ORIGINAL ARTICLE

Midazolam reduction with pre-operative melatonin in abdominal hysterectomy: double-blind randomized clinical trial

Reducción de midazolam con melatonina preoperatoria en histerectomía abdominal: ensayo clínico aleatorizado doble ciego

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Abstract

Introduction: *Midazolam is a benzodiazepine used for sedation, however, can cause respiratory depression and increases morbidity in patients. Melatonin is an effective alternative to manage anxiety in the perioperative period and could help to reduce the use of benzodiazepines during surgery. The aim of this clinical trial was to determine the efficacy of pre-operative sedation with a single-dose melatonin to reduce intraoperative use of midazolam in women under total abdominal hysterectomy (TAH).* **Materials and methods:** *This is a double-blind randomized clinical trial conducted in women over 25 years, scheduled for TAH, with American Society of Anesthesiologists Grade I or II. Each patient was randomly assigned to receive 5 mg of melatonin prolonged-release oral capsules or placebo. Midazolam use for anesthetic management was the decision of the treating anesthesiologist and sedation status was determined using the observer's assessment of alertness/sedation scale.* **Results:** *In patients receiving melatonin, the use of midazolam during surgery was less than in patients receiving placebo. In addition, melatonin produces sedation 30 min after administration, the sedative effect was maintained at 60- and 90-min. Furthermore, hospital stay was shorter in patients who received melatonin (p = 0.006).* **Conclusion:** *Melatonin is effective for reduces intraoperative midazolam consumption and hospital stay in women undergoing TAH.*

Keywords: *Perioperative. Hysterectomy. Sedation. Melatonin.*

Resumen

Introducción: *El midazolam es una benzodiazepina utilizada para la sedación, sin embargo, puede causar depresión respiratoria y aumentar la morbilidad en los pacientes. La melatonina es una alternativa eficaz para controlar la ansiedad en el período perioperatorio y podría ayudar a reducir el uso de benzodiazepinas durante la cirugía. El objetivo de este ensayo clínico fue determinar la eficacia de la sedación preoperatoria con una dosis única de melatonina para reducir el uso intraoperatorio de midazolam en mujeres sometidas a histerectomía abdominal total (HTA).* **Material y métodos:** *Se trata de un ensayo clínico aleatorizado doble ciego realizado en mujeres mayores de 25 años, programadas para TAH, con American Society of Anesthesiologists Grado I o II. Cada paciente fue asignado al azar para recibir 5 mg de cápsulas orales de liberación prolongada de melatonina o placebo. El uso de midazolam para el manejo anestésico fue decisión del anestesiólogo tratante y el*

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Date of reception: 28-12-2020
Date of acceptance: 11-04-2021
DOI: 10.24875/CIRU.20001428

Cir Cir. 2022;90(3):353-358
Contents available at PubMed
www.cirugiaycirujanos.com

estado de sedación se determinó mediante la escala OAA/S. **Resultados:** *En las pacientes que recibieron melatonina, el uso de midazolam durante la cirugía fue menor que en las pacientes que recibieron placebo. Además, la melatonina produce sedación 30 min después de la administración, el efecto sedante se mantuvo a los 60 y 90 min. Además, la estancia hospitalaria fue más corta en los pacientes que recibieron melatonina (p = 0.006).* **Conclusión:** *La melatonina es eficaz para reducir el consumo de midazolam intraoperatorio y la estancia hospitalaria en mujeres sometidas a HTA.*

Palabras clave: *Perioperatorio. Histerectomía. Sedación. Melatonina.*

Introduction

During the anesthetic procedure medications, benzodiazepines are used primarily for their sedative effects[1], although they cause cough, nausea, and vomiting[2], as well as memory impairment and cognitive functions[3]. In addition, benzodiazepines and opioids can cause respiratory depression and increase morbidity as well as hospital costs[4]. Melatonin may be an alternative to sedation offers the advantage of reducing the use of benzodiazepines and opioids. The previous evidence suggests that oral administration of melatonin before anesthetic procedures is advisable due to its sedative, anti-inflammatory, and hypnotic effects during pre-induction medication. Moreover, melatonin administration decreases the consumption of anesthetics, as well as the reduction of nausea and vomiting in the post-operative period, which reduces hospitalization time[5-8]. However, only few articles have explored the benefits of melatonin sedation in benzodiazepine use reduction in women scheduled for surgery. In contrast, some differences in the sedative effect of melatonin have been described by type of patient, type of surgery, time before entering the operating room, duration of the procedure, and melatonin doses[9]. Therefore, the aim of this clinical trial was to determine the efficacy of pre-operative sedation with a single-dose melatonin to reduce intraoperative use of midazolam in women under total abdominal hysterectomy (TAH). The secondary objectives were to determine the sedation of melatonin and whether the administration of melatonin reduces nausea and vomiting in post-hysterectomy, surgical bleeding, and hospitalization stay.

Materials and methods

Patients

Eligible patients were women over 25 years, scheduled for TAH, with Grade I or II physical status of the American Society of Anesthesiologists (ASA). Patients with liver or kidney diseases, with known allergies to melatonin, with psychiatric illnesses, those with chronic use of psychotropic drugs, and those with absolute contraindications to the neuraxial blockade were excluded from the study.

Study design

This study was a double-blind randomized clinical trial, placebo-controlled, parallel groups, single-center, and superior design conducted in Hospital General Ticoman (HGT). The HGT Institutional Review Board (Registry 204-010-04-14) examined and approved our protocol. Patients were recruited after obtaining written informed consent. The study was conducted under the principles of the Declaration of Helsinki and Good Clinical Practice guidelines of the International Conference on Harmonization.

Each patient was randomized in a 1:1 ratio, a sequence of random numbers without repetition from a web site (http://www.alazar.info/generador-de-numeros-aleatorios-sinrepeticion) made the group allocation. Patients in the intervention group received a 5 mg melatonin prolonged-release oral capsules (Cronocaps®, Mexico), while the patients assigned to the control group received a placebo (500 mg sodium chloride capsules). To ensure blinding, both placebo and melatonin capsules were identical and were masked using envelopes identified with consecutive cardinal numbers. The administration of the intervention and the placebo was carried out 90 min before surgery between 5 am and 7 am Sedation status was determined in each patient using the observer's assessment of alertness/sedation scale (OAA/S)[10] at baseline, as well as at 30, 60, and 90 min after melatonin administration. All patients were anesthetized by a neuraxial block in the L2-L3 interspace with 0.5% hyperbaric bupivacaine at a dose of 100-200 μg/kg. The midazolam use for anesthetic management was the decision of the treating anesthesiologist.

Melatonin quantification

Two saliva samples of 1 mL were obtained at 60 and 90 min after administration of melatonin or

placebo using a disposable pipette. Samples were placed in 2 mL Eppendorf tubes and stored in a freezer at −24°C. Melatonin concentration was determined using an ELISA kit following the supplier's instructions (REF. RE54041, IBL International, Hamburg, Germany).

Statistical analysis

The sample size was calculated to detect a difference of 50% between groups using an alpha of 0.05, a statistical power of 80%, an allocation with a 1:1 ratio; at least 14 patients per group were needed. The calculation was made using the sample size calculator available at https://www.sample-size.net/sample-size-proportions/.

Descriptive statistics were used to analyze the clinical characteristics of all the patients. Quantitative variables are shown as means with standard deviation (SD), while the qualitative variables are shown as frequency and percentages. Shapiro–Wilk test was used to determine the distribution of the quantitative variables, $p > 0.05$ was considered as variables had a normal distribution. A comparison between categorical variables was done by Chi-square. Independent samples t-test was used to compare the means of quantitative variables.

Efficacy was determined by calculating relative risks (RR) with 95% confidence intervals (95%CI) for the main and secondary objectives. When the result was zero for any of the groups, a continuity correction of 0.5 was added to each cell to calculate the RR. All tests were two-sided, and a significance level (p-value) of 0.05 was used. Statistical analyses were carried out by SPSS statistical software version 25 (SPSS Inc., IBM, Chicago, USA) and with an Evidence-Based Medicine calculator available in https://ebmtools.knowledgetranslation.net/calculator/prospective/. The melatonin levels graph was performed with GraphPad Prism Software version 8.4.2 (GraphPad, California, USA).

Results

Between February 01, 2014, and May 31, 2014, 36 patients were screened for eligibility in the trial, of which 30 were enrolled and randomized. Consequently, 15 patients were assigned to the melatonin group and 15 patients were assigned to the placebo group. The CONSORT diagram is shown in figure 1. The median age was 42.5 years. In the study, 14 (46.7%) patients were ASA Grade I, while 16 (53.3) patients were ASA Grade II. The baseline characteristics were balanced between groups (Table 1). No patient presented sedation at baseline.

In the trial, no patients who received melatonin required sedation with midazolam during surgery, consequently, the administration of melatonin is effective in reducing intraoperative use of midazolam ($p = 0.01$) (Table 2). Twenty women (66.6%) presented sedation. At 30 min of administration, 13 women (86.6%) showed sedation in the melatonin group and 3 (20.0%) in the placebo group. In both, 60 and 90 min, all the patients were sedated in the melatonin group, while only five patients (33.3%) presented sedation in the placebo group. Melatonin sedative efficacy was observed 30 min after administration ($p = 0.001$) and was maintained at 60 ($p = 0.001$) and 90 min ($p = 0.001$), table 2. Salivary melatonin levels were significantly higher in patients in the intervention group compared to patients in the placebo group at 60 (33.6 ± 2.40 vs. 2.02 ± 0.78, pg/mL, $p = 0.0001$) and 90 (41.1 ± 1.59 vs. 1.50 ± 0.61, pg/mL, $p = 0.0001$) min after administration (Fig. 2). In addition, melatonin did not increase the risk of nausea and vomiting in the post-hysterectomy period ($p = 0.71$) (Table 2). Finally, no patient required blood transfusion or had a surgical wound infection.

Discussion

The results of this double-blind, placebo-controlled, and randomized clinical trial showed that a single dose of 5 mg melatonin prolonged-release capsule administered 90 min before surgery is effective in reducing midazolam use in women under TAH. In the perioperative period, the use of sedatives in surgical procedures is common, including midazolam, a short-acting benzodiazepine. In this study, the use of sedative medications for anesthetic management was the treating anesthesiologist's decision.

γ-aminobutyric acid (GABA) activity is an important feature of many intravenous anesthetic's central nervous system (CNS) depressants, including propofol, barbiturates, benzodiazepines, and etomidate[11]. Similarly, the sedative effect of melatonin involves interaction with the GABA-A receptor in the CNS[12]. Comparative studies between melatonin and midazolam to cause anxiolysis demonstrate that melatonin can reduce the pharmacological needs of other anesthetics such as propofol and fentanyl[13-15]. Interestingly, none of the patients who received melatonin in this study required midazolam during surgery. This fact can be explained because the effect

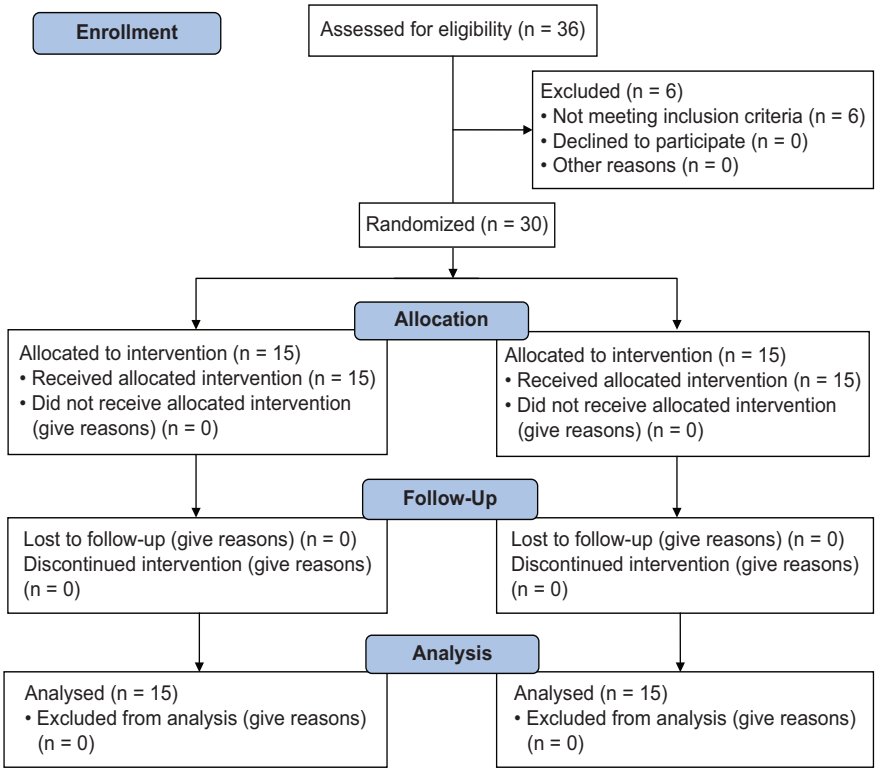

Figure 1. *CONSORT flow diagram.*

Table 1. Baseline clinical characteristics. Analysis by intention to treat 1

(n = 30)	Melatonin group (n = 15)	Placebo group (n = 15)	p*
	Median (SD)		
Age, years	40.9 (4.7)	44.07 (4.8)	0.071
	n (%)		p**
ASA grade I	7 (46.7)	7 (46.7)	1.000
ASA grade II	8 (53.3)	8 (53.3)	

*t-Student, ** χ^2.
ASA: American Society of Anesthesiologists.

of melatonin is like that observed in benzodiazepines to reduce pre-operative and post-operative anxiety in adults[16,17].

In this study, a single dose of prolonged-release 5 mg melatonin capsule administered 90 min before surgery effectively induces sedation in women scheduled for TAH. This finding is consistent with previous studies that demonstrated pre-operative melatonin sedation in patients scheduled for gynecological surgeries[7,8,18,19]. Nonetheless, this report is the first to demonstrate that pre-operative sedative efficacy of melatonin using a prolonged release formulation is not different from that observed in previous studies administering immediate-release melatonin formulations[9].

In addition, our findings support previous evidence indicating that diurnal physiological salivary levels in humans are < 10 pg/mL[20,21]. After perioperative administration, melatonin is absorbed rapidly and reaches maximum concentration at 30 min[22]. In this study, salivary melatonin concentrations rose significantly at 60 and 90 min after administration, this increase explains that all patients were sedated at 60 minutes and remained sedated at 90 min. In healthy subjects, the sedative effect of melatonin administered in a prolonged-release formulation taken during daytime showed no change in cognitive tasks within 7 h after administration compared to other anxiolytics[23]. This observation may offer an advantage of melatonin compared to other anxiolytics in patients scheduled for surgery.

A previous study suggests that anesthesia in conjunction with surgery disrupts the melatonin normal circadian rhythm by delaying the onset of nocturnal melatonin secretion[24]. Furthermore, intraoperative melatonin levels have recently been reported to decrease significantly compared to nocturnal levels[25].

Table 2 . Efficacy of melatonin (n = 30)

	Melatonin group (n = 15)	Placebo group (n = 15)	n (%) RR [95%CI]
Primary outcome			
Intraoperative use of midazolam	0 (0.0)	15 (100.0)	0.03 [0.002-0.49]
Secondary outcome			
Sedation at 30 min	13 (86.7)	3 (20.0)	4.33 [1.55-12.16]
Sedation at 60 min	15 (100.0)	5 (33.3)	2.82 [1.42-5.58]
Sedation at 90 min	15 (100.0)	5 (33.3)	2.82 [1.42-5.58]
Post-hysterectomy NV	7 (46.7)	6 (40.0)	1.67 [0.51-2.66]
	Mean (SD)		**p***
Hospital stay, days	2.73 (0.59)	3.40 (0.62)	0.006
Surgical bleeding, mL	326.7 (133.4)	396.7 (109.3)	0.753

*Independent samples t-student.
RR: relative risk; 95%CI: 95% confidence interval; mL: milliliters; NV: nausea and vomiting.

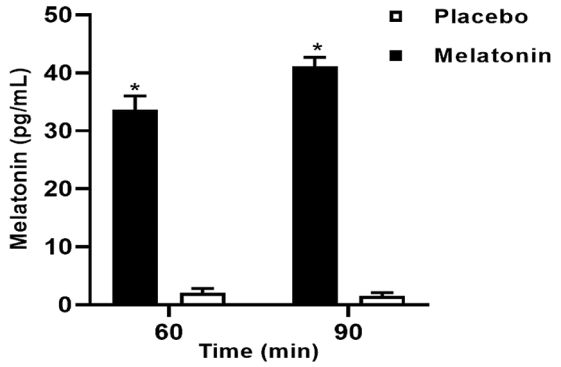

Figure 2. *Melatonin levels after melatonin or placebo administration. *Independent samples t-test, p = 0.0001.*

Disruption of melatonin levels can lead to increased anxiety in patients undergoing surgery. Our results support previous evidence suggesting that daytime administration of 5 mg melatonin increases its serum levels and this increase is associated with the sedative/anxiolytic effect[7,26-29]. Thus, our findings are consistent with those previously described that demonstrate a single dose of melatonin administered during the day reduces anxiety in the perioperative period[7,19,27,30].

Exogenous melatonin bioavailability may vary according to the route of administration[31]. Many studies use sublingual administration to avoid first-pass metabolism, and consequently to obtain greater melatonin bioavailability[7,8,13,19,27]. However, in the present study, the oral route was used to avoid interfering in the determination of the melatonin levels in saliva.

During surgery, the estimated bleeding between the groups was not different; this fact suggests that melatonin administration does not produce hemodynamic changes. This finding can be explained by the activation of melatoninergic receptors in the cardiovascular system, whose activation leads to the increased availability of nitric oxide that induces arterial muscle relaxation[32,33]. Likewise, melatonin lowers blood pressure was observed in healthy subjects[34], and in patients undergoing cataract surgery during and after the surgical procedure[15].

In patients under bariatric surgery, melatonin improved anesthetic recovery, although the days of hospitalization were not different from that observed in the placebo group[35]. In contrast, this study shows that women who received melatonin required lower hospitalization time compared to those who received placebo.

Melatonin administration has been associated with headache, dizziness, or excessive drowsiness in the post-operative period[15,18,19,30]. However, in this study, no difference in postsurgical nausea and vomiting was observed between the groups. Although the visual analog scale (VAS) is commonly used in most studies evaluating the anxiolytic effect of melatonin[36], there is a correlation between the VAS and the OAA/S used in this study[10].

This study has some limitations. First, we did not evaluate VAS like other studies. Second, no sedation measurement or melatonin quantification were performed in the post-operative period.

Conclusion

In the present study, a single dose of 5 mg melatonin prolonged-release is effective for reduces

intraoperative midazolam consumption and hospital stay in women undergoing TAH.

Funding

This work was supported by FM/DI/083/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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