Melatonin as premedication for laparoscopic cholecystectomy: *a double-blind, placebo-controlled study*

[a] Ionescu D, [b] Bãdescu C, [b] Ilie A, [c] Miclutia I, [d] Iancu C, [e] Ion D, [a] Vasian H, [a] Acalovschi I, [f] Mocan T, [g] Bondor C

[a] Anaesthesia and Intensive Care Department, University of Medicine and Pharmacy *Iuliu Hatieganu*, Cluj-Napoca, Romania
[b] Anaesthesia and Intensive Care Department, Clinica ATI, Spitalul Clinic de Adulct, Cluj-Napoca, Romania
[c] Psychiatry Department, University of Medicine and Pharmacy *Iuliu Hatieganu*, Cluj-Napoca, Romania
[d] Department of Surgery,University of Medicine and Pharmacy *Iuliu Hatieganu*,Cluj-Napoca,Romania
[e] Department of Physiology,University of Medicine and Pharmacy Carol Davila, Bucharest, Romania
[f] Department of Physiology, University of Medicine and Pharmacy *Iuliu Hatieganu*,Cluj-Napoca,Romania
[g] Department of Medical Statistics, University of Medicine and Pharmacy *Iuliu Hatieganu*, Cluj-Napoca, Romania

Correspondence to: Daniela Ionescu, e-mail: dionescuati@yahoo.com

SAJAA 2008; 14(4): 08-11

ABSTRACT

Background: There are only a few studies involving the use of melatonin for premedication for anaesthesia. The goal of our study was to compare the effects of melatonin and midazolam administered as premedication for laparoscopic cholecystectomy.

Methods: This double-blind, placebo-controlled study included 53 patients (ASA I, II) undergoing laparoscopic cholecystectomy under general anaesthesia. The patients were divided into three groups: group 1 (n = 18) included patients receiving 3 mg melatonin the night before and as premedication; group 2 (n = 17) included the patients receiving 3,75 mg midazolam (1/2 of a 7,5 mg tablet) by the same protocol as for melatonin; and group 3 (n = 18) included patients receiving placebo tablets. Preoperatively, the anxiety and sedation scores, as well as the quality of preanaesthetic sleep, were evaluated. Postoperatively, the anxiety and sedation scores and the number of remembered pictures were evaluated at 15 and 60 minutes and 6, 12 and 24 hours respectively. The intra-anaesthetic opioid requirements were also evaluated.

Results: Preoperatively the lowest anxiety score was registered in the midazolam group; also the difference between the melatonin and midazolam groups was not significant. In the placebo group the anxiety score was significantly higher as compared with melatonin or midazolam. Postoperatively anxiety scores were lowest in the melatonin group at every time interval. The scores for the remembered pictures were consistently better in the melatonin group. The sedation score was lower in the melatonin group as compared with midazolam, as were the intra-anaesthetic opioid requirements.

Conclusions: Melatonin (3 mg) can be successfully used as premedication for laparoscopic cholecystectomy, especially for day case surgery. Advantages over midazolam and placebo include better perioperative anxiolysis, and a better recovery profile as assessed by sedation and memory.

Introduction

Melatonin (5-methoxy-N-acetyltryptamine) is a hormone found in all living creatures, from algae to humans. In humans, melatonin is produced mainly by the pineal gland and, to a lesser extent, by the gastrointestinal tract and retina. These sites synthesise melatonin from the amino acid tryptophan, via the 5-hydroxyindole-O-methyl transferase enzyme pathway.[1,2] The pathway is under the influence of the hypothalamus. Melatonin produced in the pineal gland acts as an endocrine hormone, since it is released into the blood, whereas melatonin produced by the retina and the gastrointestinal tract acts as a paracrine hormone. The biological effects of melatonin are produced through the activation of the melatonin receptors, MT_1 and MT_2,[2,3] and are due to its role as a powerful antioxidant[3,4,5] that especially protects nuclear and mitochondrial DNA.[6] The MT_1 receptors are located in the pituitary gland and retina and act as G protein-coupled receptors. Clinical applications of melatonin include its use for insomnia, jet lag and other types of misalignments in the circadian rhythm, and it shows some benefits in Alzheimer's disease.[7,8]

It was only recently that Naguib et al and others have demonstrated that melatonin can be used effectively as premedication for anaesthesia and for the induction of general anaesthesia.[9,10,11,12] Lewis et al have used melatonin for the sedation of mechanically ventilated patients in intensive care.[13] The purpose of our study was to compare the effects of melatonin and midazolam used as premedication on sedation and anxiety scores, the quality of preoperative sleep, and amnesia after recovery from anaesthesia for laparoscopic cholecystectomy.

Methods

After obtaining institutional approval and informed consent, 53 patients (ASA I, II) aged 25 to 73 years, who were about to undergo laparoscopic cholecystectomy, were included in the study. Exclusions were known allergy to any of the study drugs or known abuse of centrally acting drugs and/or monoamine oxidase inhibitors. The day before surgery, the patients were given information by one of the members of the research team concerning the study and the questionnaires used for the assessment. The evening before the operation, the patients were

randomly allocated into three study groups: group 1 (n = 18) received 3 mg melatonin (Calivita International, Farmington, Connecticut, USA), group 2 (n = 17) received 3,75 mg midazolam (1/2 of a 7,5 mg tablet) (Dormicum®, Terapia, Romania) and group 3 (n = 18) received placebo tablets.

In a previous published study,[9] it was found that premedication with either 5 mg melatonin or 15 mg midazolam resulted in significant decreases in anxiety levels and increases in levels of sedation preoperatively. We therefore used 3 mg melatonin, because these tablets were the only ones available in Romania at the time of the study and to assess the effects of a lower dose. A dose of 3,75 mg midazolam (1/2 of a 7,5 mg tablet), was considered equivalent. Moreover, several studies reported sedation in both groups when using 5 mg melatonin and 15 mg midazolam and smaller doses were thus considered more appropriate.[9,10,11] The trial drugs and placebo were prepared in a volume of 3 ml. To maintain the double-blind nature of the study, the syringes were unmarked. The content of the syringe was given sublingually the night before surgery and 90 minutes before operation, in the surgical ward. The patient was asked to place the tip of the tongue behind the upper teeth, the content of the syringe was placed under the tongue, after which the patient was asked to close the mouth and not to swallow for approximately three minutes. The solution was not flavoured. Anxiety was evaluated by using CD Spielberger's questionnaire, STAI-S, which is designed to assess the actual state of anxiety. This questionnaire is validated and standardised for the Romanian population. On the advice of a qualified psychiatrist, six items were chosen from this questionnaire, related to perioperative anxiety (Table I), to produce a total score (range 6 to 24) in each patient.[14,15] Higher values represent greater anxiety.

A registrar blinded to the group assignment performed all the tests. Anxiety scores, the quality of preoperative sleep (as related by the patients: good sleep, insomnia, nightmares) and sedation scores (1 = awake, 2 = drowsy, 3 = asleep, arousable, 4 = asleep, not arousable) were evaluated before the operation at patient arrival in the operating theatre and at 15 and 60 minutes and 6 and 24 hours postoperatively. In addition, in order to evaluate preoperative amnesia, the patients were asked to recall as many as possible of five pictures shown to them before premedication (the pictures were of a ball, a pumpkin, a cow, a plane, and a tree). The number of remembered pictures was recorded as a score and the mean score was calculated at every time interval. In the operating room, a peripheral IV infusion of Ringer's solution was started. Anaesthesia was induced with fentanyl 3–4 $\mu g.kg^{-1}$ and thiopental 2–3 $mg.kg^{-1}$ and muscle relaxation maintained with atracurium 0.5–0.6 $mg.kg^{-1}$. After tracheal intubation, anaesthesia was maintained with isoflurane (end-tidal levels 1–1.5 MAC) in 50/50 % O_2/air, supplemented with fentanyl 100 µg (when blood pressure and heart rate were increased to 20% above the patient's pre-induction values). End-tidal concentrations of oxygen, isoflurane and CO_2 were determined continuously by a Vamos-Dräger multiple gas analyser (Dräger Medizintechnik, Lubeck, Germany) and ventilation was adjusted to maintain normocapnia (end-tidal CO_2 partial pressure 35-40 mmHg). SaO2, ECG were recorded continuously and blood pressure every 3 min (Spacelabs, CC Med AG, St Gallen, Switzerland). Surgery and anaesthesia times, as well as intraoperative fentanyl consumption, were also recorded.

Recovery time, defined by the time interval between discontinuation of the isoflurane and extubation, was recorded in all the groups. The severity of postoperative pain was also recorded as a VAS score (1 = no pain, 5 = maximum pain) on a visual analogue scale-verbal rating. Postoperative pain was treated with a NSAID and paracetamol when the VAS score was less than three and with incremental IV doses of meperidine for a score of greater than or equal to three.

Statistical analysis was performed by SPSS for Windows (Chicago, Illinois, version 13). Sample size was calculated taking in consideration the anxiety score in melatonin versus placebo at 60 min postoperatively on a pilot study with a power of 85%. Nominal data were reported as incidences and analysed using the chi-square test or the Fisherís exact test. Continuous and discrete data were reported as means (± standard deviation) and analysed using the two-sided t-test for an independent sample. Kruskall-Wallis test was used to compare data in study groups. Changes were considered significant at a value of $p < 0.05$

Results

There were no between-group differences with respect to age, weight, duration of surgery and anaesthesia (see Table II). Preoperatively, there were no significant differences in sedation scores between the melatonin and midazolam groups and the placebo group (Table III). There was no significant difference between preoperative anxiety scores in the melatonin and midazolam groups; also this score was higher in the melatonin group. Intra-operatively there were no significant differences in fentanyl requirements between the melatonin and midazolam groups while there were significant differences when compared with the placebo group. The recovery time was shortest in the melatonin group in comparison to the placebo and midazolam groups, but the differences were not significant (see Table II). Postoperatively, the anxiety scores in the melatonin group at every time interval were significantly lower than those in the placebo group. Compared with midazolam, anxiety scores were also lower in the melatonin group (Table III).

Table I: Anxiety score. Selected items from Spielberger's questionnaire[14,15]

	At all	A little	Enough	Very much
1. I feel calm	4	3	2	1
2. I am worried about possible problems (complications)	1	2	3	4
3. I felt rested	4	3	2	1
4. I am scared	1	2	3	4
5. I feel tense	1	2	3	4
6. I am in a good mood	4	3	2	1

Maximum score 24 points = maximal anxiety, minimum score 6 points = minimal anxiety.

As can be seen in Table III there are no statistical differences in the sedation scores between study groups at preoperative evaluation.

Postoperatively, sedation scores were significantly lower in the melatonin group compared to the midazolam group at 15 and 60 minutes ($p < 0.05$). The number of remembered pictures was higher in the melatonin group than in the midazolam group at every time interval; the greatest differences were recorded at 15 min after the operation and at 24 h (Table IV). No side effects of melatonin were noted.

Table II: Demographic data of the study groups

	Melatonin (n = 18)	Midazolam (n = 17)	Placebo (n = 18)
1. Age (years) †	43.05 (±11.40)	48.76 (±12.61)	48.38 (±10.11)
2. Weight (kg) †	76.12 (±15.36)	72.05 (±11.80)	75.44 (±12.90)
3. ASA I/II	12/6	9/8	7/10
4. Gender	13-5	16/2	15/3
5. Intraoperative fentanyl (µg)	410	420	530*
6. Recovery time (min) †	10.83 (±5.36)	13.18 (±4.73)	12.06 (±5.58)

*p<0.05
†Data are expressed as mean ± standard deviation

Table III: Pre- and postoperative anxiety and sedation scores in the study groups

Number of patients (%)	Melatonin (n = 18)	Midazolam (n = 17)	Placebo (n =18)	P Mel/Mida	P1/3 Mel/Pla	p
Anxiety score						
Preoperatively	11.6 (3.2)	10.5 (2)	13.5 (3.4)	0.27	0.09	0.019*
15 min after surgery	8.9 (2.2)	9.7(2.82)	11.7 (1.9)	0.35	0.0004	0.002*
60 min after surgery	8 (2.1)	10.4 (3.2)	11 (2.1)	0.01	0.0002	0.000*
6 h after surgery	7.9 (1.9)	9.3 (3.8)	11.6 (3.6)	0.18	0.001	0.003*
24 h after surgery	7.2 (1.7)	9.3 (2.7)	11.0 (3.4)	0.003	0.0008	0.001*
Sedation score						
Preoperatively	1 (0.0)	1.2 (0.5)	1.0 (0.2)	0.07	0.32	0.364
15 min after surgery	1.6 (0.6)	2.2 (0.6)	2.0 (0.8)	0.004	0.07	0.023*
60 min after surgery	1.1 (0.3)	1.6 (0.7)	1.1 (0.3)	0.02	1.00	0.018*
6 h after surgery	1.0 (0.2)	1.1 (0.3)	1.2 (0.5)	0.27	0.28	0.496
24 h after surgery	1 (0.0)	1 (0.0)	1.0(0.2)	1.00	0.32	0.378

* $p < 0.05$ data are expressed as mean ± standard deviation

Table IV: Scores for remembered pictures in study groups

The score for the remembered pictures	Melatonin (n = 18)	Midazolam (n = 17)	Placebo (n = 18)	P Mel/Mida	P Mel/Pla	p
15 min after surgery	4.0 (1.0)	3.1 (1.0)	3.5 (1.1)	0.0072	0.018	0.027*
60 min after surgery	4.3 (0.8)	3.6 (1.2)	4.0 (1.1)	0.048	0.053	0.132
6 h after surgery	4.5 (0.6)	3.6 (1.3)	4.1 (1.0)	0.048	0.058	0.133
24 h after surgery	4.8 (0.5)	3.7 (1.2)	4.2 (0.9)	0.012	0.037	0.036*

*P < 0.05, data are expressed as mean ± standard deviation

Discussion

There are relatively few studies on the use of melatonin as for both premedication and induction of anaesthesia. In this study we investigated the sedative, anxiolytic and amnesic effects of 3 mg melatonin compared with 3.75 mg midazolam when given as premedication for laparoscopic cholecystectomy. These are the smallest doses hitherto reported for both melatonin and midazolam when used as premedication. Other previous studies

reported the similar effects when larger doses were employed (5 mg melatonin and 15 mg midazolam).[9,10,11,12]

At the doses employed in the current study, there were no significant differences between groups in preoperative anxiety scores in the melatonin and midazolam groups; also the anxiety score was lower in the midazolam group. In comparison with our results, Acil et al and Naguib et al reported significantly reduced preoperative anxiety scores and significant preoperative sedation in both the midazolam and melatonin groups, possibly due to higher melatonin and midazolam doses.[10.11] Another possible explanation for our results is the time interval for administration of the melatonin premedication (90 min). Most other studies accepted 2 h as an optimal time interval for a complete effect of melatonin in the preoperative period.

During anaesthesia, the fentanyl requirements in the midazolam and melatonin groups were similar and significantly lower than in the placebo group. However, the lowest requirements were in the melatonin group. There were also no significant between group differences in recovery time; also the recovery time in the melatonin group was shorter when compared with the other groups. These results are consistent with those of other studies where melatonin administration was followed by a rapid recovery with good psychomotor function. Recently there were reports on the analgesic effects of melatonin, not produced by binding of opioid receptors, but by releasing endorphins.[16]

Postoperatively, the anxiety score in the melatonin group was significantly lower than in the midazolam and placebo groups at every time interval. Our results are consistent with those published by Acil et al .who have shown significantly lower postoperative anxiety levels in the melatonin group.[11] The sedation scores in our study were significantly lower in the melatonin group than in the midazolam group at 15 and 60 minutes, and lower, but not significant, at the other time intervals. Acil et al found no significant difference in sedation scores between the groups postoperatively.[10] Amnesia scores, assessed as the number of remembered pictures, were significantly better (the score of the remembered pictures was greater) in the melatonin group in comparison to the midazolam group at every evaluation time, whereas there were no significant differences between the melatonin and placebo groups. These results are consistent with those published by Naguib et al[9] and Acil et al[10] who found that melatonin has no amnesic effects. Although this effect is desirable in some situations to render patients amnesic to certain perioperative experiences, amnesia is considered undesirable in some categories of patients; such are day-case patients, where instructions for the postoperative period, or at discharge, must be remembered.

The limitations of our study include the small size of the study groups and the fact that we did not assess the psychomotor quality of the recovery in the study groups.

We may conclude that 3 mg melatonin may be an adequate dose for premedication for laparoscopic cholecystectomy. At this dose, melatonin produces anxiolysis with minimal sedation, and a hastened recovery with no amnesic effects. This premedication may be a good choice for ambulatory surgery patients and in those situations where the impairment of cognitive functions and amnesia would be detrimental to the patients. **SAJAA**

References:

1. Boutin JA, Audipot U, Ferry G, Delagrange P. Molecular tools to study melatonin pathways and actions. Trends Pharmacol Sci 2005;26:412ñ9.
2. Hattori A, Mighitaka H, Iigo M, et al. Identification of melatonin in plants and its effects on plasma melatonin levels and binding to melatonin receptors in vertebrates. Biochem Mol Biol Int 1995; 35:627ñ34.
3. Larson J, Jessen RE, Uz T, et al. Impaired hippocampal long-term potentiaton in melatonin MT2 receptors-deficient mice. Neurosci Lett 2006;393:23ñ6.
4. Uz T, Arslan AD, Kurtuncu M, et al. The regional and cellular expression profile of the melatonin receptor MT1 in the central dopaminergic system. Brain Res Mol Brain Res 2005; 136:45ñ53.
5. Lissoni P, Barni S, Crispino S, Tancini G, Frascini F. Endocrine and immune effects of melatonin therapy in metastatic cancer patients. Eur J Cancer Clin Oncol 1989; 25:784ñ95.
6. Lee YA, Hyun KJ, Tokura H. The effects of skin pressure by clothing on circadian rhythms of core temperature and salivary melatonin. Choronobiol Int 2000; 17:783ñ93.
7. Pierpaoli W, Maestroni GJ. Melatonin: a principal neuro-immunoregulatory and anti-stress hormone: its anti-aging effects. J Immunol Lett 1987; 16: 355ñ61.
8. Wurtman RJ, Zhidanova I. Improvement of sleep quality by melatonin. Lancet 1995; 346:1491.
9. Naguib M, Samarkandi AH. Premedication with melatonin: a double blind, placebo-controlled comparison with midazolam. Br J Anaesth 1999; 82:875ñ80.
10. Acil M, Basgul E, Celiker V, Karagoz AH, Demir B, Aypar U. Perioperative effects of melatonin and midazolam premedication on sedation, orientation, anxiety scores and psychomotor performance. Eur J Anaesthesiol 2004; 21:553ñ7.
11. Naguib M, Samarkandi AH. The comparative dose-response effects of melatonin and midazolam for premedication in adult patients: a double-blinded, placebo-controlled study. Anesth Analg 2000; 91:473ñ9.
12. Naguib M, Hammond DL, Schmidt PG, et al. Pharmacological effects of intravenous melatonin: comparative studies with thiopental and propofol. Br J Anaesth 2003; 90:504ñ7.
13. Lewis KS, McCarthy RJ, Rothenberg DM. Does melatonin decrease sedative use and time to extubation in patients requiring prolonged mechanical ventilation? Anesth Analg 1999; 88:S1ñ423.
14. Spielberger CD, Gorsuch RL, Lushene RD. Manual for the state-trait anxiety inventory. Palo Alto CA: Consulting Psychologist Press; 1970.
15. Spilberger CD, Sarason IG. Stress and anxiety. Washington DC: Hemisphere; 1978.
16. Shavali S, Ho B, Govitrapong P, Sawlom S, Ajjimaporn A, Klongpanichapak, S, Ebadi M. Melatonin exerts its analgesic actions not by binding to opioid receptor subtypes but by increasing the release of β–endorphin an endogenous opioid. Brain Res Bull 2005, 64(6):471-479.