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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.

The primary end point of this study was a reduction in the patients' preoperative level of anxiety 1 h after intake of study drug. Based on a predicted 33% reduction from the patient's pretreatment (baseline), our sample size estimation indicated that 18 patients per group would give a power of 0.8 at an α-error 0.05 for detecting a 33% reduction in preoperative anxiety. Mean and standard deviations in preoperative anxiety were derived from Menigaux et al. [14] and thus the total sample size was prospectively set of 40 patients. The statistical analysis was performed using a standard SPSS software package (Chicago, IL).

Data were expressed as mean values ± SD, percentages (%), and numbers (*n*). One-way analysis of variance was used to analyze continuous variables. Changes in VRS scores over time were analyzed using repeated-measures analysis of variance. Student's *t*-test was used to analyze the parametric data, and discrete (categorical) variables were analyzed using the χ^2 test, with p values <0.05 were considered statistically significant.

3. Results

Forty patients, 20 per group, were enrolled in the study and none was excluded. There were no differences between the two groups in patient demographics, duration of operation, end-tidal isoflurane concentration for maintenance of anesthesia and time to awaken from anesthesia (Table 1).

There were no significant differences between the two groups in baseline STAI score, and these scores decreased significantly >50% after premedication in both groups compared to baseline values ($p < 0.01$) with no significant differences between the two groups 1 h after drug administration and at all the following postoperative readings (Fig. 1, State and trait anxiety inventory score).

There were no significant differences in postoperative VAS for pain between the two groups (Fig. 2, Visual Analog Score). The time for first analgesic demand, and the number of patients requiring diclofenac at 6 and 12 h postoperatively were also similar in both groups (Table 2).

Patients who received melatonin premedication were more sedated than those who received pregabalin 1 h after drug administration, on arrival at the operating room, and at all the subsequent readings postoperatively ($p < 0.001$) (Fig. 3).

There were no significant differences in mean baseline vital sign values (heart rate, blood pressure, and oxygen saturation) or in subsequent values during operation and postoperatively with no incidence of bradycardia, hypotension, or desaturation requiring intervention in the two groups.

Table 1 Patient demographics and operative characteristics.

	Group M (n = 20)	Group P (n = 20)
Age (yr)	32.5 ± 4	31 ± 5
Weight (kg)	62.6 ± 4	60.8 ± 6
Height (cm)	160 ± 4	164 ± 7
ASA status (I:II)	16:4	17:3
Duration of operation (min)	88.5 ± 4.4	86 ± 7
Isoflurane %	1.2 ± 0.2	1.1 ± 0.3
Time to awaken (min)	11.2 ± 1.7	13 ± 2.1

Group M = Melatonin group, Group P = Pregabalin group.
Data expressed as mean ± SD, ratio.
There was no statistically significant difference between the 2 groups.

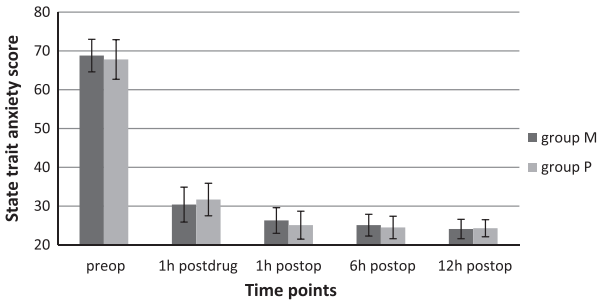

Figure 1 State and trait anxiety inventory score (STAI). Group M = Melatonin group, Group P = Pregabalin group. Columns are mean STAI and error bars are standard deviation.

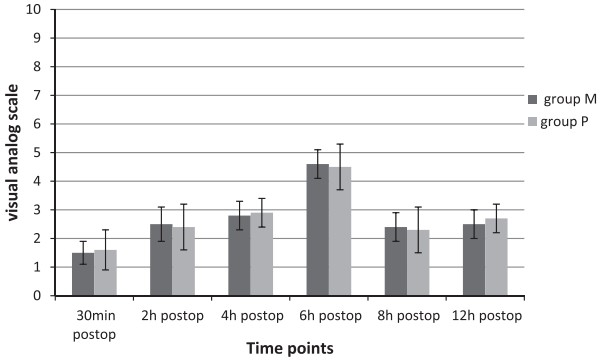

Figure 2 Visual Analog Score (VAS). Group M = Melatonin group, Group P = Pregabalin group. Columns are mean VAS and error bars are standard deviation.

Patients who received melatonin premedication were more sedated than those who received pregabalin 1 h after drug administration, and at all the subsequent readings postoperatively Fig. 3, Inverted Observer's assessment of Alertness/Sedation Scale (OASS).

Three patients in the melatonin group and one patient in the pregabalin group complained of dizziness and three patients in the melatonin group and one patient in the pregabalin group complained of headache, no other adverse effects were recorded in both groups.

4. Discussion

This current study showed that in female patients undergoing gynecological surgeries, administration of oral melatonin 6 mg or pregabalin 150 mg, 1 h before operation had equal efficacy in reducing perioperative anxiety and postoperative pain without untoward sedative effects in the pregabalin group compared to melatonin group.

To our knowledge, this was the first study that compared the 2 active drugs, melatonin, and pregabalin as regarding their efficacy in reducing perioperative anxiety and postoperative pain. Previous randomized studies had compared each of these drugs either with placebo [15–20], with midazolam [21], or with clonidine [22] in separate surveys. The selected doses of oral melatonin (6 mg) and pregabalin 150 mg used in our study were based on previous studies concluding that premedication with melatonin at a dose of 0.2 mg/kg [9] and pregabalin at a dose

Table 2 Time to first analgesic demand, and diclofenac consumption.

	Group M (n = 20)	Group P (n = 20)	p-Value
Time to first analgesic demand (min)	114.3 ± 4.8	118.1 ± 6.2	0.08
Diclofenac consumption No. of patients (%)			
At 6 h	10(50%)	8(40%)	0.75
At 12 h	12(60%)	10(50%)	0.75

Group M = Melatonin group, Group P = Pregabalin group.
Values are mean ± SD or number of patients and%.
$P > 0.05$ is considered statistically nonsignificant.

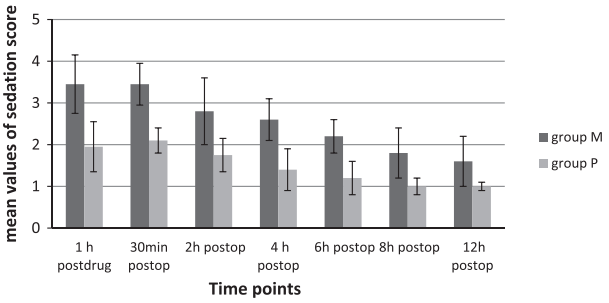

Figure 3 Inverted Observer's assessment of Alertness/Sedation Scale (OASS). Data are mean sedation score and error bars are standard deviation. Group M = Melatonin group, Group P = Pregabalin group. Statistically significant difference between the 2 groups at all time points.

of 150 mg [20] had proved adequate anxiolytic and analgesic effects without untoward adverse effects.

No differences in the anxiety scores were found between patients receiving melatonin and those receiving pregabalin 1 h after drug administration and at all the postoperative readings. The preoperative anxiolytic effect of melatonin (6–10 mg) was supported in previous clinical trials in adults when compared with placebo [8,17,18,21]. In the postoperative period, melatonin had shown to be associated with less anxiety compared with placebo up to 48 h after surgery [21,22]. Only one study had refuted melatonin's anxiolytic effects although, this study showed that the level of anxiety scores decreased 33% after melatonin premedication [16].

As regarding pregabalin, there were contradicting data about its anxiolytic efficacy.

Single doses of pregabalin 150 mg [20] and 300 mg [19] have been proved to reduce preoperative anxiety without any side effects like dizziness or persisting sedation. On the other hand, another study showed that pregabalin administration in doses from 75 to 300 mg po though increased perioperative sedation in a dose-related fashion, but failed to reduce preoperative state anxiety and postoperative pain after minor elective surgery procedures [18]. These previous studies used the simple VAS for anxiety which is less accurate than the State-Trait Anxiety Inventory score which we used as it is the most accurate score for assessing anxiety [4].

The same timing of the anxiolytic action of both drugs is related to their pharmacokinetics, where the time required reaching peak plasma concentration of melatonin ranged from 0.25 h to 13 h [23] and that of pregabalin was approximately 1 h and steady state was achieved within 24–48 h [24].

The postoperative pain scores in this study were similar in the two groups. The postoperative analgesic effect of melatonin has been proved after abdominal hysterectomy under epidural anesthesia [22] and in patients receiving IV regional anesthesia [25]. A previous animal study has shown that systemic melatonin provided dose-dependent antinociception and enhanced morphine analgesia [26].

As regarding pregabalin, different doses 75, 150 and 300 mg administered as single doses before surgery had reduced postoperative pain and opioid consumption in the early postoperative period only [18,20].

Melatonin impact on pain may be explained by the interplay between the melatonergic and GABAergic systems [27,28], enhancement of endorphin levels and the antinociception induced by opioid receptor agonists [29], and activation of MT2 melatonin receptors in the dorsal horn of the spinal cord [30]. Pregabalin appears to be a potent ligand for the alpha-2-delta subunit of voltage-gated calcium channels in the central nervous system that exhibits potent analgesic, and anxiolytic activity in a range of animal models [24].

Patients receiving pregabalin were less sedated and did not complain of any other adverse effects, and it was proved that Pregabalin is well tolerated and associated with dose-dependent adverse effects that are mild-to-moderate and are usually transient [31]. This may have to do with the relatively low dose of pregabalin we used (150 mg). As regarding adverse effects, patients who received melatonin were more sedated and three patients were dizzy, which was nearly similar to the results proved by Ismail and Mowafi who found that one patient in their melatonin group complained of dizziness [17].

There were some limitations in this study, first, we did not include placebo group for ethical concerns and as our study drugs had been compared with placebo in many previous trials, and second, that the last record of data was done at 12 h postoperative as all patients were discharged after that.

In conclusion, in female patients undergoing gynecological surgeries, administration of oral melatonin 6 mg or pregabalin 150 mg, 1 h before operation had reduced perioperative anxiety and postoperative pain, without untoward sedative effects in the pregabalin group compared to melatonin group.

Conflict of interest

None.

References

[1] Ip HY, Abrishami A, Peng PW, Wong J, Chung F. Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. Anesthesiology 2009;111:657–77.

[2] Kain ZN, Sevarino F, Alexander GM, Pincus S, Mayes LC. Preoperative anxiety and postoperative pain in women undergoing hysterectomy. A repeated-measures design. J Psychosom Res 2000;49:417–22.
[3] Degrootk I, Boeke S, Duivenvoorden HJ, Bonke B, Passchier J. Different aspects of anxiety as predictors of postoperative anxiety and physical complaints. Personality Individ Differ 1996;21(6):929–36.
[4] Kindler C, Harms C, Amsler F, Ihde-Scholl T, Scheidegger D. The visual analog scale allows effective measurement of preoperative anxiety and detection of patients' anesthetic concerns. Anesth Analg 2000;90:706–12.
[5] Shafer A, White PF, Urquhart ML, Doze VA. Outpatient premedication: use of midazolam and opioid analgesics. Anesthesiology 1989;71:495–501.
[6] Kavoussi R. Pregabalin: from molecule to medicine. Eur Neuropsychopharmacol 2006;16:128–33.
[7] Naguib M, Samarkandi AH. Premedication with melatonin: a double-blind, placebo controlled comparison with midazolam. Br J Anaesth 1999;82:875–80.
[8] Naguib M, Samarkandi AH. The comparative dose-response effect of melatonin and midazolam for premedication of adult's patients: a double-blinded placebo-controlled study. Anesth Analg 2000;91:473–9.
[9] Naguib M, Samarkandi AH, Moniem MA, Mansour Eel-D, Alshaer AA, Al-Ayyaf HA, Fadin A, Alharby SW. The effects of melatonin premedication on propofol and thiopental induction dose-response curves: a prospective, randomized, double-blind study. Anesth Analg 2006;103:1448–52.
[10] Caumo W, Torres F, Moreira Jr NL, Auzani JA, Monteiro CA, Londero G, Ribeiro DF, Hidalgo MP. The clinical impact of preoperative melatonin on postoperative outcomes in patients undergoing abdominal hysterectomy. Anesth Analg 2007;105:1263–71.
[11] Maranets I, Kain ZN. Preoperative anxiety and intraoperative anesthetic requirement. Anesth Analg 1999;89:1346–51.
[12] Morley AP, Papageorgiou CH, Marinaki AM, Cooper DJ, Lewis CM. The effect of preoperative anxiety on induction of anesthesia with propofol. Anaesthesia 2008;63:467–73.
[13] Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, Schwam EM, Siegel JL. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. J Clin Psychopharmacol 1990;10:244–51.
[14] Menigaux C, Adam F, Guignard B, Sessler DI, Chauvin M. Preoperative gabapentin decreases anxiety and improves early functional recovery from knee surgery. Anesth Analg 2005;100:1394–9.
[15] Yousaf F, Seet E, Venkatraghavan L, Abrishami A, Chung F. Efficacy and safety of melatonin as an anxiolytic and analgesic in the perioperative period: a qualitative systematic review of randomized trials. Anesthesiology 2010;113:968–76.
[16] Capuzzo M, Zanardi B, Schiffino E, Buccoliero C, Gragnaniello D, Bianchi S, Alvisi R. Melatonin does not reduce anxiety more than placebo in the elderly undergoing surgery. Anesth Analg 2006;103:121–3.
[17] Ismail SA, Mowafi HA. Melatonin provides anxiolysis, enhances analgesia, decreases intraocular pressure, and promotes better operating conditions during cataract surgery under topical anesthesia. Anesth Analg 2009;108:1146–51.
[18] White P, Tufanogullari B, Taylor J, Klein K. The effect of pregabalin on preoperative anxiety and sedation levels: a dose-ranging study. Anesth Analg 2009;108:1140–5.
[19] Gonano C, Latzke D, Sabeti M, Kettner SC, Chiari A, Gustorff B. The anxiolytic effect of pregabalin in outpatients undergoing minor orthopedic surgery. J Psychopharmacol 2011;25(2):249–53.
[20] Spreng U, Dahl V, Ræder J. Effect of a single dose of pregabalin on post-operative pain and pre-operative anxiety in patients undergoing discectomy. Acta Anaesthesiol Scand 2011;55:571–6.
[21] Acil M, Basgul E, Celiker V, Karagöz AH, Demir B, Aypar U. Perioperative effects of melatonin and midazolam premedication on sedation, orientation, anxiety scores, and psychomotor performance. Eur J Anaesthesiol 2004;21:553–7.
[22] Caumo W, Levandovski R, Paz M. 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. J Pain 2009;10:100–8.
[23] Chase JE, Gidal BE. Melatonin: therapeutic use in sleep disorders. Ann Pharmacother 1997;31(10):1218–26.
[24] Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. Epilepsia 2004;45(6):13–8.
[25] Mowafi HA, Ismail SA. Melatonin improves tourniquet tolerance and enhances postoperative analgesia in patients receiving intravenous regional anesthesia. Anesth Analg 2008;107:1422–6.
[26] Kim SY, Jeong JJ, Chung WY, Kim HJ, Nam KH, Shim YH. Perioperative administration of pregabalin for pain after robot-assisted endoscopic thyroidectomy: a randomized clinical trial. Surg Endosc 2010;24:2776–81.
[27] Golombek DA, Escolar E, Burin LJ, De Brito-Sanchez MG, Cardinali DP. Time-dependent melatonin analgesia in mice: inhibition by opiate or benzodiazepine antagonism. Eur J Pharmacol 1991;194:25–30.
[28] Golombek DA, Martini M, Cardinali DP. Melatonin as an anxiolytic in rats: time dependence and interaction with the central GABAergic system. Eur J Pharmacol 1993;237:231–6.
[29] Yu CX, Zhu B, Xu SF, Cao XD, Wu GC. The analgesic effects of peripheral and central administration of melatonin in rats. Eur J Pharmacol 2000;403:49–53.
[30] Yu CX, Zhu CB, Xu SF, Cao XD, Wu GC. Selective MT_2 melatonin receptor antagonist blocks melatonin-induced antinociception in rats. Neurosci Lett 2000;282:161–4.
[31] Gajraj NM. Pregabalin: its pharmacology and use in pain management. Anesth Analg 2007;105:1805–15.