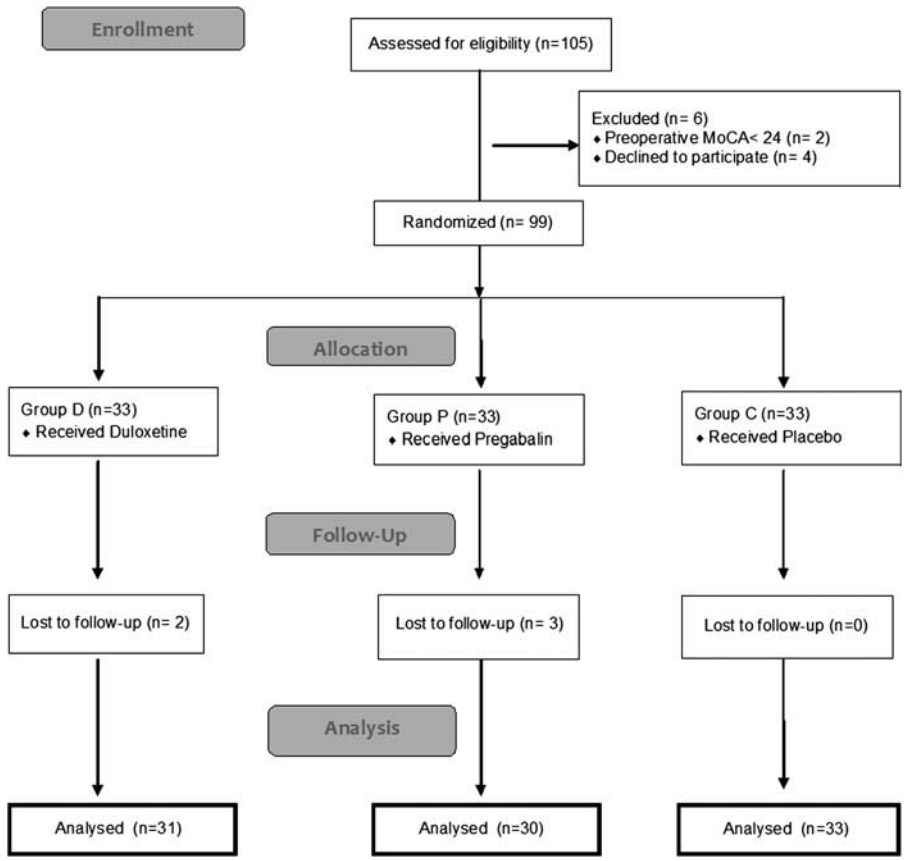

FIGURE 1. Flow chart of the study. MoCA indicates Montreal Cognitive Assessment.

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TABLE 2. Assessment of the MoCA Scores of Study Groups

MoCA	Duloxetine (n = 31)	Pregabalin (n = 30)	Control (n = 33)	*P*
Preoperative score	2.87 ± 1.76	26.63 ± 1.88	26.57 ± 2.00	0.806
Postoperative score	25.70 ± 2.10	24.80 ± 2.38	26.09 ± 2.26	0.073
P	0.001**	0.001**	0.001**	
Difference	−1 (−2, −1)	−2 (−3, −1)	0 (−1, 0)	0.001**

Data were detailed as mean ± SD or median (first quartile, third quartile).
MoCA indicates Montreal Cognitive Assessment.
**$P < 0.01$.

The mean MoCA score reduction of the duloxetine group was significantly higher than that of the control group ($P = 0.001$) (Table 2).

There was a statistically significant difference at the postoperative first minute between the groups. The mean VAS score of the pregabalin group was significantly lower than that of the control group ($P = 0.022$). Although the mean VAS score of the duloxetine group was lower than that of the control group, the difference was not statistically significant ($P = 0.083$). Likewise, the difference between the pregabalin and duloxetine groups was not significant ($P = 0.673$).

At the postoperative 30th minute, the mean VAS scores of the pregabalin and duloxetine groups were significantly lower than that of the control group ($P = 0.001$, and 0.010, respectively). There was no difference between the pregabalin and duloxetine groups ($P > 0.05$).

Similarly, the mean VAS scores of the pregabalin and duloxetine groups were significantly lower than that of the control group ($P = 0.001$, and 0.001), and there was no difference between the pregabalin and duloxetine groups ($P > 0.05$) at the postoperative 60th minute.

At the postoperative 120th minute, the mean VAS scores of all groups were similar to each other ($P > 0.05$).

At the postoperative 24th hour, the mean VAS scores of the pregabalin and duloxetine groups were significantly lower than that of the control group ($P = 0.001$ and 0.001), and the mean VAS scores of the pregabalin and duloxetine groups were similar ($P > 0.05$). Similarly, at the postoperative 48th hour, the mean VAS scores of pregabalin and duloxetine groups were significantly lower than that of the control group ($P = 0.001$ and 0.001), and the mean VAS scores of the pregabalin and duloxetine groups were similar ($P > 0.05$) (Table 3). The binary comparisons of the groups are listed in Table 4. Post hoc assessment of VAS scores of the groups clearly showed that the mean VAS scores of the pregabalin and duloxetine groups were similar to each other at all timepoints.

The time for the first analgesic need was significantly longer in the pregabalin (221.00 ± 71.12 min) and duloxetine (211.45 ± 69.75 min) groups compared with the control (109.85 ± 45.13 min) group ($P = 0.001$ and 0.001). The difference between the pregabalin and duloxetine groups was not significant ($P > 0.05$). The total amount of analgesic requirements in the first 24 hours significantly differed between the study groups ($P < 0.001$) (Table 5).

The most common complication was nausea in all of the groups; 9 (45%) patients in the pregabalin group, 7 (35%) in the duloxetine, and 4 (20%) patients in the control group complained about nausea. The difference among groups was not significant ($P = 0.218$). The distribution of intraoperative and postoperative complications are listed in the Table 6. The ratios of all complications were similar between the groups ($P > 0.05$).

DISCUSSION

In the current study, preoperative administration of pregabalin 75 mg and duloxetine 60 mg reduced postoperative pain scores until the postoperative 24th hour. The effectiveness of both drugs were similar. However, the reduction in cognitive functions, as assessed by MoCA scores, was significantly higher in the pregabalin group than in the duloxetine and control groups. Perioperative complications were similar in all of the groups.

The concept of "multimodal analgesia" has become popular for the management of postoperative pain in the last 2 decades. The main strategy of multimodal analgesia is the achievement of sufficient analgesia by additive or synergistic effects between different classes of analgesics with different mechanisms of action, or multiple simultaneous treatment techniques administered through different routes.

TABLE 3. The Assessment of Postoperative Pain Scores of the Study Groups

VAS	Duloxetine (n = 31)	Pregabalin (n = 30)	Control (n = 33)	*P*
1st min	0 (0, 1)	0 (0, 0)	0 (0, 1)	0.049*
30th min	2 (2, 3)	2 (1, 2)	3 (2, 3)	0.001**
60th min	3 (3, 4)	3 (3, 4)	4 (4, 5)	0.001**
120th min	4 (3, 5)	4 (4, 6)	5 (4, 6)	0.079
24th hour	3 (2, 4)	3 (2, 4)	4 (4, 4)	0.001**
48th hour	2 (1, 3)	2 (1, 3)	3 (3, 4)	0.001**

Data were detailed as median (first quartile, third quartile).
VAS indicates Visual Analogue Scale.
*$P < 0.05$.
**$P < 0.01$.

TABLE 4. The Post Hoc Assessment of VAS Scores of the Study Groups

VAS	Duloxetine-Pregabalin	Duloxetin-control	Pregabalin-control
1st min	0.673	0.083	0.022*
30th min	0.051	0.010*	0.001**
60th min	0.820	0.001**	0.001**
120th min	0.882	0.057	0.078
24th hour	0.851	0.001**	0.001**
48th hour	0.515	0.001**	0.001**

VAS indicates Visual Analogue Scale.
*$P < 0.05$.
**$P < 0.01$.

TABLE 5. The Delay of First Analgesia Request and the Number of Rescue Analgesics Requested Among Groups

	Duloxetine (n = 31)	Pregabalin (n = 30)	Control (n = 33)	*P*
Delay of first analgesic request (min)	210 (150, 240)	225 (150, 300)	120 (75, 120)	0.001**
The number of rescue analgesics requested				
1	1 (3.2)	0 (0)	0 (0)	0.001**
2	3 (9.7)	4 (13.3)	1 (3.0)	
3	27 (87.1)	26 (86.7)	20 (60.6)	
4	0 (0)	0 (0)	12 (36.4)	

Data were detailed as median (first quartile, third quartile) or n (%).
**$P < 0.01$.

This type of analgesia has been shown to provide effective pain management, with a reduction in the doses of each drug, or with fewer repetitions of the same technique, and thus a lower incidence of adverse effects.[20,21]

In the recent years, pregabalin has been in the focus of studies concerning acute postoperative pain strategies after major surgeries. It reduces the hyperexcitability of the dorsal horn neurons induced by tissue damage,[22] and inhibits the release of excitatory neurotransmitters such as glutamate, noradrenalin, and substance P, by binding to regulatory subunits of voltage-activated calcium channels.[23] As a result of these potential advantages, several studies have aimed to evaluate its efficacy on postoperative pain.[5,7,24,25] However, the results are still conflicting; Kim et al[5] have assessed the analgesic effect of preoperatively administered pregabalin 150 mg on postoperative pain intensity and rescue analgesic requirement following video-assisted thoracoscopic surgery, and they reported that single-dose pregabalin successfully reduced pain scores and incidence of additional rescue analgesics in the first 24 hours postoperatively. In a meta-analysis conducted by Liu et al,[26] 16 randomized controlled trials (gabapentin group n = 8 and pregabalin group n = 8) evaluating the effects of gabapentinoids were analyzed. In this systematic review, preoperative use of gabapentinoids was reported to successfuly reduce postoperative pain, total morphine consumption, and morphine-related complications following spine surgery. In contrast, Kiatchai et al have studied the effect of preoperative 150 mg pregabalin on patients who underwent hysterectomy with spinal anesthesia. In that study, intrathecal morphine was applied during spinal anesthesia. The researchers reported that preoperative administration of single-dose pregabalin 150 mg did not reduce 24-hour postoperative morphine consumption, time to first analgesic rescue, and pain scores after abdominal hysterectomy.[27] Intrathecal morphine administration is known to provide an effective and long lasting postoperative analgesia due to its hydrophilicity, decreased systemic absorption, and slow rate of clearance from the opioid receptors.[28] Hence, there is a possibility of intrathecal morphine administration to mask the postoperative effect of pregabalin use on opioid consumption and pain scores. Likewise, in the study of George et al,[29] preoperative uses of 75 and 150 mg pregabalin were compared with placebo with regard to analgesic efficacy, and no significant difference was found after total hysterectomy surgery. As Lam et al[30] have suggested in their previous study, the most possible reason for these conflicting results is the type of operation. Perioperative use of pregabalin was shown to be effective in a pronociceptive pain surgical model such as spine surgery[31] and orthopedic surgeries.[32] In the current study, the efficacy of low-dose pregabalin was evaluated on patients undergoing lumbar disc herniation repair, and it was found to effectively reduce postoperative pain scores. In the meta-analysis of Mishriky et al,[33] a single dose of pregabalin from 75 to 300 mg was suggested to have consistent opioid-sparing effect, and, in a Cochrane review, a high incidence of adverse effects (68%) was reported after a single dose of 300 mg pregabalin.[34] Hence, we preferred to use a lower dose (75 mg×2) of pregabalin, and the analgesic effect of this low dose was similar to a single dose of duloxetine 60 mg postoperatively.

TABLE 6. Assessment of Complications of the Study Groups

	Duloxetine (n = 31)	Pregabalin (n = 30)	Control (n = 33)	*P*
Complication				
No	20 (32.8)	17 (27.9)	24 (39.3)	0.410
Yes	11 (33.3)	13 (39.4)	9 (27.3)	
Nausea	7 (35.0)	9 (45.0)	4 (20.0)	0.218
Vomiting	1 (20.0)	2 (40.0)	2 (40.0)	0.866
Hypotension	1 (25.0)	1 (25.0)	2 (50.0)	1.000
Dizziness	0 (0)	2 (66.7)	1 (33.3)	0.412
Bradycardia	0 (0)	1 (100)	0 (0)	0.310
Allergia	1 (100)	0 (0)	0 (0)	0.646
Itching	1 (100)	0 (0)	0 (0)	0.646

Data were detailed as n (%).

The analgesic mechanism of duloxetine is thought to be related to its ability to enhance both serotonin and norepinephrine neurotransmission in descending inhibitory pain pathways in the brain and spinal cord, Moreover, it is known to have an antinociceptive effect through Na+ channel blocks.[35] As a result, duloxetine is believed to be an effective adjuvant for the management of neuropathic pain and attenuation of postoperative pain.[36] Attia and colleagues assessed the effect of preoperative duloxetine use and reported that duloxetine provided lower postoperative pain scores in the 24th and 48th hours. Duloxetine was effective especially when combined with a nonsteroid anti-inflammatory drug.[10] In the study of Bedin et al,[37] preoperative 60 mg duloxetine managed to reduce postoperative fentanyl consumption after spine surgery; however postoperative pain scores did not differ significantly between groups. In the current study, duloxetine significantly reduced pain scores in the first 24 hours postoperatively. After the administration of the second dose, the pain scores significantly decreased again until the postoperative 48th hour.

Although the pain scores in the pregabalin group were lower in the duloxetine group at all timepoints, the difference was not statistically significant. However, postoperative reduction in cognitive functions, as assessed by MoCA, was significantly greater in the pregabalin group. Pregabalin is known to be associated with undesirable side effects, such as sedation,[33] dizziness, visual disturbance,[38] and cognitive dysfunction.[39] Salinsky et al[39] evaluated the effect of 300 mg daily pregabalin on cognitive functions of healthy volunteers, and they reported that pregabalin-induced mild negative cognitive effects and neurotoxicity. In contrast, duloxetine seems to be a more favorable drug in terms of postoperative cognitive function. Ho et al[9] reported that, when compared

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with placebo, duloxetine 60 mg did not increase somnolence after knee replacement surgery.

General anesthesia is well known to have an important role in the pathogenesis of postoperative cognitive dysfunction (POCD).[40] Both anesthesia and surgery have been shown to increase the brain concentration of interleukin 6 and cytokine tumor necrosis factor-α and to provoke central nervous system inflammation.[41] However, the effect of different anesthesia techniques is still controversial. In a recent study,[42] Qiao and colleagues suggested sevoflurane-based anesthesia to cause a higher incidence of POCD than propofol-based anesthesia in elderly patients undergoing major surgery. They showed that the plasma concentrations of interleukin 6 and tumor necrosis factor-α were significantly higher throughout the first postoperative week in the sevoflurane group. In contrast, Egawa et al[43] compared sevoflurane-based and propofol-based anesthesia for incidence of POCD in patients undergoing lung surgery. They monitored regional oxygen saturation throughout the operation and reported that there was no difference between the groups for incidence of cerebral desaturation during surgery. The incidences of POCD were similar between the groups either after 5 days or 3 months postoperatively. Chen et al performed a meta-analysis of 5 randomized controlled trials to compare the effects of sevoflurane and desflurane anesthesia on postoperative cognitive functions of elderly patients.[44] They reported that following commands, time for extubation and orientation and recovery room discharge were significantly shorter in the desflurane group than in the sevoflurane group. However, there was no significant difference in the incidence of POCD or the time for opening the eyes between the groups. According to the findings of these studies, we preferred desflurane for maintanence of anesthesia, and the anesthetic procedure was homogeneous for all participants.

MoCA has a major advantage, as its sensitivity for MCI was reported to be as high as 90%.[11] In contrast, its specificity is only 50% for MCI.[45] Although low specificity has an increased risk of false-positive results, the rates are different for the Turkish population. According to the Turkish validation study of Kaya et al,[16] MoCA has a sentivitiy of 81% and specifity of 86% for MCI when the cut-off point is set as <24. Thus, MoCA is a valid and reliable screening test for patients with MCI and dementia in the Turkish population. In the current literature, our study is the first to compare the effects of pregabalin and duloxetine on postoperative cognitive functions, and these findings may suggest that duloxetine can be an useful alternative to pregabalin, as it has a similar analgesic effect on postoperative pain with fewer incidences of drug-related deterioration in cognitive function.

The main limitation of the current study is the lack of information about the opioid-sparing effect of pregabalin and duloxetine. The reason is our institutional pain management strategy. We prefer to use intramuscular diclofenac sodium for postoperative pain management after repair of lumbar disc herniation operations instead of intravenous opioids.

CONCLUSIONS

Preoperative use of duloxetine 60 mg can be an useful alternative to pregabalin 75 mg, as it has similar analgesic effect on postoperative pain with fewer incidences of drug-related cognitive side effects.

REFERENCES

1. Woolf CJ, Hong M. Preemptive analgesia—treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg*. 1993;77:362–379.
2. Reuben SS, Bhopatkar S, Maciolek H, et al. The preemptive analgesic effect of rofecoxib after ambulatory arthroscopic knee surgery. *Anesth Analg*. 2002;94:55–59.
3. Buvanendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. *Curr Opin Anaesthesiol*. 2009;22:588–593.
4. Jones DL, Sorkin LS. Systemic gabapentin and S(+)-3-isobutyl-γ-aminobutyric acid block secondary hyperalgesia. *Brain Res*. 1998;810:93–99.
5. Kim JC, Byun S, Kim S, et al. Effect of preoperative pregabalin as an adjunct to a multimodal analgesic regimen in video-assisted thoracoscopic surgery: a randomized controlled trial. *Med (United States)*. 2017;96:e8644.
6. Ahn S, Byun SH, Park K, et al. Analgesic efficacy of preemptive pregabalin administration in arthroscopic shoulder surgery: a randomized controlled trial. *Can J Anaesth*. 2016;63:283–289.
7. Myhre M, Diep LM, Stubhaug A. Pregabalin has analgesic, ventilatory, and cognitive effects in combination with remifentanil. *Anesthesiology*. 2016;124:141–149.
8. Jokela R, Ahonen J, Tallgren M, et al. Premedication with pregabalin 75 or 150 mg with ibuprofen to control pain after day-case gynaecological laparoscopic surgery. *Br J Anaesth*. 2008;100:834–840.
9. Ho KY, Tay W, Yeo MC, et al. Duloxetine reduces morphine requirements after knee replacement surgery. *Br J Anaesth*. 2010;105:371–376.
10. Attia JZ, Mansour HS. Perioperative duloxetine and etoricoxib to improve postoperative pain after lumbar laminectomy: a randomized, double-blind, controlled study. *BMC Anesthesiol*. 2017;17:162.
11. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53:695–699.
12. Hewitt J, Marke M, Honeyman C, et al. Cognitive impairment in older patients undergoing elective colorectal surgery. *Scott Med J*. 2018;63:11–15.
13. Hou R, Wang H, Chen L, et al. POCD in patients receiving total knee replacement under deep vs light anesthesia: a randomized controlled trial. *Brain Behav*. 2018;8:e00910.
14. Pişkin Ö, Küçükosman G, Altun DU, et al. The effect of sugammadex on postoperative cognitive function and recovery. *Brazilian J Anesthesiol (English Ed)*. 2016;66:376–382.
15. Selekler K, Cangoz B, Uluc S. Power of discrimination of Montreal Cognitive Assessment (MOCA) scale in Turkish patients with mild cognitive impairment and Alzheimer's disease. *Turkish J Geriatr*. 2010;13:166–171.
16. Kaya Y, Aki OE, Can UA, et al. Validation of Montreal Cognitive Assessment and discriminant power of Montreal Cognitive Assessment subtests in patients with mild cognitive impairment and Alzheimer dementia in Turkish population. *J Geriatr Psychiatry Neurol*. 2014;27:103–109.
17. Lee JK, Chung KS, Choi CH. The effect of a single dose of preemptive pregabalin administered with cox-2 inhibitor: a trial in total knee arthroplasty. *J Arthroplasty*. 2015;30:38–42.
18. Rajappa GC, Vig S, Bevanaguddaiah Y, et al. Efficacy of pregabalin as premedication for post-operative analgesia in vaginal hysterectomy. *Anesthesiol Pain Med*. 2016;6:e34591.
19. Sebastian B, Talikoti AT, Nelamangala K, et al. Effect of oral pregabalin as preemptive analgesic in patients undergoing lower limb orthopedic surgeries under spinal anaesthesia. *J Clin Diagnostic Res*. 2016;10:UC01–UC04.
20. Kehlet H, Dahl JB. The value of "Multimodal" or "Balanced Analgesia" in postoperative pain treatment. *Anesth Analg*. 1993;77:1048–1056.
21. Buvanendran A, Kroin JS, Tuman KJ, et al. Effects of perioperative administration of a selective cyclooxygenase 2 inhibitor on pain management and recovery of function after knee replacement: a randomized controlled trial. *JAMA*. 2003;290:2411–2418.
22. Field MJ, Holloman EF, McCleary S, et al. Evaluation of gabapentin and S-(+)-3-isobutylgaba in a rat model of postoperative pain. *J Pharmacol Exp Ther*. 1997;282:1242–1246.

23. Fink K, Dooley DJ, Meder WP, et al. Inhibition of neuronal Ca 2+ influx by gabapentin and pregabalin in the human neocortex. *Neuropharmacology*. 2002;42:229–236.
24. Abdelfattah AAM, Rizk F, Hawash N, et al. Randomized trial of preoperative administration of oral pregabalin for postoperative analgesia in patients scheduled for radiofrequency ablation of focal lesions in the liver. *Int J Hyperth*. 2018:1–5. Available at: www.tandfonline.com/doi/full/10.1080/02656736.2018.1424946.
25. Chen N, Soneru C, Kacker A. Does a single dose of pregabalin help with postoperative pain after septoplasty? *Laryngoscope*. 2018;128:1023–1024.
26. Liu B, Liu R, Wang L. A meta-analysis of the preoperative use of gabapentinoids for the treatment of acute postoperative pain following spinal surgery. *Medicine (Baltimore)*. 2017;96:e8031.
27. Kiatchai T, Sanansilp V, Triyasunant N, et al. Effects of pregabalin on postoperative pain after hysterectomy under spinal anesthesia with intrathecal morphine: a randomized controlled trial. *J Anesth*. 2017;31:861–868.
28. Ummenhofer WC, Arends RH, Shen DD, et al. Comparative spinal distribution and clearance kinetics of intrathecally administered morphine, fentanyl, alfentanil, and sufentanil. *Anesthesiology*. 2000;92:739–753.
29. George RB, McKeen DM, Andreou P, et al. A randomized placebo-controlled trial of two doses of pregabalin for postoperative analgesia in patients undergoing abdominal hysterectomy. *Can J Anaesth*. 2014;61:551–557.
30. Lam DMH, Choi SW, Wong SSC, et al. Efficacy of pregabalin in acute postoperative pain under different surgical categories a meta-analysis. *Med (Baltimore)*. 2015;94:e1944.
31. Jiang HL, Huang S, Song J, et al. Preoperative use of pregabalin for acute pain in spine surgery. *Med (Baltimore)*. 2017;96:e6129.
32. Li F, Ma J, Kuang M, et al. The efficacy of pregabalin for the management of postoperative pain in primary total knee and hip arthroplasty: a meta-analysis. *J Orthop Surg Res*. 2017;12:49–59.
33. Mishriky BM, Waldron NH, Habib AS. Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis. *Br J Anaesth*. 2015;114:10–31.
34. Ra M, Straube S, Pj W, et al. Pregabalin for acute and chronic pain in adults (Review). *Cochrane Database Syst Rev*. 2009: CD007076.
35. Wang SY, Calderon J, Wang GK. Block of neuronal Na +channels by antidepressant duloxetine in a state-dependent manner. *Anesthesiology*. 2010;113:655–665.
36. Biddiss E, Knibbe TJ, McPherson A. The effectiveness of interventions aimed at reducing anxiety in health care waiting spaces: a systematic review of randomized and nonrandomized trials. *Anesth Analg*. 2014;119:433–448.
37. Bedin A, Caldart Bedin RA, Vieira JE, et al. Duloxetine as an analgesic reduces opioid consumption after spine surgery. *Clin J Pain*. 2017;33:865–869.
38. Fassoulaki A, Melemeni A, Tsaroucha A, et al. Perioperative pregabalin for acute and chronic pain after abdominal hysterectomy or myomectomy: a randomised controlled trial. *Eur J Anaesthesiol*. 2012;29:531–536.
39. Salinsky M, Storzbach D, Munoz S. Cognitive effects of pregabalin in healthy volunteers: a double-blind, placebo-controlled trial. *Neurology*. 2010;74:755–761.
40. Lili X, Zhiyong H, Jianjun S. A preliminary study of the effects of ulinastatin on early postoperative cognition function in patients undergoing abdominal surgery. *Neurosci Lett*. 2013; 541:15–19.
41. Cao XZ, Ma H, Wang JK, et al. Postoperative cognitive deficits and neuroinflammation in the hippocampus triggered by surgical trauma are exacerbated in aged rats. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34:1426–1432.
42. Qiao Y, Feng H, Zhao T, et al. Postoperative cognitive dysfunction after inhalational anesthesia in elderly patients undergoing major surgery: the influence of anesthetic technique, cerebral injury and systemic inflammation. *BMC Anesthesiol*. 2015;15:154.
43. Egawa J, Inoue S, Nishiwada T, et al. Effects of anesthetics on early postoperative cognitive outcome and intraoperative cerebral oxygen balance in patients undergoing lung surgery: a randomized clinical trial. *Can J Anesth*. 2016;63:1161–1169.
44. Chen G, Zhou Y, Shi Q, et al. Comparison of early recovery and cognitive function after desflurane and sevoflurane anaesthesia in elderly patients: a meta-analysis of randomized controlled trials. *J Int Med Res*. 2015;43:619–628.
45. Smith T, Gildeh N, Holmes C. The Montreal Cognitive Assessment: validity and utility in a memory clinic setting. *Can J Psychiatry*. 2007;52:329–332.