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Research Article

Efficacy of preoperative melatonin versus pregabalin on perioperative anxiety and postoperative pain in gynecological surgeries

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KEYWORDS

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Abstract *Background:* We compared the efficacy of melatonin and pregabalin on perioperative anxiety and postoperative pain in patients undergoing laparoscopic gynecological surgeries.
Methods: In this randomized double-blind study, 40 patients, 25–35 yr undergoing gynecological surgeries were divided into 2 equal groups to receive either melatonin capsule 6 mg (Group M), or pregabalin capsule 150 mg (Group P) 1 h before induction of general anesthesia. Our primary outcome was preoperative acute anxiety level 1 h after drug administration, 1, 6, and 12 h after operation. The secondary outcomes were postoperative visual analog scale (VAS) for pain, analgesic consumption, sedation level using the inverted observer's assessment of alertness/sedation scale (OAA/S) scale, and incidence of adverse effects.
Results: The anxiety scores decreased significantly >50% after premedication in both groups compared to baseline values ($p < 0.01$) with no statistically significant difference between the two groups (30.4 ± 4.5 in group M versus 31.7 ± 4.2 in group P, $p > 0.05$). Postoperative VAS for pain, time for first analgesic demand and number of patients requiring postoperative analgesia did not differ between groups, and the sedation score was higher in melatonin group compared to pregabalin group 1 h after drug (3.45 ± 0.7 versus 1.95 ± 0.6, $p < 0.001$, respectively) and at

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all the subsequent readings postoperatively with equal incidence of adverse effects in both groups. *Conclusion:* Oral melatonin 6 mg or pregabalin 150 mg administered 1 h before operation had reduced perioperative anxiety and postoperative pain in patients undergoing gynecological surgeries, without untoward sedative effects in the pregabalin group compared to melatonin group.

1. Introduction

Preoperative anxiety serves a critical role in the chain of events that control the postoperative pain response [1,2]. Numerous studies have demonstrated a positive correlation between anxiety and pain, with less anxious patients experienced less postoperative pain [3].

Young female patients and patients with no previous anesthetic experience had higher anxiety scores [4]. Although benzodiazepines are effective in reducing preoperative anxiety, its anxiolytic effect is frequently accompanied by undesirable sedation and previous clinical studies failed to demonstrate a positive impact on postoperative pain [5]. Gabapentinoids might be a useful alternative to benzodiazepines as pregabalin (an analog of gabapentin) which has been alleged to possess anxiolytic and analgesic effects [6]. Also, several studies reported that melatonin which is a hormone secreted by the pineal gland, has analgesic potential in addition to its anxiolytic and sedative effects without disturbances of the cognitive and psychomotor skills [7–10].

We designed this study to compare the efficacy of melatonin and pregabalin in reducing perioperative anxiety and postoperative pain in patients undergoing laparoscopic gynecological surgeries.

Our primary outcome was preoperative acute (state) anxiety level and the secondary outcomes were postoperative pain and analgesic consumption.

2. Materials and methods

After approval of the local ethics committee and obtaining informed written patient's consent, 40 female patients, ASA physical status I–II, 25–35 yr old scheduled for gynecological surgeries (laparoscopic adhesiolysis for infertility) were enrolled in this randomized, double-blind study. The study was conducted at Ain shams Maternity hospital from May 2011 to April 2012. Details of the trial protocol can be obtained from the department of Anesthesiology, Faculty of Medicine, Ain Shams University.

Exclusion criteria included patients with clinically significant medical or psychiatric problems or were taking opioid-containing medications on a long-term basis, history of chronic pain, regular medication with analgesics, or allergic to any of the study drugs.

The patients were randomly assigned using a computer-generated random numbers into 2 equal groups to receive either one melatonin capsule 6 mg (Melatonin 3 mg tablet; Sigma Chemical, St. Louis, MO, Group M), or pregabalin capsule (150 mg; Lyrica, Pfizer Inc., Group P) approximately 1 h before induction of general anesthesia. To maintain blindness, all drugs were prepared in identical-appearing capsules and were put in numbered envelopes. The study drugs were administered by the ward nurse who was not involved in any part of the study later, and no other preoperative medication was given.

Anxiety levels were assessed by a blinded observer using the Spielberg state and trait anxiety inventory STAI [11], a score for each ranging between 20 and 80 may then be calculated by an investigator using a scoring key [12] with higher scores indicating more anxiety. Assessment was done before taking the study drugs (preop), 1 h after (immediately before induction of general anesthesia) by the same observer who assess it an hour before. Postoperative assessment was performed at 1, 6, and 12 h after operation by a different observer from the one who had carried out the preoperative evaluation. They presented the test questions in a random order to prevent order effects.

On arrival at the operating room, electrocardiogram, pulse oximetry, and non-invasive arterial blood pressure were applied. Baseline vital signs were obtained and subsequent values were recorded every 5 min throughout surgical procedure. Anesthesia was induced with fentanyl 1.5 μg/kg and propofol 1.5–2 mg/kg until loss of eyelash reflex. Tracheal intubation was facilitated with atracurium 0.5 mg/kg. Anesthesia was maintained with isoflurane (1–2%) in 40% oxygen, and intermittent doses of muscle relaxant to maintain adequate muscle relaxation throughout the procedure. The respiratory tidal volume was adjusted to keep end-tidal CO_2 at 4.8–5.2%. The isoflurane concentration was adjusted to keep heart rate and blood pressure within 20% of pre-induction values throughout the anesthesia period. All surgical procedures were completed by the same surgeon. At the end of surgery, atropine 0.02 mg/kg and neostigmine 0.05 mg/kg were given IV for antagonism of neuromuscular blockade. Time to awaken (from the end of anesthesia until the patients opened their eyes on command) was recorded.

All the patients were transferred to the post-anesthesia care unit (PACU), and diclofenac 75 mg was prescribed every 6 h or as requested by the patients. Postoperative pain intensity was rated by the patients using a 0–10 cm visual analog scale (VAS), with 0 = no pain and 10 = the worst pain imaginable, and time to the first dose of postoperative analgesia was recorded.) The patient's level of sedation was assessed using the inverted observer's assessment of alertness/sedation (OAA/S) scale with a score of 1 = awake, alert to 5 = asleep, unarousable [13]. The ward nurses were instructed to omit the six hourly doses if they considered that the patient was over sedated or pain free (pain level $\leqslant 4$ on VAS, sedation level $\geqslant 3$ on OAA/S). The postoperative data (e.g., vital signs, pain, and sedation scale) were assessed at 30 min, 2 h, 4 h, 6 h, 8 h, and 12 h after the end of surgery. The occurrence of any side effects such as nausea, vomiting, respiratory depression, dizziness, tremors, diplopia, headache, and pruritus was recorded. Postoperative nausea and vomiting were treated with 4 mg IV ondansetron.

The patients, attending anesthesiologists, data observers, and nurses in the recovery room who were involved in the patients' care were all blinded to the study group assignment.