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Preoperative Anxiolytic Effect of Melatonin and Clonidine on Postoperative Pain and Morphine Consumption in Patients Undergoing Abdominal Hysterectomy: A Double-Blind, Randomized, Placebo-Controlled Study

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Abstract: Recent evidence has demonstrated analgesic, anti-inflammatory, and anxiolytic properties of melatonin. Taking into account that higher anxiety makes the control of postoperative pain more difficult, one can hypothesize that melatonin anxiolytic and analgesic effects improve the control of postoperative pain. Thus, we conducted a randomized, double-blind, placebo-controlled study with 59 patients undergoing abdominal hysterectomy to test the hypothesis that melatonin is as effective as clonidine and that both are more effective than placebo in reducing postoperative pain. Additionally, we compared their anxiolytic effects on postoperative pain. Patients were randomly assigned to receive oral melatonin (5 mg) (n = 20), clonidine (100 μg) (n = 19), or placebo (n = 20) orally. In addition to primary outcomes of pain intensity and analgesic consumption, secondary outcome measures included postoperative state anxiety. In anxious patients 6 hours after surgery, the number of patients needed to be to prevent moderate to intense pain during the first 24 hours after surgery was 1.52 (95% CI, 1.14 to 6.02) and 1.64 (95% CI, 1.29 to 5.93), respectively, in the melatonin and clonidine groups compared with placebo. Also, the anxiolytic effect of melatonin and clonidine resulted in reduced postoperative morphine consumption by more than 30%. However, in the mildly anxious, it was not observed the treatment effect on pain.

***Perspectives:** The preoperative anxiolysis with melatonin or clonidine reduced postoperative pain and morphine consumption in patients undergoing abdominal hysterectomy. The effects these 2 drugs were equivalent and greater than with placebo.*

***Key words:** Patient-controlled analgesia (PCA), acute pain, analgesics, melatonin, morphine, anxiolytic, clonidine, surgery, hysterectomy.*

The most common and anticipated problems in the perioperative setting are anxiety and pain. Anxiety can produce aggressive reactions, which result in an increase in the distress experienced by the patient, and make the management and control of postoperative pain more difficult.[44] Furthermore, higher levels of postoperative pain and anxiety may increase patient discomfort and postoperative morbidity.[4,24] Taking into account that pain is a sensory and emotional experience,[25] it makes sense to intensify the preoperative treatment to improve postoperative pain control.

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Although the use of preoperative benzodiazepines as anxiolytics is the most common practice of premedication, previous randomized, clinical studies failed to demonstrate a positive impact on postoperative pain.[9,23] The pineal hormone melatonin (*N*-acetyl-5-methoxytryptamine) has several putative functions that may make it an attractive option for premedication, including the regulation of circadian rhythms and sedative, analgesic, anti-inflammatory, and antioxidative effects.[18] In 1 recent randomized clinical trial, a coanalgesic effect of melatonin (5 mg) administered on the night before the surgery and 1 hour before the start of surgery was demonstrated.[11] Another drug with beneficial properties for use as premedication is the α_2-agonist clonidine. It reduces sympathetic activity, the incidence of shivering, and oxygen consumption during recovery from anesthesia[39] and lowers anesthetic requirements for both opioid agent and volatile anesthetic.[19] Additionally, a small clonidine dose (100 μg) used preoperatively and postoperatively provides clinically relevant anxiolytic effect.[22]

Even though the melatonin effect has been demonstrated in 1 study in which it was used preoperatively,[11] its clinical impact on pain and anxiety has not been sufficiently explored to indicate it widely. Therefore, it is necessary to compare melatonin with another pharmacological intervention used preoperatively with known coanalgesic and anxiolytic effects, because the clinical efficacy of a new therapeutic option cannot be compared only with placebo but with other therapeutic options with similar properties to assess whether melatonin provides enough benefit over that already available.[12] Accordingly, one can hypothesize that preoperative melatonin is at least equivalent to clonidine in reducing postoperative pain and anxiety and enhancing postoperative clinical recovery. Thus, we designed this study to test the hypothesis that melatonin is as effective as clonidine and that both are more effective than placebo in providing analgesia in patients undergoing abdominal hysterectomy. The study also examines the effect of anxiolysis produced by each treatment group on postoperative pain and morphine consumption.

Methods

Study Population

After approval by the ethics committee and written informed consent was given, 63 patients, ASA classification I to II, ages 19 to 60 years, scheduled to undergo total abdominal hysterectomy for myomatosis, were enrolled into the randomized, double-blind, placebo-controlled study. Patients with contraindications to regional anesthesia, mental impairment, chronic pain, or a history of congestive heart failure, valvular heart disease, renal or hepatic disease, use of psychotropic drugs in the present or in the past, and language or communication difficulties were excluded. Also, patients with a body mass index (BMI) higher than 25 kg/m^2, a history of psychiatric disorder, and/or those patients with positive screening (scores ≥8) for minor psychiatric disorders (somatic symptoms, depressive mood, depressive thoughts, and decreased energy) on the World Health Organization's (WHO) Self-Reporting Questionnaire (SRQ-20) were also excluded.[28]

Randomization and Interventions

The treatment allocation method used was advanced simple randomization without blocking or stratification. Before the recruitment phase of the study, the envelopes containing all protocol materials were prepared and numbered sequentially, which were grouped so that each envelope had an independent 50% probability of being included in either group. A sheet indicating the allocated treatment was then placed in the envelope and the envelopes were sealed. A random number was used to assign each consecutively numbered envelope to receive 5 mg oral melatonin (Sigma Chemical; St Louis, MO), oral clonidine 100 μg (Boehringer Ingelheim Pharmaceuticals; Ridgefield, CT), or placebo the night before (10 PM) and 1 hour before surgery. Thirty-six hours after the surgery, the melatonin and the placebo groups received placebo, whereas the clonidine group received oral clonidine (100 μg). Throughout the course of the study, the sealed envelopes were removed and opened sequentially by a pharmacy technician who delivered the tablets of melatonin (5 mg), clonidine (100 μg), or placebo only after prospective patients had been screened and had consented to participation. No other preoperative medication was given. During the entire protocol timeline, blinding, and randomization were undertaken by 2 investigators who were not involved in the patient's evaluation. Other individuals involved in the patient's care were unaware of the treatment group to which the patient belonged.

Assessment

The first evaluation was 1 week before the hospitalization in the ambulatory Perioperative Medicine and Anesthesia Service area. Patient characteristics were collected using a structured questionnaire, and each patient underwent psychological testing. The 4 evaluators received 1 month (60 hours) of training with role-playing activities and discussion, focusing on difficulties that might occur during the interviews. They presented the tests in a random order to prevent order effects and were assisted in 15% of the interviews by the principal investigator. To ensure blinding, postoperative assessment was performed by a different physician from the 1 who had carried out the preoperative evaluation. The staff that provided instructions on controlled analgesia (PCA) use and program changes was unaware as to which group the patient belonged. The second evaluation was the day before the surgery, after admission to the hospital. On the night before surgery, all patients were evaluated by the same anesthetist, who provided them with information on the perioperative course and instructed them on how to use the PCA pump. Moreover, each patient underwent anxiety assessment using the State-Trait Anxiety Inventory (STAI)[5] and the visual analog scale (VAS) pain scoring system.[41] All of the psychological tests