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Original Contribution

A randomized, placebo-controlled study of pregabalin for postoperative pain intensity after laparoscopic cholecystectomy

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Abstract

Study Objective: To determine the efficacy of two different doses (150 mg and 300 mg) of preoperative pregabalin on pain relief and total opioid consumption after laparoscopic cholecystectomy.

Design: Prospective, randomized, placebo-controlled, double-blinded study.

Setting: Training and research hospital.

Patients: 90 adult, ASA physical status 1 and 2 patients.

Interventions: Patients were randomly assigned to three groups to receive orally one hour before surgery, a placebo (Group 1), pregabalin 150 mg (Group 2), or pregabalin 300 mg (Group 3). Patients were observed for pregabalin side effects, somnolence via Ramsay Sedation Scale, dizziness, confusion, and ataxia.

Measurements: In the operating room, heart rate and noninvasive systolic and diastolic blood pressures were measured. Visual analog scale (VAS), Ramsay Sedation Scale, and Aldrete scores were also recorded on arrival at the Postanesthesia Care Unit (time 0), 15, 30, 60, 120 minutes and 3, 4, 6, 8, 10, 12 and 24 hours after surgery. Additional doses of drugs (fentanyl and/or metoclopramide) were also recorded.

Main Results: Preemptive pregabalin decreased pain scores and postoperative fentanyl consumption in patients after laparoscopic cholecystectomy in a dose-dependent manner. There were no differences between the groups in side effects.

Conclusion: Preoperative pregabalin may be a useful analgesic for patients after laparoscopic cholecystectomy, as it lowers pain intensity and opiod consumption, and does not increase the frequency of side effects.

1. Introduction

Postoperative pain management improves both the success of the surgical intervention and patient comfort by attenuating the perioperative complications that are associated with pain.

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Preventive analgesia is used prior to incision to improve postoperative analgesia. Gabapentin, clonidine, dexmedetomidine, and ketamine are the common drugs used for preemptive analgesia [1-3]. Pregabalin is a newly synthesized derivative of gabapentin [1]. It is a new gamma aminobutyric acid (GABA) analog with analgesic, anticonvulsive, and anxiolytic properties [4].

The aim of the present study was to determine the effect of two different doses of preoperative pregabalin on postoperative pain relief and fentanyl consumption.

2. Materials and methods

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Türkiye Yüksek İhtisas Education and Research Hospital, and written, informed consent was obtained from each patient. A total of 90 ASA physical status 1 and 2 patients who were over 18 years of age and scheduled for laparoscopic cholecystectomy, were enrolled in this prospective, double-blinded, placebo-controlled study. Exclusion criteria were inability to cooperate, pregnancy, emergency surgical intervention, ASA physical status of 3 or higher, severe renal and/or hepatic dysfunction, history of allergy to pregabalin, limited or insufficient respiratory reserve, conversion to open cholecystectomy, and duration of surgery in excess of 60 minutes.

Patients were randomized to three equal groups by sealed envelope assignment. Group 1 was the control group and subjects were given an oral placebo one hour before surgery; Group 2 received 150 mg and Group 3 received 300 mg of pregabalin orally one hour before surgery. None of the patients received other premedication.

When patients arrived at the operating room, a peripheral venous cannula was inserted and 500 mL of 0.9% saline was started. Monitoring for all patients included electrocardiogram, pulse oximeter, end-tidal carbon dioxide capnography, and noninvasive systolic (SBP) and diastolic blood pressures (DBP).

All patients received thiopental sodium 6 mg/kg, fentanyl citrate 1.5 μg/kg, and rocuronium bromide 0.6 mg/kg for the induction of anesthesia. Endotracheal intubation was accomplished once adequate muscle relaxation was achieved. Anesthesia was maintained with sevoflurane (end-tidal concentration 1% - 1.5%) in a 45% oxygen and 55% air mixture. Sevoflurane administration was adjusted by the attending anesthesiologist, who was not involved in the study, with the goal of maintaining mean arterial blood pressure within 20% of preinduction values. All patients received an orogastric tube. The effect of the muscle relaxant was antagonized with atropine sulfate 0.015 mg/kg and neostigmine 0.04 mg/kg at the end of surgery. Patients with a respiratory rate (RR) greater than 8 breaths/min and whose oxygen saturation values were over 97% while ventilated with room air, were extubated.

Patients were transferred to the Postanesthesia Care Unit (PACU), where Ramsay Sedation Scale, Modified Aldrete, and visual analog scale (VAS; 0 = no pain and 10 = worst imaginable pain) scores were obtained. Pain, sedation, and recovery were scored by a study-blinded anesthesiologist. If a VAS score was 5 or more, intravenous fentanyl 25 μg was given and repeated if required. Patients were also observed for side effects: nausea, vomiting, pruritus, and urinary retention. Postoperative follow-up times were the moment that each patient was transferred to the PACU (time 0), 15, 30, 60, 120 minutes, and 3, 4, 6, 8, 10, 12, and 24 hours after surgery. The additional doses of drugs needed (fentanyl and/or metoclopramide) were also recorded.

2.1. Statistical analysis

Data were analyzed using SPSS for Windows, version 11.5 software (SPSS, Chicago, IL, USA). Closeness of the continuous variables to normal values was tested with the Shapiro Wilk test. Descriptive statistics are given as means ± SD for normally distributed data and medians (interquartile ranges) for both nonnormality distributed continuous data and ordinal variables. Statistical significance of values for age, weight, and duration of surgery that were distributed evenly among the groups was tested by one-way analysis of variance (ANOVA). Continuous variables that were not distributed in an even manner were tested by Kruskal Wallis test. Once the results of the Kruskal Wallis tests were found to be significant, nonparametric multiple comparison test was used. Nominal variables were analyzed by Pearson's Chi-Square test.

To put forward a difference between the repeated hemodynamic measurements between the groups, repeated-measures ANOVA was used. When the results of this test were found to be significant, Bonferroni Corrections for

Table 1 Demographic characteristics and operative data of the groups

	Group 1 (n = 30)	Group 2 (n = 30)	Group 3 (n = 30)
Age (yrs)	51.4 ± 15.7	54.5 ± 14.7	52.7 ± 11.8
Gender (M/F)	6/24	7/23	8/22
Weight (kg)	74.9 ± 13.7	77.1 ± 14.5	74.8 ± 13.9
Hypertension (n)	7 (%23.3)	8 (%26.7)	7 (%23.3)
Diabetes mellitus (n)	2 (%6.7)	3 (%10.0)	1 (%3.3)
COPD (n)	2 (%6.7)	-	1 (%3.3)
Surgery duration (min)	38.9 ± 9.4	42.4 ± 12.2	41.7 ± 7.9

Group 1 patients received an oral placebo one hour before surgery; Group 2 patients received pregabalin 150 mg orally one hour before surgery; Group 3 received pregabalin 300 mg orally one hour before surgery. COPD = chronic obstructive pulmonary disease.

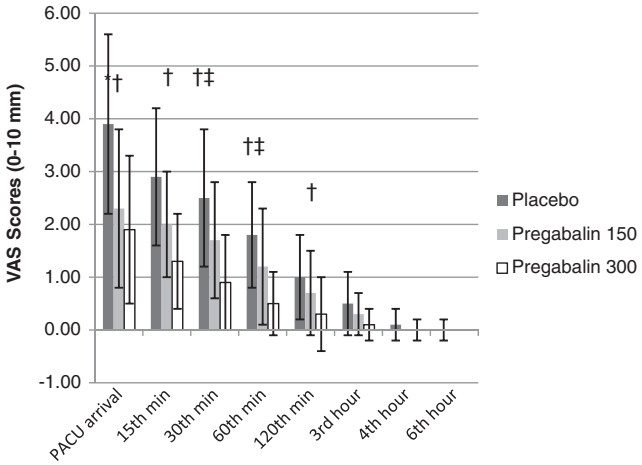

Fig. 1 Pain scores (visual analog scores) at rest after surgery in the placebo (Group 1), pregabalin 150 mg (Group 2), and pregabalin 300 mg (Group 3) groups. PACU = Postanesthesia Care Unit. *$P < 0.01$, Group 1 vs Group 2; †$P < 0.001$, Group 1 vs Group 3; ‡$P = 0.00625$, Group 2 vs Group 3.

Multiple Comparisons was used to define the measurement times that gave rise to this difference.

The statistical significance between VAS, Ramsay Sedation Scale, and Aldrete scores among the groups were analyzed with the Friedman test. When the statistical test results were found to be significant, the follow-up times that gave rise to a difference were established by Wilcoxon's Signed-Rank test after Bonferroni Correction. Nausea, vomiting, pruritus, urinary retention, and any need for additional doses of drugs was tested by the McNemar's Chi-Square test after Bonferroni Correction.

A P-value < 0.05 indicated statistical significance. In all possible multiple comparisons the Bonferroni Correction was used. When variations at other measurement times were compared with those taken at time 0, in relation to VAS, Ramsay Sedation, and Aldrete scores, there were 28 potential variations among the groups.

Table 2 Ramsay Sedation scores in the pregabalin and placebo groups

Measurement times	Group 1 (n = 30)	Group 2 (n = 30)	Group 3 (n = 30)	P-value[a]
0 min	1.5 ± 0.5	1.7 ± 0.5	1.8 ± 0.6	0.169
15 min	1.60 ± 0.56*	1.90 ± 0.30	1.93 ± 0.25*	0.002
30 min	1.8 ± 0.5	1.9 ± 0.3	2.0 ± 0.0	0.043
60 min	2.0 ± 0.2	2.0 ± 0.0	2.0 ± 0.0	0.368
120 min	2.0 ± 0.0	2.0 ± 0.0	2.0 ± 0.0	1.000
3 hrs	2.0 ± 0.0	2.0 ± 0.0	2.0 ± 0.0	1.000
4 hrs	2.0 ± 0.0	2.0 ± 0.0	2.0 ± 0.0	1.000
6 hrs	2.0 ± 0.0	2.0 ± 0.0	2.0 ± 0.0	1.000

Group 1 patients received an oral placebo one hour before surgery; Group 2 patients received pregabalin 150 mg orally one hour before surgery; Group 3 received pregabalin 300 mg orally one hour before surgery.

[a] $P < 0.00625$ was accepted to be statistically significant (Bonferroni Correction).

* $P < 0.005$, Group 1 vs Group 3 (statistically significant difference).

Table 3 Fentanyl consumption (μg) in the pregabalin and placebo groups

Measurement times	Group 1 (n = 30)	Group 2 (n = 30)	Group 3 (n = 30)	P-value
0 min	37.5 ± 19.4*,†	10.8 ± 15.6*	8.3 ± 16.5†	< 0.001
15 min	14.2 ± 19.3‡	6.7 ± 13.0	1.7 ± 9.1‡	< 0.001
30 min	15.8 ± 20.2‡	6.7 ± 16.0	3.3 ± 12.7‡	< 0.001
60 min	5.8 ± 14.2	6.7 ± 16.0	0.8 ± 4.6	0.182
120 min	0	1.7 ± 6.3	0.8 ± 4.6	0.360

Group 1 patients received an oral placebo one hour before surgery; Group 2 patients received pregabalin 150 mg orally one hour before surgery; Group 3 received pregabalin 300 mg orally one hour before surgery.

* $P < 0.001$, Group 1 vs Group 2 (statistically significant difference).

† $P < 0.001$, Group 1 vs Group 3 (statistically significant difference).

‡ $P < 0.01$, Group 1 vs Group 3 (statistically significant difference).

3. Results

Patients' demographic characteristics and operative data are shown in Table 1. No statistically significant differences were noted in age, gender, body weight, or systemic diseases ($P > 0.05$). Intraoperative SBP, DBP, and heart rate changes over time were similar in the groups.

A significant decrease in the VAS scores of Group 2 and Group 3 was noted at time 0 in comparison to Group 1 (placebo group). For the measurements at 15, 30, 60, and 120 minutes, there was a significant decrease in VAS scores in Group 3 versus Group 1. Visual analog scores in Group 3 compared with Group 2 were significantly lower at 30 and 60 minutes postoperatively (Fig. 1). Ramsay Sedation scores were significantly higher in the 300 mg pregabalin group versus placebo group at 15 minutes postoperatively. There was no statistically significant difference in Ramsay scores between groups at any other measurement times (Table 2). Aldrete scores in Group 3 were statistically significantly higher than those of Group 1 at 60 minutes postoperatively.

Table 4 Frequency of side effects

Side effects	Group 1 (n = 30)	Group 2 (n = 30)	Group 3 (n = 30)	P-value
Nausea	5	3	3	0.110
Vomiting	9	3	3	0.056
Pruritus	3	1	0	0.033
Urinary retention	1	0	0	0.330
Somnolence	1	0	0	0.130

Group 1 patients received an oral placebo one hour before surgery; Group 2 patients received pregabalin 150 mg orally one hour before surgery; Group 3 received pregabalin 300 mg orally one hour before surgery.

No statistically significant differences were noted among the groups.

Total fentanyl consumption in Group 1 was higher than either Groups 2 or 3 (Table 3). Frequency of opioid side effects was similar among the groups (Table 4).

4. Discussion

Pain that develops after surgery is a transient neuropathic pain and pregabalin is believed to attenuate the central neuronal sensitization that contributes to postoperative pain [5]. Preemptive application of gabapentin and pregabalin may improve analgesia during the postoperative period, and may lower the need for opioid demand and side effects such as nausea, vomiting, pruritus, and urinary retention [6-9].

In our study a significant decrease in VAS scores of patients in the 150 mg (Group 2) and 300 mg (Group 3) pregabalin groups versus the placebo group were noted. We found a significant decrease in fentanyl consumption, especially in Group 3. We observed no side effects of pregabalin, such as ataxia or confusion, in any Group 2 or Group 3 patient. These findings support the theory that a single preoperative dose of pregabalin does not affect postoperative recovery of patients but does improve pain relief. The pregabalin 150 and 300 mg groups required significantly fewer antiemetics when compared with the placebo group. Less opioid usage may be the reason for less antiemetic requirement.

Gabapentinoids may increase the analgesic effects of morphine, nonsteroidal antiinflammatory drugs, and COX II inhibitors [10-12]. Paech et al failed to show a significant effect of preoperative pregabalin 100 mg on postoperative pain intensity or total opioid consumption in minor gynecological surgery patients [13]. Hill et al [14] showed that pregabalin was more effective than ibuprofen in maintaining analgesia in patients in surgery of the mouth during local anesthesia. Agarwal et al [15] established that postoperative pain and fentanyl requirements were lower in the pregabalin group than the placebo group. In contrast, Chang et al [16] showed that perioperative administration of 300 mg of pregabalin did not decrease the frequency or severity of postlaparoscopic shoulder pain.

Pregabalin decreases pain intensity and opioid consumption after laparoscopic cholecystectomy, without increasing the frequency of side effects.

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