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Original contribution

Preliminary investigation of preoperative pregabalin and total intravenous anesthesia doses: a randomized controlled trial☆

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Abstract

Study objective: To determine the efficacy of 2 different doses (150-300 mg) of preoperative pregabalin on propofol and remifentanil doses for total intravenous anesthesia in laparoscopic cholecystectomy.

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

Setting: Training and research hospital.

Patients: Forty-eight adult, American Society of Anesthesiologists physical status 1 and 2 patients.

Interventions: Patients were randomly assigned to 3 groups to receive orally 1 hour before surgery, a placebo group (group 1), pregabalin 150 mg (group 2), or pregabalin 300 mg (group 3).

Measurements: In the operating room, heart rate, systolic and diastolic blood pressures, SpO_2, bispectral index, and body temperature were recorded just before anesthesia induction; 1 and 5 minutes after induction; and at minutes 10, 15, 20, 25, 30, 35, and 40 of the surgery. Required propofol and remifentanil doses to obtain bispectral index value less than 60 were also recorded.

Main Results: The remifentanil doses used in the pregabalin groups at minutes 10, 15, 20, 25, and 30 and propofol doses at minutes 15, 20, 25, and 30 were statistically significantly lower in comparison to the placebo group.

Conclusion: The observations provide preliminary evidence that preoperative pregabalin may decrease anesthetic agent requirement in total intravenous anesthesia patients.

1. Introduction

Pregabalin, a gabapentinoid compound, is a structural derivative of the inhibitory neurotransmitter γ-amino butyric acid but is not functionally related to it. Pregabalin binds to the neuronal α2δ-1 subunit of voltage-gated calcium channels, preventing the release of nociceptive neurotransmitters including glutamate, substance P, and noradrenaline [1-3]. It has been approved for the treatment of neuropathic pain and anxiety disorders [4,5]. In addition to being used for treatment of neuropathic pain and anxiety, gabapentinoids have also been used in recent years for the management of postoperative pain in anesthetic practice. It has also been suggested that gabapentinoids be used in routine practice for this aim. Pregabalin has a more pronounced sedative and anxiolytic pharmacologic profile than its predecessor, gabapentin.

☆ Conflict of interest: None.

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Pregabalin also reduces postoperative pain and opioid consumption [6]. Perioperative pregabalin studies generally focused on antinociceptive and opioid-sparing effects of this molecule, whereas it has pronounced anxiolytic and sedative effects [7,8]. There is no satisfied study that has formally assessed the sedative and hypnotic effects of pregabalin consumption as an anesthetic adjuvant.

Our hypotheses are that the sedative and anxiolytic effects of pregabalin can produce dose-related reductions in the doses of propofol and that antinociceptive effect of this drug can produce dose-related reductions in the doses of remifentanil used for total intravenous anesthesia (TIVA).

2. Methods

This study was conducted at the Anesthesiology and Reanimation Clinic of the Turkey Yüksek İhtisas Training and Research Hospital after obtaining the necessary approvals from the local ethics committee (07.01.2013-297). Before performing the study procedures, written informed consent forms were obtained from the participating patients. The study was conducted according to a randomized, double-blind, placebo-controlled, 2-dose comparison study design.

Forty-eight American Society of Anesthesiologists I to II patients aged ≥18 years with planned laparoscopic cholecystectomies were included in the study. The exclusion criteria of this study included gestation; emergency surgical procedures; hepatic disease, for example, twice the normal level of liver enzymes; renal dysfunction (blood urea nitrogen >30 mg/dL or creatinine >2 mg/dL); history of allergy to gabapentin or pregabalin; chronic gabapentinoid usage; psychoactive drug or substance usage; limited or insufficient respiratory function (Forced expiratory volume in one second [FEV1] <70%); and cases that were changed to open procedures.

All patients were examined during a preoperative visit performed on the morning of the surgery. During this visit, the patients were informed regarding to surgery, anesthesia, and the study. Randomization was performed using the closed envelope method, and the patients were divided into 3 groups. The first group was the control group; patients in this group were administered a placebo capsule 1 hour before surgery. The second and third groups were administered 150 mg and 300 mg oral pregabalin, respectively, 1 hour before surgery. No additional premedications were administered to any patients.

In the operating room, intravenous access was established via the antecubital vein, and 500 mL of 0.9% saline solution was administered. The patients' noninvasive blood pressures, heart rate, body temperature, bispectral index (BIS), and peripheral oxygen saturation (SpO_2) were monitored. During the surgery, the patients were warmed with a floor heating system. Anesthetic induction was performed with 2 mg/kg propofol, remifentanil infusion at a rate of 1 μg/kg per minute, and 0.6 mg/kg rocuronium. One minute after induction, the remifentanil dose was lowered to 0.05 μg/kg per minute, and propofol infusion was started at 25 μg/kg per minute. Endotracheal intubation was performed after sufficient muscle relaxation was achieved. Anesthetic maintenance was standardized with a 50% oxygen/air mixture and remifentanil and propofol infusions. Measurements were taken before the induction of anesthesia; after intubation (fifth minute after induction); and at minutes 10, 15, 20, 25, 30, 35, and 40 of the surgery. In the event of a 20% increase in systolic blood pressure or heart rate, the remifentanil dose was increased to a rate of 0.05 μg/kg/min. The patients' propofol infusion rates were titrated to maintain a BIS number between 50 and 60. At BIS values greater than 60, the propofol infusion rate was increased to 25 μg/kg per minute. At the end of the surgery, the effect of the neuromuscular blockade was antagonized with 0.015 mg/kg atropine sulfate and 0.04 mg/kg neostigmine.

Any patients with a respiratory rate ≥8 per minute, BIS value ≥98, and a SpO_2 ≥ 97% while breathing room air were extubated. During their follow-up in the ward, the patients were screened for surgical recall according to modified Brice Questionnaire [9].

3. Statistical analysis

The data analysis was performed with the SPSS 15.0 for Windows package program. With the achieved sample size, the study had approximate power of 28%, 63%, and 89% to detect relative differences in mean propofol use of 20%, 30%, and 40%, respectively, between the placebo group and either of the 2 pregabalin doses at the overall 0.05 significance level (adjusting for 3 comparisons). The normality of the distribution of continuous variables was evaluated using the one sample Kolmogorov-Smirnov test. Descriptive statistics were shown as mean ± SD, whereas nominal variables were shown as number of cases (percentages). The 1-way analysis of variance (ANOVA) was used to determine if the difference between the groups in respect to normally distributed continuous variables was statistically significant. On the other hand, the Kruskal-Wallis test was used to determine if the difference with respect to nonnormally distributed continuous variables was statistically significant. If the statistical result of the Kruskal-Wallis test was found to be significant, the nonparametric multiple comparison test was used to identify groups contributing to the difference. Nominal variables were investigated using the Pearson χ^2 test.

The repeated-measures ANOVA was used to determine if differences in hemodynamic measurements between groups were statistically significant. If the result of the repeated-measures ANOVA was found to be significant, multiple tests with the Bonferroni correction were performed to identify measurement times that caused the difference. In all tests, $P < .05$ was considered statistically significant.