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CLINICAL RESEARCH

Analgesic Effects of a Single Preoperative Dose of Pregabalin after Laparoscopic Sleeve Gastrectomy

Maria Carolina Cabrera Schulmeyer · Jaime de la Maza · Cristian Ovalle · Carlos Farias · Isabel Vives

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Abstract
Background The treatment of pain in obese patients is always a challenge. These patients have low pain thresholds, and the use of opioids can be especially harmful. Intraoperative nervous fiber section and the high temperatures of electrical scalpels probably contribute to the generation of postoperative neuropathic pain. We hypothesized that an antineuropathic pain drug like pregabalin could be helpful to optimize postoperative analgesia by reducing the requirement for opioids and their associated side effects.
Methods Eighty adults undergoing laparoscopic sleeve gastrectomy were randomly assigned to orally receive either placebo capsules (control) or pregabalin (150 mg) 2 h before surgery. Postoperative morphine consumption during the first 24 postoperative hours was registered. Visual analog pain scores (VAS) were assessed at 1, 2, 4, 6, 8, 12, 16, and 24 h after surgery. Both the incidence of adverse reactions and patient satisfaction were also assessed.
Results Over a 24-h period, the morphine consumption in the pregabalin group was 11.51±7.93 mg, whereas in the control group, it was 23.07±9.57 mg ($p<0.0001$). VAS scores were significantly lower in the pregabalin group. Postoperative nausea and vomiting and the consumption of antiemetics were reduced in the pregabalin group.
Conclusions A single preoperative oral dose of 150 mg pregabalin is useful for reducing morphine consumption after a sleeve gastrectomy, and it guarantees effective and safe analgesia with a low incidence of adverse effects.

Keywords Pregabalin · Neuropathic pain · Postoperative pain · Laparoscopic sleeve gastrectomy

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M. C. Cabrera Schulmeyer · J. de la Maza
Air Force Hospital of Santiago de Chile
and University of Valparaiso,
Valparaiso, Chile

C. Ovalle · C. Farias
Air Force Hospital of Santiago de Chile,
Santiago, Chile

I. Vives
Department of Anesthesiology,
Air Force Hospital of Santiago de Chile, Air Force of Chile,
University of Valparaiso,
Valparaiso, Chile

M. C. Cabrera Schulmeyer (✉)
Fernandez Mira 796, Las Condes,
Santiago, Chile
e-mail: carol218@vtr.net

Introduction

In the last few years, there have been great advances in the understanding of the physiopathological mechanisms that trigger the postoperative pain response, which has been redefined as incisional pain [1–3]. It has been suggested that one aim of this pain therapy is to prevent the central neural sensitization that contributes to enhanced postoperative pain [4]. Due to their typically low pain thresholds, control of pain in obese patients is always a challenge; opioids can be especially harmful due to postoperative nausea, vomiting, and respiratory depression [5, 6]. Although laparoscopic sleeve gastrectomy is considered to be less invasive, it can produce moderate to severe postoperative pain. Intraoperative nervous fiber section and the high temperatures of electrical scalpels probably

contribute to the generation of neuropathic pain [7, 8]. Therefore, as part of a multimodal analgesia, an antineuropathic pain drug like pregabalin can be helpful for the optimization of postoperative analgesia in obese patients. Pregabalin binds potently to the $\alpha 2$-δ subunit of voltage-dependent calcium channels that are widely distributed in the spinal cord and brain. Pregabalin modulates calcium influx at nerve terminals and thereby reduces the release of neurotransmitters, such as glutamate, noradrenalin, serotonin, calcitonin gene-related peptide, dopamine, and substance P, which results in a lowering of the central sensitization phenomenon [9, 10]. The objective of the present study was to investigate the effects of a single preoperative dose of pregabalin on postoperative pain in obese patients following a laparoscopic sleeve gastrectomy.

Methods

After the investigation protocol had been approved by the hospital's committee of ethics, written informed consent was obtained from each patient before he or she was enrolled in the study. Between September 2008 and April 2009, male and female patients were eligible for participation if they were aged 18–70 years, American Association of Anesthesiology classification I or II (to evaluate the physical status of the patients), and undergoing elective sleeve gastrectomy under general anesthesia. Exclusion criteria included known allergies to pregabalin or morphine and the presence of renal, endocrine, or important hepatic diseases. Patients with an active gastric ulcer or severe coagulopathy and patients with a history of alcohol or drug abuse in the 3 months before surgery were also excluded. Patients suffering from chronic pain or patients who consumed analgesics during the previous 2 weeks were also excluded.

The study design was randomized and double blinded; patients were randomly allocated according to computer-generated randomization. Each patient was assigned to either the placebo group or the pregabalin group in a double-blind fashion. Two hours before the operation, each patient was given a tablet of 150 mg pregabalin or a similar placebo tablet; these were consumed orally with the aid of sips of water. No investigator or data collector was aware of the group assignment after all patients had been randomized. No other premedication was administered to the patients. Once in the operating room, a crystalloid i.v. infusion of 3–5 ml kg^{-1} h^{-1} was started, and the mean blood pressure, heart rate, and peripheral oxygen saturation were monitored (Datex ohmeda). The anesthesia technique was standardized in both groups. It was induced with remifentanil target-control infusion at 5 ng/ml i.v. and a propofol i.v. bolus of 2.5 mg kg^{-1} based on ideal weight (height in centimeters, 100). Subsequently, vecuronium (0.1 mg kg^{-1} ideal weight) was given i.v. to facilitate orotracheal intubation. Anesthesia was maintained using remifentanil and isoflurane in oxygen and air. All patients received an intraoperative dose of ketoprofen (100 mgs i.v.) and at the end of surgery a morphine bolus (EV of 0.1 mg/kg of ideal weight), prior to isoflurane closure. Remifentanil was stopped after completion of the last surgical suture. During the postoperative period, an infusion of ketoprofen was administered (300 mg in 24 h), and intravenous morphine (2 mg bolus) was used as rescue therapy.

Primary outcomes were the requirement for morphine in the 24-h postoperative period and the severity of postoperative pain. Secondary outcomes were the incidence of side effects such as postoperative nausea and vomiting (PONV), sedation, dizziness, somnolence, or respiratory depression and patient satisfaction. The assessment of postoperative rest pain was done using the visual analog scale (VAS) of 11 points (with 0=no pain and 10=the maximum imaginable pain for the patient) at 1, 2, 4, 6, 8, 12, 16, 18, and 24 postoperative hours. The satisfaction of the patient relative to the analgesic therapy was graded as very good, good, regular, bad, or very bad.

Statistical Analysis

Based on a preliminary study, to calculate the necessary sample size, it was considered that a 20% decrease in morphine consumption after the preoperative administration of 150 mg pregabalin would be successful, from analyzing the data from the preliminary study. For the results to be of statistical significance with $\alpha=0.05$ and a potency of 80%, it was necessary to recruit 25 patients to each experimental group. For statistical analysis, Stata 10.0 software was used.

The descriptive data were presented as mean±standard deviation. For the comparison of continuous variables with a normal distribution, Student's t test was used. Nonparametric variables were analyzed using the Wilcoxon rank-sum test (Mann–Whitney) for independent samples. Either two-way analysis of variance or the Friedman test was used to test for variable differences in groups. Categorical data were analyzed using the r Fisher exact test, as appropriate. The level of statistical significance was considered to be $p<0.05$.

Results

A total of 85 patients were assessed for eligibility; three were excluded because they refused to participate, and of the 82 subjects receiving medication after randomization, 80 subjects completed the study. Two subjects were considered as dropouts after initial randomization and were therefore not subjected to further statistical analysis (these patients needed re-exploration on account of postoperative

bleed). Of the 80 patients who completed the study, 39 received pregabalin, and 41 received placebo. The demographic characteristics of each group were similar, and there were no differences in the duration of surgery, anesthesia, and intraoperative remifentanil consumption (Table 1). The mean blood pressure, heart rate, oxygen saturation, and respiratory rate were not different between the groups at any time point.

During the first 24 postoperative hours, the pregabalin group consumed 11.51±7.93 mg of morphine, whereas the placebo group was given 23.07±9.57 mg ($p<0.05$). The VAS scores were significantly lower in the group that received preoperative pregabalin in the first 24 postoperative hours (Fig. 1). The incidence of PONV was higher in the group that received placebo; 19 placebo group patients and ten pregabalin group patients experienced PONV ($p<0.05$). In concordance, the need for antiemetic treatment was greater in the control group. Over 24 h, pregabalin group patients consumed 3.07±1.63 mg of ondansetron, whereas the control group patients consumed 6.06±4.45 ($p<0.05$). Regarding patient satisfaction, there was no statistically significant difference between the groups. The majority of patients in both groups considered the analgesic therapy to be either good or very good. It should be noted that the only two patients who evaluated their treatment as bad came from the placebo group; however, this was not statistically significant.

No other adverse events such as sedation, dizziness, somnolence, or respiratory depression were recorded in any patient from either group.

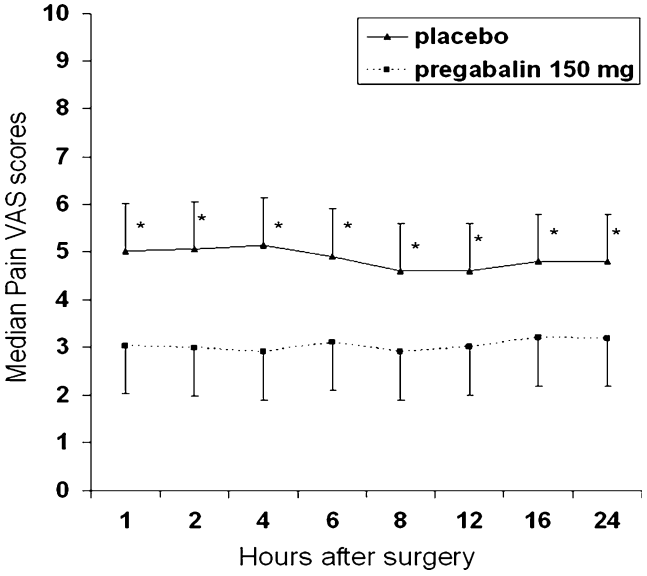

Fig. 1 Postoperative pain scores (median, 95% CI). Patients scored pain using a visual analog scale (VAS), with 0 being no pain and 10 being the worst imaginable pain (*$p<0.05$)

Discussion

The present study demonstrated the effectiveness of a single dose of 150 mg pregabalin administered 2 h preoperatively to obese patients undergoing laparoscopic sleeve gastrectomy. These benefits included lower morphine consumption during the first 24 postoperative hours and a lower incidence of PONV. The pregabalin group also had significantly lower VAS scores in the first 24 postoperative hours. Although there were no statistically significant differences in patient satisfaction, it is important to reflect on the fact that two patients from the placebo group evaluated the treatment as bad.

The selection of obese patients undergoing laparoscopic sleeve gastrectomy was based on the fact that laparoscopic surgery is considered to be less invasive than open surgery. The presence of severe to moderate postoperative pain is a frequent occurrence in these patients, and it presents a problem for the management of analgesia [11]. This difficulty results from the requirement to use doses of morphine that invariably lead to PONV. Although skin incisions during laparoscopic surgery are small, the tissue damage to intra-abdominal structures is of a considerable magnitude. In addition, the use of a high-temperature electronic scalpel in this technique can create lesions in nerves that can trigger sensitization and therefore neuropathic pain. As the surgeon causes sustained and repeated injuries to nerves and their endings, the presence of

Table 1 Patient characteristic data presented as mean (range) and mean (±SD)

Variable	Placebo ($n=41$)	Pregabalin ($n=39$)
Age (year)	40 (25–67)	39 (24–65)
Weight (kg)	99±23	100±16
Height (cm)	161±21	162±18
BMI (kg m^{2})	38.1±6	38.2±5
Duration of surgery (min)	79±26	78±26
Duration of anesthesia (min)	80±31	81±29
Intraoperative Remifentanil consumption (μg)	2340±450	2260±550

There were no significant differences between groups ($p<0.05$)

neuropathic pain resulting from surgery is therefore logical. Thus, the aim is to maintain the painful response within a physiological margin and avoid the establishment of sensitization and physiopathological responses. Experimental models of neuropathic pain and inflammatory hyperalgesia have shown that pregabalin has antinociceptive and antihyperalgesic properties [12]. The mechanism of action of antihyperalgesic drugs such as pregabalin is different from the traditional mechanisms described for analgesic drugs. Its main mode of action is to diminish the hypersensitization of neurons of the dorsal horn that is induced by tissue damage. Pregabalin is rapidly absorbed with peak blood concentrations occurring within 1 h. The average bioavailability exceeds 90% and is independent of dose, which may produce a more predictable patient response. The elimination half-life of pregabalin ranges from 5.5 to 6.7 h and is independent of dose. It has no interactions with other drugs and is very well tolerated. The most commonly reported adverse effects are mild drowsiness, dizziness, and fatigue, but it has no effect on arterial pressure or heart rate [9].

The use of pregabalin for postoperative acute pain is recent and is a subject of extensive research. Research by Hill et al. [13] into the use of 400 mg pregabalin after a dental extraction demonstrated that it was more effective than ibuprofen for the management of postoperative pain. Recently, Agarwal et al. [14] published a study in which a single preoperative dose of pregabalin (150 mg) was used for laparoscopic cholecystectomy. This study demonstrated its effectiveness for reducing both postoperative pain and the postoperative requirement of patients for fentanyl. On the other hand, Paech et al. [15], in a study of 90 women undergoing minimum gynecological surgery, did not find better pain relief or differences in postoperative pain in patients given 100 mg of pregabalin preoperatively compared to placebo subjects. Furthermore, in two studies of gynecological patients, Jokela et al. [16, 17] also did not discover any differences in postoperative pain following preoperative doses of 150 and 300 mg of pregabalin. Differences in the pregabalin dosages and the different types of patients and surgeries investigated can explain these contrasting results.

One limitation of the present study is the decision to use only a single dose of pregabalin. We administered the 150 mg of pregabalin because it is the recommended effective dose to start. We did not consider the different BMI of the patients because the oral bioavailability of pregabalin is high at 90% and is independent of dose. It would also be of interest to assess prolongation of the treatment for 48 or even 72 postoperative hours. Another important limitation is that the severity of dynamic postoperative pain was not assessed. A final consideration was our use of the postoperative rescue analgesic technique; it would have been easier to demonstrate a difference in the consumption of analgesics using a patient-controlled analgesia system.

In conclusion, pregabalin, administered preoperatively, is a new and successful drug for the multimodal treatment of postoperative acute pain. This efficacy may be explained by its use of mechanisms that had previously not been effectively evaluated [18]. Although it is necessary to continue investigating and evaluating the use of pregabalin for other types of surgeries and for longer periods, it is likely that its use will bring only benefits for the patients undergoing surgery.

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