Melatonin premedication does not enhance induction of anaesthesia with sevoflurane as assessed by bispectral index monitoring

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ABSTRACT

Introduction: Exogenous melatonin has sedating and hypnotic actions. The present prospective double-blind randomised study investigated the effect of melatonin premedication on the induction of anaesthesia with sevoflurane.

Methods: 71 women of reproductive age, scheduled for a hysteroscopy, were randomised into the melatonin or the control group. 30 minutes before the induction of anaesthesia, patients in the melatonin and control groups sublingually received 9 mg of melatonin or placebo, respectively. In the operating room, patients were attached to a standard monitor and bispectral index (BIS) monitor. Anaesthesia was induced with 8 percent sevoflurane in oxygen via an anaesthetic system primed with 8 percent sevoflurane. BIS values were recorded every 30 seconds, during the first 300 seconds of sevoflurane administration. Inspired and expired sevoflurane concentrations, heart rate and oxygen saturation were also recorded at the same time intervals. Noninvasive blood pressure was recorded before and after the completion of measurements.

Results: BIS values (p-value is 0.725, F is 0.125, degrees of freedom [df] 1), inspired (p-value is 0.468, F is 0.535, df 1) and expired (p-value is 0.388, F is 0.756, df 1) sevoflurane concentrations, heart rate (p-values is 0.516, F is 0.427, df 1) and oxygen saturation (p-value is 0.401, F is 0.717, df 1), did not differ between the two groups, at any time point of measurement. Systolic blood pressure before (p-value is 0.131, t 1.530, df 67) and after measurement (p-value is 0.8288, t 0.218, df 54) as well as diastolic blood pressure before (p-value is 0.370, t 0.902, df 67) and after measurement (p-value is 0.764, t 0.302, df 54) did not differ between the two groups.

Conclusion: Melatonin premedication under the present study design failed to enhance the induction of anaesthesia with sevoflurane.

Keywords: anaesthesia induction, bispectral index monitoring, central nervous system monitoring, exogenous melatonin, melatonin, sevoflurane

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INTRODUCTION

Melatonin, the main hormone of the pineal gland, is involved in circadian rhythm regulation and sleep in humans.[1] Exogenous melatonin administration during the day, when endogenous levels of the hormone are very low, enhances sleep induction,[2] decreases sleep latency[3] and core temperature, and increases sleepiness.[4] Melatonin has been used as premedication in both adults and children.[5,6] High doses of melatonin given intravenously to rats have been shown to have anaesthetic and antinociceptive properties,[7] and also produced effects on electroencephalographical variables similar to those of thiopental or propofol.[8] Our hypothesis is that melatonin administration may enhance the inhalational induction of anaesthesia with sevoflurane. The present study was designed to assess the effect of melatonin premedication on bispectral index (BIS) values during the induction of anaesthesia with sevoflurane.

METHODS

After approval from the Hospital Ethics Committee and patient written informed consent were obtained, 71 female patients aged 25–40 years, physical status ASA I–II, and scheduled for a hysteroscopy on a day case basis, were recruited for the study. Exclusion criteria were body weight exceeding 20% of the ideal body weight, a history of oesophageal reflux, hyper- or hypothyroidism, epilepsy, use of opioids, benzodiazepines, antiepileptics, antidepressants, drug abuse and alcohol. During the preoperative visit, the inhalational induction tidal volume technique was explained to all patients.

Table I. Demographics of the patients in the melatonin and control groups.

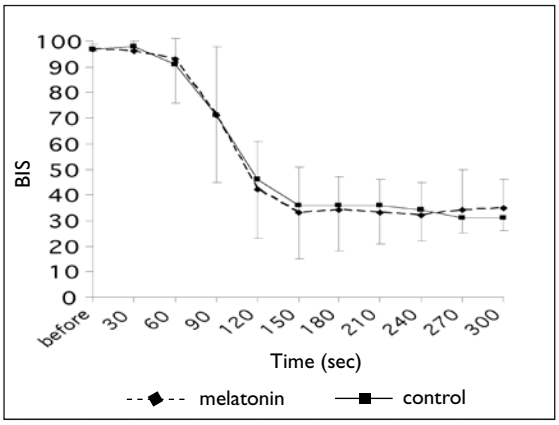
Variable	Melatonin	Control	p-value
Age (years)	34 ± 5	36 ± 7	0.244
Weight (kg)	59 ± 7	62 ± 8	0.139
Height (cm)	164 ± 6	164 ± 6	0.994

Values are expressed as mean ± SD.

Patients were randomly assigned to receive melatonin (n = 37) or placebo (n = 34) 30 mins before the induction of anaesthesia. Randomisation was done using sealed envelopes containing odd and even numbers that were created from a computer-generated table, with odd numbers indicating assignment to the melatonin group and even numbers to the control group. An independent anaesthesiologist who did not participate in the study was responsible for group assignment and melatonin administration. Patients assigned to the melatonin group sublingually received 9 mg of melatonin. Three tablets of melatonin (Natures Bounty Inc, Bohemia, NY, USA) of 3 mg each were turned to powder and dissolved in 3 ml of water. The placebo consisted of refined sugar and was also dissolved in 3 ml of water. The contents of the syringe were placed under the patient's tongue while they were instructed not to swallow for 3 mins.

In the operating room, patients were attached to the electrocardiograph, noninvasive blood pressure, pulse oximeter (SpO_2) (Datex-Ohmeda S/5, Finland) and BIS monitor (BISxp A-2000™ Monitor, System Rev 3.21, ASPECT™ Medical Systems, 2332 KG, Leiden, The Netherlands). A 20 G peripheral vein catheter was inserted in the non-dominant hand. In each patient, a 5-minute period was allowed for BIS values to stabilise. BIS baseline values were derived from recording the median of three consecutive individual BIS values. The anaesthetic breathing system was primed with 8% sevoflurane in oxygen with a fresh gas flow of 6 L/min until the inspired concentration, indicated by the infrared analyser, was > 7%. Subsequently, the patient was asked to breathe normally through the face mask with the vaporiser set at 8% sevoflurane in oxygen at 6 L/min fresh gas flows. BIS values were recorded every 30 seconds for the first 300 seconds by an independent anaesthesiologist who was blinded to the study design. Inspired and expired sevoflurane concentrations, heart rate and SpO_2 were recorded every 60 seconds for the first 300 seconds of anaesthesia. Noninvasive blood pressure was recorded before and after the completion of the 300-second recording period.

Patient age, body weight and height, as well as blood pressure before and after completion of the study between the two groups, were compared with an unpaired Student's *t*-test. BIS values, inspired and expired sevolfurane concentrations, heart rate and SpO_2 between the two groups were compared using two-way ANOVA with repeated measures. Statistical analysis was carried out using the Statistical Package for Social Sciences version 11.0 (SPSS Inc, Chicago, IL, USA).



		Before	30s	60s	90s	120s	150s	180s	210s	240s	270s	300s
BIS	M	97 ± 1.1	97 ± 1.6	93 ± 11.9	73 ± 25.2	48 ± 21.6	37 ± 18.1	36 ± 17.4	35 ± 14.5	32 ± 10.8	31 ± 6.3	31 ± 5.9
	C	97 ± 1.9	95 ± 6.1	94 ± 7.9	76 ± 22.6	48 ± 23.1	39 ± 23.1	37 ± 15.6	35 ± 14.5	33 ± 12	33 ± 13.2	32 ± 9.6

Fig. 1 BIS values before and at 30-second intervals between 0–300 seconds of induction, in the melatonin (M) and the control (C) groups. Values are expressed as mean ± SD.

RESULTS

The two groups were comparable in terms of age, body weight and height (Table I). The BIS values did not differ between the two groups at any time during the recording period (p = 0.725, F = 0.125, df 1) (Fig. 1). Inspired and expired sevolfurane concentrations, heart rate and SpO_2 also did not differ at any time point during the first 300 seconds of anaesthesia (Table II). Blood pressure did not differ before or after the completion of the study between the two groups (Table III).

DISCUSSION

The results showed that sublingual melatonin did not enhance the induction of anaesthesia with sevoflurane as assessed by BIS values. Previous studies have shown that 5 mg of melatonin given sublingually significantly decreased anxiety and increased sedation preoperatively.[5,9] However, increased levels of sedation after melatonin premedication were evident either at 60 and 90 mins[9] or at 90 mins,[5] compared with the placebo group. This time period is longer than the period we allowed from melatonin administration to the induction of anaesthesia. The half-life of melatonin reported by different studies was 0.80 hours, 0.54 hours, and 0.68 hours after intake by mouth at 80 mg, 2 mg and 100 mg, respectively.[10-12] The wide range of the melatonin dose may be due to different formulations of the substance with different degrees of absorption. Another reason may be that the melatonin dosage has not been standardised

Table II. Inspired and expired sevoflurane concentration, heart rate, pulse oximetry at 30-second intervals from 0–300 seconds of induction, in the melatonin and control groups.

	Time (sec)											df	F	p-value
	0	30	60	90	120	150	180	210	240	270	300			
INS												1	0.535	0.468
M	7.4 ± 0.49	7.16 ± 0.80	7.31 ± 0.56	7.39 ± 0.44	7.25 ± 0.51	7.31 ± 0.45	7.26 ± 0.49	7.26 ± 0.50	7.12 ± 0.71	7.23 ± 0.54	7.38 ± 0.48			
C	7.6 ± 0.50	7.19 ± 1	7.36 ± 0.66	7.45 ± 0.46	7.34 ± 0.54	7.3 ± 0.70	7.26 ± 0.50	7.30 ± 0.55	7.33 ± 0.50	7.30 ± 0.66	7.25 ± 0.49			
EXP												1	0.756	0.388
M	7.34 ± 0.59	6.1 ± 1.88	6.77 ± 1.26	6.74 ± 1.29	6.69 ± 1.18	6.88 ± 0.95	6.66 ± 1.12	6.71 ± 0.97	6.6 ± 1.14	6.8 ± 1.06	6.89 ± 0.76			
C	7.47 ± 0.71	6.1 ± 2	6.2 ± 1.9	6.81 ± 1.34	6.23 ± 1.69	6.26 ± 1.43	6.5 ± 1.23	6.47 ± 1.21	6.57 ± 1.06	6.7 ± 0.99	6.78 ± 1.06			
HR												1	0.427	0.516
M	86 ± 16	91 ± 16	84 ± 12	78 ± 10	76 ± 11	78 ± 14	78 ± 17	79 ± 19	79 ± 18	78 ± 19	78 ± 19			
C	87 ± 16	93 ± 18	89 ± 19	82 ± 15	78 ± 12	78 ± 12	78 ± 12	79 ± 14	81 ± 18	82 ± 20	82 ± 21			
SpO_2												1	0.41	0.841
M	99 ± 0.84	99 ± 0.5	100 ± 0.5	99 ± 0.61	99 ± 0.56	99 ± 0.56	99 ± 0.54	99 ± 0.74	99 ± 0.47	99 ± 0.50	99 ± 0.48			
C	97 ± 0.95	99 ± 0.75	100 ± 0.7	100 ± 0.48	99 ± 0.58	99 ± 0.62	99 ± 0.66	99 ± 0.64	99 ± 0.68	99 ± 0.67	99 ± 0.72			

M: melatonin; C: control; INS: inspired sevoflurane concentration; EXP: expired sevoflurane concentration; HR: heart rate; SpO_2: oxygen saturation
Values are expressed as mean ± SD.

and high doses are administered as the substance is deprived of side effects. In a study by Waldhauser et al, changes in serum melatonin levels exhibited an absorption rate constant (ka) 1.72/hr (half-life 0.40 hours) and an elimination rate constant (ke1) 0.87/hr (half-life 0.80 hours).[11] In our study, we assessed the effect of melatonin on the induction of inhalation anaesthesia with sevoflurane based on its pharmacokinetic rather than pharmacodynamic characteristics as we administered melatonin 30 mins before induction.

The results of several studies on the effect of melatonin administration preoperatively on anxiety and sedation are varied. In studies showing that melatonin decreases anxiety and produces sedation preoperatively, the investigators reported no impairment of cognitive function and psychomotor skills.[5,9,13] On the contrary, Capuzzo et al administered 10 mg of melatonin in elderly patients preoperatively, and found no difference in anxiety between the treatment and placebo groups.[14] The varied results of studies assessing the effect of melatonin on preoperative anxiety may be due to differences in age, gender, dosage or route of administration. However, although our patients were similar in age, all females and received 9 mg of melatonin, which is 40% above the dosage used in two of Naguib and Samarkandi's studies,[9,13] we found no effect on BIS values either before or during the induction period of anaesthesia. As we allowed only a 30-min lapse from melatonin administration to anaesthesia induction, this period of time might not have been long enough to obtain the maximum pharmacokinetic effect. In a recent study, Naguib et al used 0.2 mg/kg of melatonin 50 mins before the induction of anaesthesia and found a significant reduction in the doses of propofol or thiopental used, although the end-points were a loss of response to verbal command and eyelash reflex.[15]

We did not measure melatonin plasma concentration, and this may be considered to be a limitation of our study. In a previous study, we found no changes in melatonin serum levels after sevoflurane anaesthesia.[16] Also, decreased stress scores after acupressure application on the extra 1 acupoint were not associated with significant changes in melatonin levels.[17] However, Arai et al found that there was a decrease in endogenous melatonin levels 5 mins after the induction of anaesthesia with sevoflurane.[18] Nevertheless, the present study was designed to investigate the possible enhancement of induction of anaesthesia with sevoflurane by melatonin in an ambulatory anaesthesia setting. Other agents like opioids or benzodiazepines have been tested for this purpose. Midazolam did not speed up the inhalational induction with sevoflurane.[19] Fentanyl had an effect in doses of 1–2 μg/kg. Higher doses did not increase the speed of induction any further.[20] However, both benzodiazepines and opioids, when administered as premedicants, depress the respiration and decrease the tidal volume, which in turn

Table III. Systolic and diastolic arterial pressure before and after the completion of measurements in the melatonin and control groups.

	Mean ± SD (mmHg)	t	df	p-value
SAP before measurements		1.530	67	0.131
Melatonin group	127 ± 18			
Control group	132 ± 13			
SAP after measurements		0.218	54	0.828
Melatonin group	108 ± 19			
Control group	109 ± 19			
DAP before measurements		0.902	67	0.370
Melatonin group	79 ± 13			
Control group	81 ± 9			
DAP after measurements		0.302	54	0.764
Melatonin group	67 ± 16			
Control group	69 ± 16			

SAP: systolic arterial pressure; DAP: diastolic arterial pressure

decrease the uptake of the volatile agent.

Patients might benefit from melatonin premedication as, to our knowledge, melatonin has no effect on respiration and is not expected to interfere with spontaneous breathing and volatile anaesthetic uptake. The reasons why melatonin did not enhance the inhalation induction may be that we adjusted its administration to its pharmacokinetic rather than its pharmacodynamic characteristics. Thus the 30 mins of administration of melatonin for induction may not be long enough to speed up the induction of anaesthesia with sevoflurane. On the other hand, the low blood/gas partition coefficient of sevoflurane does ensure a rapid induction and any further shorter induction is clinically undetectable.

Finally, BIS values appear to be an appropriate end-point for detecting a more rapid induction of general anaesthesia using sevoflurane. In contrast to subjective tests used as end-points for loss of consciousness, BIS monitoring is an objective measure, independent of patient cooperation. Its use in patients undergoing interventional radiological procedures provided a good guide for sedation as the BIS values correlated well with the sedation agitation scale.[21] In conclusion, melatonin premedication under the present study conditions did not enhance the inhalation induction of anaesthesia with sevoflurane.

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