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Isoflurane increases, but sevoflurane decreases blood concentrations of melatonin in women

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Abstract: The blood concentrations of melatonin are elevated by stress-induced sympathetic nerve excitation and are affected by some anesthetics. Isoflurane has an effect to increase sympathetic nerve activity when compared with sevoflurane. This study was performed to investigate the effects of these two anesthetics on the blood concentrations of melatonin. Female patients were anesthetized with either isoflurane or sevoflurane. We obtained blood samples before and 5 min after 5% isoflurane (ISO group) or 7% sevoflurane (SEV group) anesthesia. The blood melatonin concentrations during anesthesia in the ISO group increased significantly, from 65 ± 60 to 170 ± 90 pg·ml^{-1}; mean ± SD ($P < 0.05$), whereas those in the SEV group decreased, from 60 ± 50 to 30 ± 30 pg·ml^{-1} ($P < 0.05$). In conclusion, isoflurane increases, but sevoflurane decreases blood melatonin concentrations.

Key words Melatonin · Isoflurane · Sevoflurane · Sympathetic nerve activity

Introduction

Melatonin is produced and secreted by the pineal gland [1,2] and its secretion regulates and modifies circadian rhythms and sleep [3]. The circulating melatonin levels are modulated by a variety of factors, such as stressors causing sympathetic nerve excitation [4,5], some agents such as diazepam [6,7], and inhalational anesthetics.

Isoflurane has a property to cause sympathetic nerve excitation with high inhalational concentrations [8–10] when compared with sevoflurane [11,12]. In fact, under volatile induction and maintenance of anesthesia (VIMA), hyperdynamic circulatory responses are shown with isoflurane 5%, while VIMA on 7% sevoflurane suppresses circulatory responses. Also, patients anesthetized with isoflurane emerge from general anesthesia more slowly than those anesthetized with sevoflurane [13]. These facts indicate that isoflurane may have a higher potential to increase circulating melatonin levels than sevoflurane. In this study, we therefore evaluated the effects of isoflurane and sevoflurane on blood concentrations of melatonin. We chose maintenance concentrations of isoflurane and sevoflurane of 5% and 7%, respectively, based upon our daily clinical practice.

Patients and methods

With the approval of the Ethics Committee for Medical Research of Kochi Medical School, and after obtaining informed consent from the patients, we recruited 18 American Anesthiology Association (ASA) physical status I patients who were scheduled for elective gynecological surgery. Patients with a medical history or physical evidence of significant cardiovascular disorders, alcohol or drug abuse, sleep disorders, or neuropsychiatric disorders were excluded from the study.

All patients received diazepam, 0.25 mg·kg^{-1} orally in the ward, 1 h before anesthesia. In the operating room, at 8:30 a.m., an 18- or 20-gauge intravenous catheter was placed in the basilic vein of one of the patient's hands. The first blood samples for control were collected through this catheter. Then, 35 ml·kg^{-1}·h^{-1} of acetated Ringer's solution was administered during the induction of anesthesia. The inhalational anesthetics, in 4 l·min^{-1} oxygen, were delivered into a circuit system. Respiratory gases were sampled at a mask elbow connector. All patients were monitored with noninvasive arterial pressure, EKG, pulse oximetry, end-tidal anesthetic, and CO2 concentration and FIO2.

Patients were randomized into two groups: an SEV group ($n = 9$) and an ISO group ($n = 9$). In the SEV group, anesthesia was induced by increasing the inhala-

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Table 1. Group comparability

	ISO group	SEV group
Age (years)	40 ± 8	40 ± 12
Height (cm)	156 ± 6	155 ± 9
Weight (kg)	49 ± 6	52 ± 8
End-tidal anesthetic concentration (%)	3.0 ± 0.1	5.1 ± 0.2
(multiples of MAC)	(2.6 ± 0.1)	(2.5 ± 0.1)

Values are means ± SD. There were no statistically significant differences between the groups
MAC, minimal alveolar concentration; ISO, isoflurane; SEV, sevoflurane

tional concentration of sevoflurane in 100% oxygen by 0.5% every three breaths, up to 7%, and the concentration was maintained at 7% for 5 min before obtaining the second blood samples from the basilic vein of the other hand. In the ISO group, induction of anesthesia was made in an incremental way, similar to that in the SEV group, using isoflurane up to 5%. Then, anesthesia was maintained with 5% isoflurane for 5 min before taking the second blood samples. Ventilation was manually assisted to maintain end-tidal CO2 between 30 and 35 mmHg. Heart rate (HR) and systolic arterial pressure (SAP) were recorded at the time of blood sampling.

The sampled blood for the melatonin measurement was immediately centrifuged. The serum was stored at −80°C and was analyzed within 3 days. Melatonin concentration was measured by high-performance liquid chromatography with electrochemical detection (HPLC apparatus; IRICA, Kyoto, Japan) [14]. The analytical detection limit was 15 pg/ml. The intra- and interassay coefficients of variance were less than 5%.

Data values are presented as means ± SD. Demographic data were analyzed with the Mann-Whitney *U*-test. Statistical analyses of the melatonin concentrations were performed using the Wilcoxon signed-ranks test to compare differences within each group and the Mann-Whitney *U*-test to compare differences between the groups. A *P* value of less than 0.05 was considered statistically significant.

Results

The two groups were comparable with respect to age, body weight, and height (Table 1). The two groups had similar preanesthetic values for serum melatonin concentration (Fig. 1), SAP (Fig. 2), and HR (Fig. 3). The circulating melatonin levels during anesthesia significantly increased from 65 ± 60 to 170 ± 90 pg·ml^{-1} in the ISO group ($P < 0.05$), whereas these levels decreased, from 60 ± 50 to 30 ± 30 pg·ml^{-1} in the SEV group ($P <$

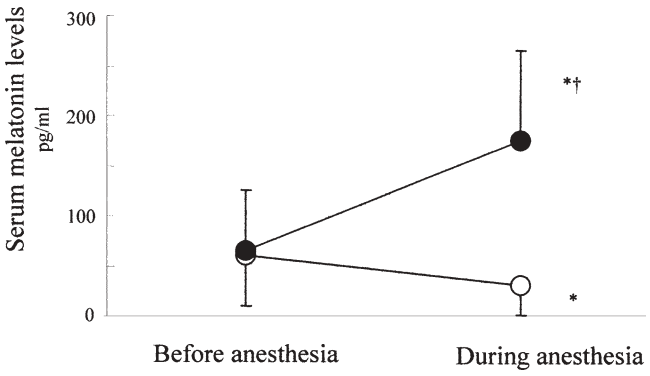

Fig. 1. Serum concentrations of melatonin before and during anesthesia in the isoflurane group I (ISO; *closed circles*), and the sevoflurane group (SEV; *open circles*). *$P < 0.05$ versus before anesthesia; †$P < 0.05$ versus SEV group. Values for results are presented as means ± SD

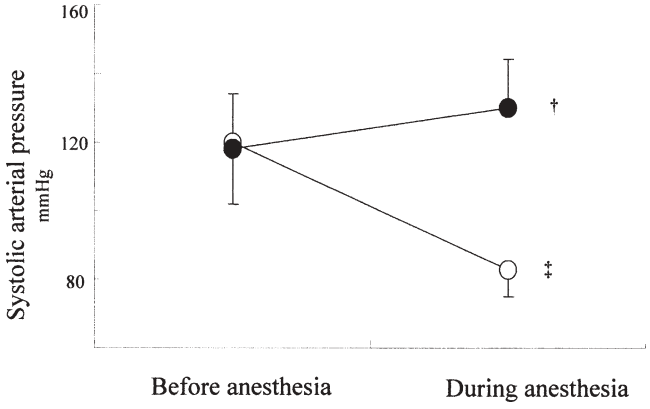

Fig. 2. Systolic arterial pressure before and during anesthesia in the ISO group (*closed circles*), and SEV group (*open circles*). ‡$P < 0.01$ versus before anesthesia; †$P < 0.05$ versus SEV group. Values for results are presented as means ± SD

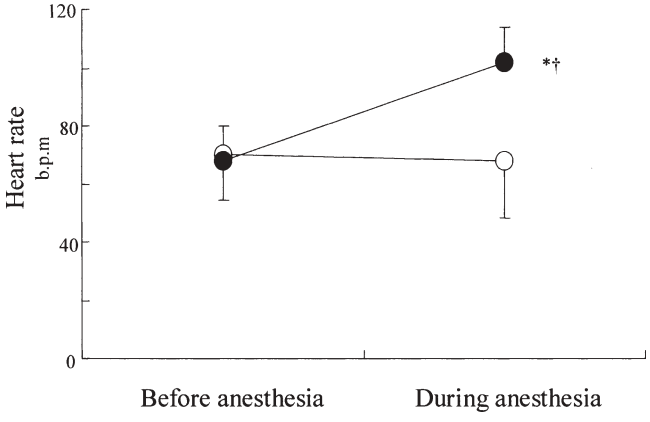

Fig. 3. Heart rate before and during anesthesia in the ISO group (*closed circles*), and SEV group (*open circles*). *$P <$ 0.05 versus before anesthesia; †$P < 0.05$ versus SEV group. Values for results are presented as means ± SD

0.05). Isoflurane had a tendency to increase SAP, from 118 ± 16 to 130 ± 14 mmHg, but the difference from baseline was not significant. In contrast, sevoflurane significantly reduced SAP, from 120 ± 18 to 83 ± 8 mmHg ($P < 0.01$). Isoflurane significantly increased HR, from 68 ± 16 to 102 ± 20 beat·min^{-1} ($P < 0.05$), but sevoflurane did not change HR. The end-tidal concentrations of these anesthetics during the anesthesia were equipotent (Table 1), if minimum alveolar concentration values for isoflurane and sevoflurane were assumed to be 1.15% and 2.05%, respectively [13].

Discussion

Our study showed that isoflurane increased, but sevoflurane decreased the blood levels of melatonin, in parallel with hemodynamic changes.

Melatonin is the specific product of the pineal gland [1,2]. Animal studies show that sympathetic nerve fibers from the superior cervical ganglia stimulate beta-adrenergic receptors on the pinealocytes within the pineal gland, thereby increasing the synthesis and secretion of melatonin [1,2]. Also, stress-induced sympathetic nerve excitation increases melatonin concentrations in the blood in humans [4,5].

In this study, isoflurane increased the hemodynamic state, in contrast to sevoflurane, which reduced it. Taking our results and those of some other studies into consideration [8,11,15], we believe that isoflurane may have induced sympathetic nerve excitation (in contrast to sevoflurane), and thereby isoflurane increased the circulating melatonin concentrations, when compared with sevoflurane.

However, there could be another mechanism whereby these anesthetics change circulating melatonin levels. In fact, γ-aminobutyric acid (GABA)ergic transmission influences melatonin synthesis [7]. Therefore, these anesthetics may have changed GABAergic transmission differentially. Moreover, melatonin is metabolized in the liver [15], and these two anesthetics led to different hemodynamic states. Thus, the effects of these anesthetics on hepatic blood flow may have altered melatonin clearance.

We took the blood samples under mask inhalation before intubation and operation, because the activity of the sympathetic nervous system and the secretion of melatonin could be easily affected by stress, and we wanted to see the plain effects of these anesthetics on sympathetic activity and the blood concentrations of melatonin. We maintain inhalational sevoflurane on 7% at induction of anesthesia in our daily clinical practice, and according to a study [8], inhalation of 5% isoflurane activates the sympathetic nerves within 5 min. Furthermore, an inhalational concentration of 5% isoflurane could be equipotential to that of 7% sevoflurane if it is assumed that minimum alveolar concentration values for isoflurane and sevoflurane are 1.15% and 2.05%, respectively. Therefore, we maintained the inhalational concentrations of the two anesthetics as shown above.

A major limitation of the present study was our limited investigation, in women only. Although gonadotropins and gonadal steroids affect melatonin secretion from the pineal gland [16], the influence of sex steroids on melatonin secretion seems to be minimal [17]. We therefore believe that the present results in women would be comparable with those in men. However, we need further studies.

The profile of inhalational anesthetics in altering circulating melatonin concentrations may be one of the factors that influence emergence from general anesthesia. In fact, recovery has a tendency to be faster in patients anesthetized with propofol, which leads to lower melatonin levels, when compared with patients recovering from isoflurane anesthesia, which leads to higher melatonin levels [15]. In the present study, we did not investigate the relationship between melatonin levels and emergence from general anesthesia. Therefore, further detailed studies are needed.

In conclusion, isoflurane increases the circulating blood concentration of melatonin, whereas sevoflurane reduces it.

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