The Comparative Dose-Response Effects of Melatonin and Midazolam for Premedication of Adult Patients: A Double-Blinded, Placebo-Controlled Study

Mohamed Naguib, MB, BCh, MSc, FFARCSI, MD*,
and Abdulhamid H. Samarkandi, MB, BS, KSUF, FFARCSI†

Departments of Anesthesia, *University of Iowa College of Medicine, Iowa City, Iowa, and †King Saud University, Riyadh, Saudi Arabia

We designed this prospective, randomized, double-blinded, placebo-controlled study to compare the perioperative effects of different doses of melatonin and midazolam. Doses of 0.05, 0.1, or 0.2 mg/kg sublingual midazolam or melatonin or placebo were given to 84 women, approximately 100 min before a standard anesthetic. Sedation, anxiety, and orientation were quantified before, 10, 30, 60, and 90 min after premedication, and 15, 30, 60, and 90 min after admission to the recovery room. Psychomotor performance of the patient was evaluated at these times also, by using the digit-symbol substitution test and Trieger dot test. Patients who received premedication with either midazolam or melatonin had a significant decrease in anxiety levels and increase in levels of sedation preoperatively compared with control subjects. Patients in the three midazolam groups experienced significant psychomotor impairment in the preoperative period compared with melatonin or placebo. After operation, patients who received 0.2 mg/kg midazolam premedication had increased levels of sedation at 90 min compared with 0.05 and 0.1 mg/kg melatonin groups. In addition, patients in the three midazolam groups had impairment of performance on the digit-symbol substitution test at all times compared with the 0.05 mg/kg melatonin group. Premedication with 0.05 mg/kg melatonin was associated with preoperative anxiolysis and sedation without impairment of cognitive and psychomotor skills or affecting the quality of recovery.

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We designed this prospective, randomized, double-blinded, placebo-controlled study to compare the effects of different doses of melatonin and midazolam for premedication of adult patients. *N*-Acetyl-5-methoxytryptamine (melatonin) is synthesized mainly by the pineal gland and, to a lesser extent, by extrapineal tissues, such as the retina, Harderian gland, and gastrointestinal tract. Exogenous administration of melatonin facilitates sleep onset and improves quality of sleep (1,2). Recently, we evaluated the perioperative effects of 5 mg of sublingual melatonin, 15 mg of midazolam or placebo (3). We noted that 5 mg of sublingual melatonin can be used effectively for premedication of adult patients (3).

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Address correspondence and reprint requests to Mohamed Naguib, MD, University of Iowa College of Medicine, Department of Anesthesia, 200 Hawkins Dr., 6JCP, Iowa City, Iowa 52242-1009. Address e-mail to mohamed-naguib@uiowa.edu.

Methods

After obtaining institutional approval and informed consent, we studied 84 ASA physical status I women, ages 17–43 yr (mean 27.9 ± 6.2 SD) and weighing 41.4–89 kg (mean 68.2 ± 12.8 SD), undergoing gynecological laparoscopic procedures. No patient was pregnant or lactating, abusing centrally acting drugs, consuming monoamine oxidase inhibitors, or allergic to the drugs under study. The day before surgery, a psychologist explained to the patient the study plan and the different scales used in the assessment.

Approximately 2 h before surgery, patients were transported to an isolated quiet room in the operating suite. A pulse oximeter probe was placed on all patients, and Spo_2, arterial blood pressure, and heart rate were recorded continuously. Resuscitative equipment was available at the bedside. Patients were randomly allocated to one of seven groups (n = 12 in each) to receive either 0.05, 0.1, 0.2 mg/kg sublingual midazolam, 0.05, 0.1, 0.2 mg/kg sublingual melatonin, or sublingual saline (placebo). We used midazolam ampule solution (0.5%) originally intended for IV use

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(Dormicum®) and colloidal melatonin (Innovative Natural Products, Escondido, CA). Study drugs and placebo were prepared to a fixed volume of 3 mL (in a syringe from which the needle had been removed) and marked only with a coded label to maintain the double-blinded nature of the study. The contents of the syringe was given sublingually approximately 100 min before the induction of general anesthesia by a resident not involved in the management of the patient or in data collection. The patient was first asked to place the tip of the tongue to the back of the upper teeth. The drug was then, placed under the tongue, the patient was asked to close her mouth, and was instructed, "Don't swallow!"; at 180 s, the patient was permitted to swallow the medication. We did not add any flavor to midazolam, because it has been reported that the addition of candy flavor did not improve acceptance of or compliance with sublingual midazolam administration (4).

A visual analog scale (VAS) was used for the patients to evaluate their anxiety. The scale is a 50-cm long and 10-cm high card, diagonally divided to a white and a bright red triangle. The centimeter scale was on the rear side of the card (5,6). The extremes were marked "no anxiety" at the white end; and "anxiety as bad as ever can be" at the red end. The same psychologist blinded to group assignment performed all test scoring and calculations in the perioperative period. The psychologist evaluated anxiety VAS, orientation score (0 = none; 1 = orientation in either time or place; 2 = orientation in both), and sedation score (1 = awake; 2 = drowsy; 3 = asleep, but arousable; 4 = asleep, but not arousable) before, and 10, 30, 60, and 90 min after the administration of premedication and after operation at 15, 30, 60, and 90 min after admission to the recovery room. In addition, patients were asked to perform the digit-symbol substitution test (DSST) (7,8) and Trieger dot test (TDT) (9) at these times. The DSST forms part of the performance scale of the Wechsler adult intelligence test. These tests were used to quantitatively assess the cognitive and psychomotor activity.

All patients were positioned with 30° head elevation and used the same writing implement (ballpoint pen, medium point, black) for all tests. The DSST score represented the number of correct symbol substitutions made in 60 s and the score was normalized according to a table (the normalized DSST or NDSST score). The TDT score represented the total number of missed dots (of 42) that were connected. TDT deviation represented the cumulative shortest distance (in millimeters) between the drawn line and missed dots. The time to perform the TDT was measured in seconds by using a stopwatch. To account for interpatient differences in test-taking ability, the anxiety VAS, NDSST, and TDT scores; TDT deviations; and time-to-perform TDT test were normalized to baseline scores, deviation, and time for each patient. Changes in scores of different tests and TDT deviation and TDT time relative to baseline values were compared.

Amnesia was assessed by showing patients two simple line diagrams before premedication. Patients were queried 24 h later as to recall of the diagrams, the entry into the operating room, and IV catheter insertion in the operating room.

In the operating room, an IV infusion of lactated Ringer's solution was started. Anesthesia was induced with 1 μg/kg fentanyl, 2 mg/kg propofol, and 0.2 mg/kg mivacurium. After tracheal intubation, anesthesia was maintained with isoflurane and 70% nitrous oxide in oxygen, supplemented with fentanyl. End-tidal concentrations of oxygen, nitrous oxide, isoflurane, and carbon dioxide were determined continuously by a multiple-gas analyzer (Capnomac; Datex Instrumentarium, Helsinki, Finland). Ventilation was adjusted to maintain normocapnia (end-tidal CO_2 partial pressure 35–40 mm Hg). Hemoglobin oxygen saturation was monitored by pulse oximetry. Temperature was monitored by a nasopharyngeal thermistor and was maintained at 36.5 ± 0.5°C. Neuromuscular function was monitored by a peripheral nerve stimulator. Surgery time (incision to surgery end), and anesthesia time (the induction to emergence) were recorded. In the recovery room, postoperative pain was quantitated by using a 100-mm VAS, and was assessed at 15, 30, 60, and 90 min after arrival to the recovery room. Postoperative pain was treated with incremental doses of IV morphine sulfate and the total dose administered was noted. Postoperative nausea and vomiting were treated with 4 mg IV ondansetron. On the second day, the patients were questioned by the same psychologist about their premedication: "Was the premedication satisfactory or not" and "If needed, would they prefer the same or another premedication in the future".

With a sample size in each of the seven groups of 12, a 0.05 level χ^2 test has 86% power to detect a difference in proportions characterized by a variance of proportions ($V = S(p_i - p_0)^2/G$) of 0.045 and an average proportion of 0.607. Based on the findings of our previous study (3), we assumed that placebo would have an effect in 20% of patients, whereas different doses of midazolam and melatonin would have an effect in at least 50% of patients.

We used Dunnett's test to compare the control group to each of the other groups. Comparisons among the groups who received midazolam or melatonin were performed by using the Duncan multiple range test, χ^2 test, Fisher's exact test, and the Kruskal-Wallis test for multiple comparisons. For multiple comparisons in the later test, the null hypothesis was

Table 1. Patient Data

	Midazolam (mg/kg)			Melatonin (mg/kg)			
	0.05	0.1	0.2	0.05	0.1	0.2	Placebo
No.	12	12	12	12	12	12	12
Age (yr)	23.4 (3.9)	26.2 (6.6)	28.9 (6)	30.3 (5.6)	28.4 (6.1)	28.2 (6.1)	29.8 (6.1)
Weight (kg)	67.4 (16.2)	65.2 (13)	68.6 (10.8)	62.3 (15.4)	69.4 (10)	72.3 (12)	71.9 (11)
Height (cm)	156.3 (6.3)	155.3 (6.5)	156.5 (3.6)	156.3 (5.8)	155.5 (3.7)	151.7 (10)	156.4 (6)
Surgery time (min)	72 (33.7)	87.8 (33.7)	61.8 (35.5)	53.8 (31.4)	70.4 (36.8)	60.2 (37.2)	64.8 (26.5)
Anesthesia time (min)	87.8 (31.8)	102 (35.5)	77.9 (37)	70.3 (30.1)	92.1 (42.3)	76.3 (38.1)	82.8 (26.5)
Intraoperative fentanyl (μg)	102 (17)	100 (30)	110 (41)	104 (33)	129 (50)	108 (29)	108 (36)
Number of patients requiring one or more injections of morphine in recovery room	6	7	5	6	5	4	4
Cumulative morphine consumption (mg)	39	48	42.5	41	40	47	36

Mean (SD). No significant differences.

rejected if ZSTAT was larger than the critical value ZC, where

$$1 - \mathrm{PHI}(\mathrm{ZC}) - \mathrm{ALPHA}/(\mathrm{K}[\mathrm{K} - 1]),$$

PHI is the cumulative standard normal distribution function, ALPHA is the desired overall significance level, and K is the number of groups compared.

Number needed to treat (NNT) was calculated for effect data (10–12). The NNT is the number of patients who needed to be treated with melatonin (or midazolam) rather than the placebo for one additional patient benefit. Statistical analyses were performed by using the BMDP statistical package (7.01; University of California Press, Berkeley, CA, 1994) and StatXaxt for Windows (4.0.1; CYTEL Software, Cambridge, MA, 1999) on a Dell computer (Pentium III processor) operated by Microsoft Windows 98 (Roselle, IL). Unless otherwise specified, results were expressed as means ± SD, and were considered significant when $P < 0.05$.

Results

Patients in the seven groups were comparable in age, weight, height, surgery time, and anesthesia time (Table 1). Figure 1 shows a significantly ($P < 0.05$) greater effect of both midazolam and melatonin compared with the placebo for preoperative anxiety VAS. However, there were no differences in anxiety VAS between the groups after surgery. Patients receiving midazolam and melatonin had increased levels of sedation at 60 and 90 min ($P < 0.02$) after premedication compared with the placebo group (Table 2). Furthermore, patients in the 0.2 mg/kg midazolam group had ($P < 0.05$) higher levels of sedation compared with the control group at 30 min after premedication (Kruskal-Wallis test). At 90 min, sedation was in

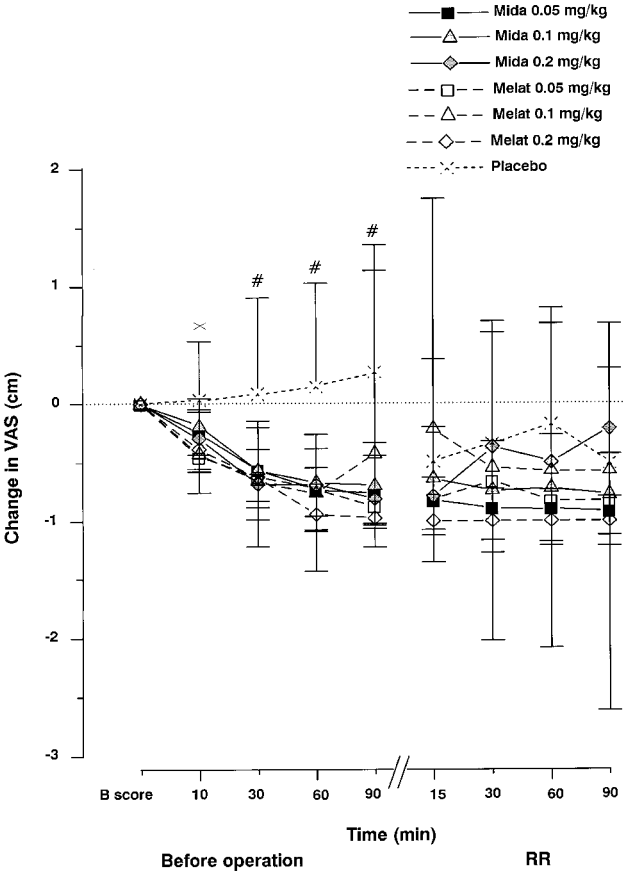

Figure 1. Change in anxiety visual analog score (VAS) (mean ± SD) relative to baseline (B). See text for explanation of the anxiety VAS. *$P < 0.05$ placebo versus all melatonin groups. #$P < 0.05$ placebo versus all groups. Mida = midazolam, Melat = melatonin, RR = recovery room.

33.3%, 33.3%, and 66.7% of patients who had received 0.05, 0.1, and 0.2 mg/kg sublingual midazolam and in 41.7%, 33.3%, and 66.7% of patients who had received 0.05, 0.1, and 0.2 mg/kg melatonin, respectively. The (NNT) were, respectively, 3 (95% CI = 1.7–15.1), 3

Table 2. Pre- and Postoperative Sedation in the Seven Groups

	Midazolam (mg/kg)			Melatonin (mg/kg)				
	0.05	0.1	0.2	0.05	0.1	0.2	Placebo	*P*
30 min after premedication								0.068
Awake	11 (91.7)	7 (58.3)	4 (33.3)	9 (75)	10 (83.3)	7 (58.3)	11 (91.7)	
Drowsy	1 (8.3)	1 (8.3)	2 (16.7)	0	0	1 (8.3)	0	
Asleep, but arousable	0	4 (33.3)	4 (33.3)	3 (25)	2 (16.7)	4 (33.3)	1 (8.3)	
Asleep, but not arousable	0	0	2 (16.7)	0	0	0	0	
60 min after premedication								0.013
Awake	6 (50)	7 (58.3)	1 (8.3)	7 (58.3)	8 (66.7)	5 (41.7)	12 (100)	
Drowsy	3 (25)	1 (8.3)	3 (25)	1 (8.3)	0	0	0	
Asleep, but arousable	3 (25)	4 (33.3)	7 (58.3)	4 (33.3)	4 (33.3)	7 (58.3)	0	
Asleep, but not arousable	0	0	1 (8.3)	0	0	0	0	
90 min after premedication								0.009
Awake	8 (66.7)	8 (66.7)	4 (33.3)	7 (58.3)	8 (66.7)	4 (33.3)	12 (100)	
Drowsy	0	2 (16.7)	0	0	0	0	0	
Asleep, but arousable	4 (33.3)	2 (16.7)	7 (58.3)	5 (41.7)	4 (33.3)	8 (66.7)	0	
Asleep, but not arousable	0	0	1 (8.3)	0	0	0	0	
15 min after surgery								0.055
Awake	5 (41.7)	5 (41.7)	5 (41.7)	6 (50)	5 (41.7)	5 (41.7)	8 (66.7)	
Drowsy	0	3 (25)	3 (25)	2 (16.7)	7 (58.3)	1 (8.3)	2 (16.7)	
Asleep, but arousable	7 (58.3)	4 (33.3)	3 (25)	4 (33.3)	0	6 (50)	1 (8.3)	
Asleep, but not arousable	0	0	1 (8.3)	0	0	0	1 (8.3)	
30 min after surgery								0.4
Awake	6 (50)	6 (50)	5 (41.7)	6 (50)	7 (58.3)	7 (58.3)	10 (83.3)	
Drowsy	5 (41.7)	4 (33.3)	2 (16.7)	3 (25)	1 (8.3)	3 (25)	1 (8.3)	
Asleep, but arousable	1 (8.3)	2 (16.7)	5 (41.7)	3 (25)	4 (33.3)	2 (16.7)	1 (8.3)	
Asleep, but not arousable	0	0	0	0	0	0	0	
60 min after surgery								0.17
Awake	8 (66.7)	6 (50)	6 (50)	11 (91.7)	8 (66.7)	9 (75)	10 (83.3)	
Drowsy	3 (25)	4 (33.3)	3 (25)	1 (8.3)	0	2 (16.7)	2 (16.7)	
Asleep, but arousable	1 (8.3)	2 (16.7)	3 (25)	0	4 (33.3)	1 (8.3)	0	
Asleep, but not arousable	0	0	0	0	0	0	0	
90 min after surgery								<0.007
Awake	12 (100)	7 (58.3)	7 (58.3)	12 (100)	12 (100)	10 (83.3)	10 (83.3)	
Drowsy	0	5 (41.7)	3 (25)	0	0	2 (16.7)	2 (16.7)	
Asleep, but arousable	0	0	2 (16.7)	0	0	0	0	
Asleep, but not arousable	0	0	0	0	0	0	0	

Values are *n* (%).

(1.7–15.1), 1.5 (1.1–2.5), 2.4 (1.4–7.2), 3 (1.7–15.1), and 1.5 (1.1–2.5). Postoperatively, there was no difference in the level of sedation between the groups except at 90 min in which patients in the 0.2 mg/kg midazolam group showed an increased level of sedation compared with 0.05 and 0.1 mg/kg in the melatonin groups (Table 2).

The mean dose of fentanyl administered in the intraoperative period was similar between the groups (Table 1). Neither postoperative pain scores nor morphine consumption were different between the groups at any time during their stay in the recovery room (Table 1).

Orientation scores were similar, except at 15 min after operation. At that time, the number of patients that were not orientated in both time and place in 0.05, 0.1, and 0.2 mg/kg midazolam and melatonin groups were 5 (41.7%), 4 (33.3%), 5 (41.7%), 2 (16.7%), 2 (16.7%), and 6 (50%), respectively, compared with 1 (8.3%) patient in the placebo group ($P < 0.05$).

In the control and 0.05, 0.1, and 0.2 mg/kg midazolam and melatonin groups, the baseline NDSST scores were 9.2 ± 2, 12.3 ± 7, 10.2 ± 3, 9 ± 2, 9.7 ± 2, 8.7 ± 3, and 9.1 ± 3, respectively (P = NS); the TDT score for missed dots were 8.2 ± 6, 6.1 ± 4, 8.6 ± 5, 12 ± 8, 13.8 ± 7, 9.2 ± 7, and 5.4 ± 4, respectively ($P = 0.01$); the TDT deviation were 2.5 ± 3, 3.5 ± 2.6, 5.3 ± 5, 4 ± 4, 3.5 ± 2.7, 5.5 ± 4.7, and 3.4 ± 2.9 mm, respectively (P = NS); and the TDT time was 13 ± 3, 12 ± 5.6, 15 ± 4, 14 ± 4, 13 ± 6, 18 ± 6, and 13 ± 5 s, respectively ($P = 0.03$). Thirty minutes after the administration of premedication, patients in the three midazolam groups had significantly poorer performance on the NDSST test compared with melatonin and placebo groups (Figure 2). However, there was no difference in the TDT score, deviation, or time needed to perform

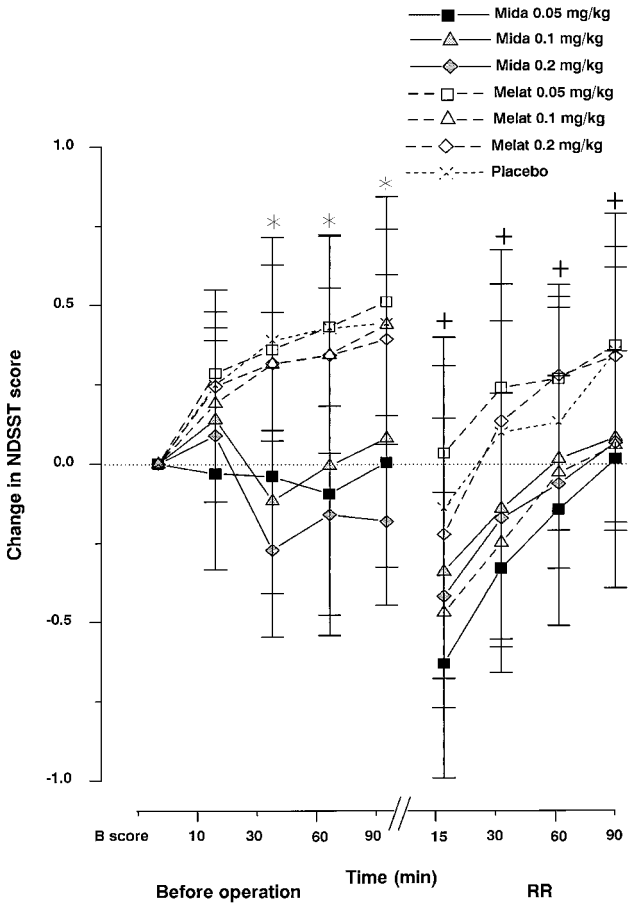

Figure 2. Changes in the normalized digit-symbol substitution test (NDSST) scores (mean ± SD) relative to baseline (B). *$P < 0.05$ midazolam groups versus placebo and melatonin groups; $^{+}P < 0.05$ melatonin 0.05 mg/kg group versus midazolam groups. Mida = midazolam, Melat = melatonin, RR = recovery room.

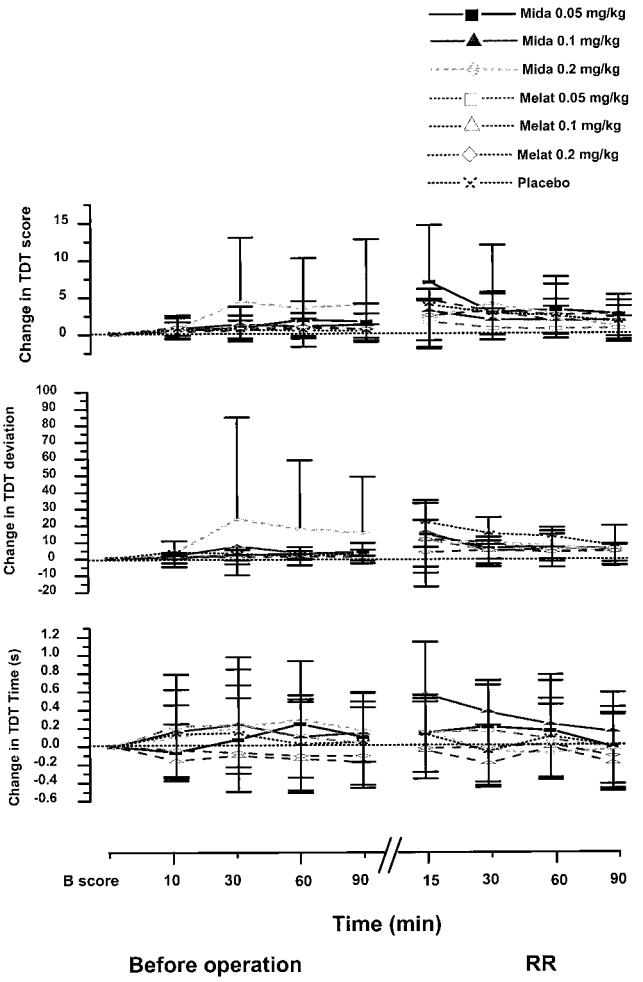

Figure 3. Changes in Trieger dot test (TDT) scores for missed dots, deviation and the time to perform the test (mean ± SD) relative to baseline (B). No significant differences were observed. Mida = midazolam, Melat = melatonin, RR = recovery room.

the TDT test among all of the groups either before operation or in the recovery room (Figure 3). After operation, the placebo and 0.05 mg/kg melatonin groups performed the DSST significantly better at 15, 30, and 90 min than the midazolam groups (Figure 2). Patients who were deeply sedated (asleep, but not arousable; Table 2) were unable to perform the DSST and TDT and were not included in the statistical analysis.

In the 0.2 mg/kg midazolam group, at 24 h one patient did not recall the two simple line diagrams. All other patients in the three midazolam groups recalled the two diagrams (Figure 4). Patients who received 0.2 mg/kg midazolam had a higher incidence of amnesia for the two preoperative events ($P < 0.05$) (Figure 4). All patients in the 0.05 and 0.2 mg/kg midazolam groups and in the 0.05 mg/kg melatonin group were satisfied with their premedication. In each of the other study groups, 10 patients (83.3%) were satisfied with their premedication. This is to be contrasted with seven patients (58.3%) in the placebo group who were satisfied with their premedication ($P = 0.019$). All patients in the midazolam and melatonin groups would prefer to have the same premedication and seven patients (58.3%) in the placebo group said they would prefer to have another premedicant in future. No side-effects were noted.

Discussion

We have demonstrated that patients who received premedication with 0.05, 0.1, or 0.2 mg/kg sublingual midazolam or melatonin had a significant decrease in anxiety levels (Figure 1) and increase in levels of sedation preoperatively compared with those who received placebo (Table 2). However, in the preoperative period, only patients in the three midazolam groups experienced significant impairment in psychomotor skills, as indicated by the performance on the DSST relative to baseline (Figure 2). After operation, patients

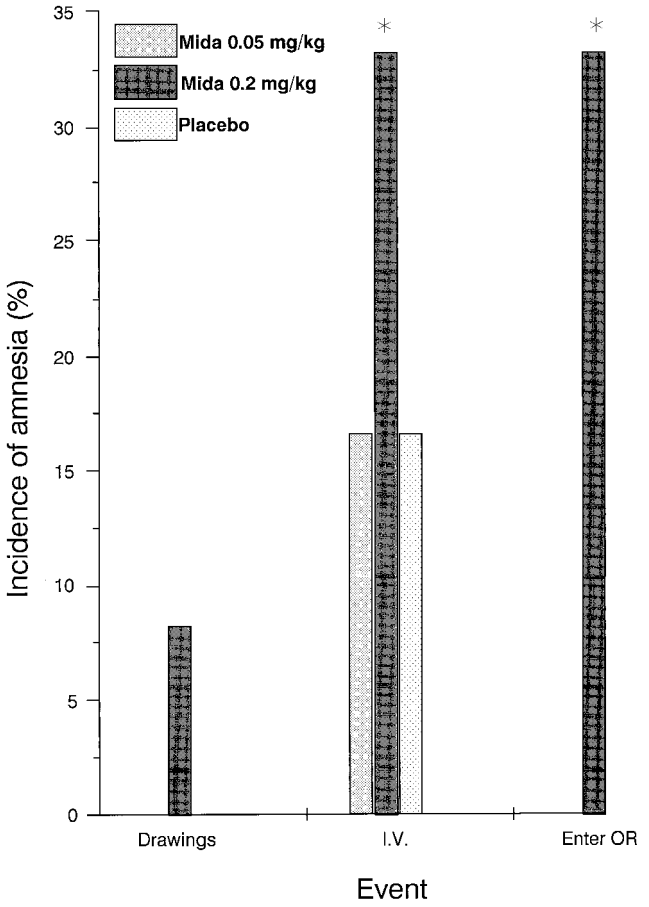

Figure 4. Incidence of amnesia for the diagrams shown before the premedication, for insertion of the IV catheter in the operating room, and for entry into the operating room (OR). *$P < 0.05$ compared with the other groups. Mida = midazolam.

who received 0.2 mg/kg midazolam premedication had increased levels of sedation at 90 min compared with the 0.05 and 0.1 mg/kg melatonin groups. In addition, patients in the three midazolam groups had impairment of performance on the DSST at 15, 30, 60, and 90 minutes postoperatively compared with the melatonin 0.05 mg/kg group. However, there were no significant differences among the midazolam, melatonin, and control groups on the TDT performance either before or after operation or in postoperative anxiety levels. Amnesia was notable only with the 0.2 mg/kg midazolam group for two preoperative events.

In our previously published study (3), we also noted that premedication with either 15 mg of midazolam or 5 mg of melatonin had significant decreases in anxiety levels and increases in levels of sedation preoperatively compared with the control subjects. We also noted that midazolam produced the highest scores of sedation at 30 and 60 minutes after the administration and significant psychomotor impairment in the preoperative period compared with melatonin or placebo (3).

The onset and the peak effect of midazolam-induced sedation were at 30 and 60 minutes, respectively, after sublingual administration. Other investigators have reported similar observations (13). Although the onset of melatonin-induced sedation was at 30 minutes after sublingual administration, the peak effect was at 90 minutes. We noted a similar pattern in our previously reported study (3). In fact, it has been shown, in a sleep-disturbed blind man and in patients with delayed sleep-phase syndrome, that successful amelioration of sleep disturbances was achieved when melatonin was administered two hours before bedtime (14,15). Melatonin was ineffective when administered at bedtime to the blind person, even when larger doses were used.

This study also demonstrated that both midazolam and melatonin were equally effective as premedicants for preoperative sedation. At 90 minutes, the NNT scores were similar between patients who received similar doses of midazolam or melatonin. The NNT defines the treatment-specific effect of an intervention (12). The clinical implication of this NNT is that, for example, one would treat three patients with 0.05 mg/kg midazolam or 2.4 patients with 0.05 mg/kg melatonin to produce preoperative sedation in one patient. A NNT score of 2 or 3 indicates that a treatment is effective (12).

Before operation, the DSST scores improved in the melatonin and control groups 10 minutes after the administration of melatonin and saline, respectively (Figure 2). This reflects learning behavior in these groups. In contrast, significant impairment in performance on the DSST relative to baseline was only in the midazolam group. This observation is consistent with our previously published data (3). These findings are also consistent with other studies that have shown psychomotor decrements after premedication midazolam (16,17). In contrast, several studies have demonstrated that melatonin (even in doses up 240 mg divided into three doses) did not impair either psychomotor performance or tests of memory and visual sensitivity (3,18). After operation, the placebo and 0.05 mg/kg melatonin groups performed the DSST significantly better at 15, 30, and 90 minutes than the midazolam groups (Figure 2).

It has been shown that the DSST is a more sensitive test than TDT for detection of the cognitive and psychomotor impairments (3,19). In this study, there was no difference in the TDT score, deviation, or time needed to perform the TDT test among all groups, either before operation or in the recovery room (Figure 3).

Benzodiazepines impair acquisition of new information with no effect on retention or retrieval of previously stored information (20). Midazolam, in particular, is reported to provide significant amnesia (21). In this study, midazolam diminished anterograde recall

for the two preoperative events (entry into the operating room and IV catheter insertion) compared with melatonin and placebo groups. In accordance with our previously reported study (3), the results of this study indicated that melatonin had no amnestic effects (Figure 4). Although it is desirable in some situations to render patients amnesic to perioperative experiences, amnesia is considered undesirable in patients who wish to or need to have recall in the immediate postoperative period. For example, prolonged amnesia of the patient is not desired in the outpatient setting, as discharge may be delayed and instructions forgotten.

In conclusion, the administration of either 0.05, 0.01, and 0.2 mg/kg melatonin or midazolam was associated with adequate preoperative sedation, anxiolysis, and patient satisfaction. Doses of 0.2 mg/kg midazolam produced the highest scores of sedation at 30, 60, and 90 minutes after the administration. After operation, the psychomotor test results indicated that the course of recovery was faster in the 0.05 mg/kg melatonin group. The dose of 0.2 mg/kg midazolam decreased recall for two preoperative events compared with other groups. We conclude that premedication with 0.05 mg/kg melatonin was associated with preoperative anxiolysis and sedation without impairment of cognitive and psychomotor skills and without prolonging recovery. Therefore, 0.05 mg/kg melatonin appears to be an adequate dose for premedication. Melatonin appears to be a good choice for ambulatory surgery patients and in situations in which impairments of cognitive and psychomotor functions would be detrimental to the patient's well-being.

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