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Original contribution

Analgesic efficacy of pregabalin in acute postmastectomy pain: placebo controlled dose ranging study☆,☆☆

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Abstract

Study objective: We hypothesized that oral administration of a single dose of pregabalin 2 hours before modified radical mastectomy (MRM) would produce dose-related reduction in postoperative opioid consumption.

Design: Prospective randomized controlled clinical trial.

Setting: Postanesthesia care unit.

Patients: One hundred twenty adult women scheduled for unilateral (MRM) with axillary evacuation.

Interventions: Patients were randomized to receive either, placebo capsule, pregabalin 75 mg, pregabalin 150 mg, or pregabalin 300 mg.

Measurements: The assessment parameters were the postoperative analgesic effect using visual analog scale (VAS) pain scores, the subsequent 24-hour morphine consumption, and the systemic adverse effects of pregabalin doses.

Main results: The VAS score at rest and movement was significantly decreased only in group P300 and group P150 in comparison to group P0 and group P75 at 0 hour ($P < .01$).

The median (interquartile range) consumption of morphine in the first postoperative 24 hours was significantly decreased in group P300 in comparison to group P0 and group P75 (P300 vs P0: 6.5 [5-6.5] vs 20.5 [15.8-20.5] [$P < .001$]; P300 vs P75: 6.5 [5-6.5] vs 20 [14-20] [$P < .001$]), but there was no significant difference between group P300 and group P150. In addition, there was a significant decrease in consumption of morphine in group P150 in comparison to group P0 and group P75 (P150 vs P0: 7 [5-7] vs 20.5 [15.8-20.5] [$P < .001$]; P150 vs P75: 7 [5-7] vs 20 [14-20] [$P < .001$]). There were statistical significant increase in dizziness and blurred vision in group P300 in comparison to other groups ($P < .05$).

Conclusions: A single preoperative oral dose of pregabalin 150 mg is an optimal dose for reducing postoperative pain and morphine consumption in patients undergoing MRM.

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[1] Contribution: This author helped design the study, conducted the study, analyzed the results and prepared the manuscript.

[2] Attestation: Diab Fuad Hetta approved the final manuscript, attests to the integrity of the original data and the analysis reported in this manuscript, and is the archival author.

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1. Introduction

Chronic postsurgical pain (CPSP) is a common complication after radical mastectomy, with reported incidence between 20 [1] and 68% [2]. Surgical incision has been known to induce hyperalgesia, which can contribute to persistent pain after surgery [3]. There is increase evidence in the literature that adequate treatment of acute pain after modified radical mastectomy (MRM) might decrease the risk of the development of chronic pain postoperatively. In recent years, pregabalin has been introduced as an adjunct in the multimodal management of postoperative pain [4].

A large number of clinical trials have evaluated the efficacy and adverse effects of pregabalin in the reduction of acute postoperative pain. However, these trials have demonstrated conflicting results mostly due to differences in dosage, dosing regimen, severity, and type of pain. Some studies have reported no analgesic benefit of perioperative use of pregabalin [5–8], and others have proved reduction in analgesic consumption and pain scores [9–11]. The doses of pregabalin used in these trials have ranged from 75 to 600 mg, either single or divided doses. In some trials, the analgesic efficacy was at the expense of increase in adverse events, mainly sedation and dizziness [12,13]. The aim of this study was to give gradually increasing doses of preoperative pregabalin to get the optimal analgesic effect with minimal adverse effects. We hypothesized that oral administration of a single dose of pregabalin ranging from 75 to 300 mg 2 hours before MRM would produce a dose-related reduction in postoperative opioid consumption.

2. Methods

The study was approved by the Institutional Ethics Committee, South Egypt Cancer Institute, Assiut University, and a written informed consent was obtained from all patients. A total of 120 adult women, American Society of Anesthesiologists physical status class I and II, scheduled for unilateral MRM with axillary evacuation were consecutively enrolled. The enrollment period began on October 20, 2013, and continued until March 10, 2015.

The exclusion criteria were patients with a known allergy to pregabalin or morphine, pregnancy or breastfeeding, a history of drug or alcohol abuse, patients with impaired kidney or liver functions, patients with chronic pain or regularly receiving analgesics, and previous or current use of gabapentinoids.

The night before surgery, in the anesthesia clinic, all patients were instructed how to evaluate their own pain intensity using the visual analog scale (VAS), scored from 0 to 10 (where 0 = no pain and 10 = the worst pain imaginable) and how to use patient-controlled analgesia (PCA).

Patients were randomly divided into 4 groups, where patients received orally 2 hours before surgery the study medication: placebo capsule (group P0), pregabalin 75 mg (group P75), pregabalin 150 mg (group P150), or pregabalin 300 mg (group P300).

The hospital pharmacists performed the randomization schedule using a computer-generated random number list. They masked the study medication by packing placebo and pregabalin into 2 identical capsules in color and appearance to make the drugs unrecognizable. The study drugs were packed in opaque plastic containers labeled with the randomization numbers. The randomization code was opened at the end of the study. Upon arrival to the operating room, peripheral venous line was established. Monitoring probes (electrocardiography, noninvasive blood pressure, and pulse oximeter) were applied.

None of patients received other premedications, and the anesthetic protocol was standardized for all patients. General anesthesia was induced with propofol 2 to 3 mg/kg and fentanyl 2 μg/kg, followed by cisatracurium 0.15 mg/kg to facilitate endotracheal intubation. Anesthesia was maintained with sevoflurane in 40% oxygen in air, maintaining the bispectral index between 40 and 60 and cisatracurium 0.03 mg/kg on demand. Heart rate and mean arterial blood pressure (MAP) were maintained within 20% of the preoperative baseline values by giving intravenous bolus doses of fentanyl 50 μg if the MAP or heart rate increased more than 20% from the baseline values. Ephedrine 10 mg was given intravenously as needed to keep MAP more than 65 mm Hg. Atropine 0.01 mg/kg was given intravenously if heart rate decreased less than 50 beats/min. All patients received intravenous paracetamol 1 g and prophylactic antiemetic, ondansetron 4 mg, at skin closure. At the end of surgery, residual neuromuscular paralysis was reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg.

After recovery from anesthesia, all patients were transferred to the postanesthesia care unit for a 24-hour observation period.

Postoperative analgesia composed of PCA with an initial morphine bolus of 0.1 mg/kg once the patient requested analgesia, followed by 1-mg boluses on demand without background infusion with a lockout period of 5 minutes. The pain intensity at rest and arm movement 90° was evaluated by VAS score, the maximum pain scores at different time intervals (0-2, 2-4, 4-8, 8-16, and 16-24 hours) for each patient were considered for statistical analysis. All patients were instructed to keep their VAS score at 3 or less. Adverse events were evaluated on the basis of the package labeling for pregabalin, the occurrences of sedation, blurred vision, confusion, dizziness, headache, and dry mouth were recorded. In addition, occurrences of nausea and vomiting were recorded and treated with ondansetron 4 mg. All adverse events were assessed on the basis of answers to standardized questions in the first postoperative day by the anesthesia resident blinded to the study protocol.

The level of sedation was assessed immediately preoperatively and within 4 hours postoperatively by the Ramsay Sedation Scale (awake levels were as follows: 1, anxious, agitated, or restless; 2, cooperative, oriented, and tranquil; 3, responds to command; asleep levels were dependent on patient's response to a light glabellar tap or loud auditory stimulus; 4, brisk response; 5, a sluggish response; and 6, no response). The highest score was recorded.

The primary outcome measure was the analgesic effect of pregabalin using VAS score. The secondary outcomes were