Effect of tramadol on bispectral index during anesthesia with desflurane

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Background: This study is aimed to investigate the effect of tramadol on the bispectral index (BIS) during anesthesia with desflurane.

Methods: One hundred fifty adults, ASA class 1 and 2 patients, scheduled for general anesthesia for elective surgical procedures were included in this study. None of the patients were premedicated and anesthesia was induced with propofol 2 mg/kg and maintained with air-oxygen (FiO2 0.5) and desflurane, adjusted to keep the BIS between 50 and 60. Forty minutes before completing surgery, the subjects were randomly allocated into 3 groups to receive saline (control group), tramadol 1.5 mg/kg (T1 group) or 3.0 mg/kg (T2 group) intravenously. Hemodynamics and BIS values were then recorded every 5 minutes until completion of the operation, during which time the concentrations of desflurane were not modified.

Results: The mean BIS values after tramadol administration weren’t significantly different from the control group throughout the period of observation. No significant changes in the hemodynamics were noted, except systolic and diastolic arterial blood pressure in the T1 and T2 groups significantly increased in the first 5 minutes after the tramadol injection.

Conclusions: The results indicate that the administration of tramadol while maintaining anesthesia with desflurane, adjusted to keep the BIS between 50 and 60, does not modified BIS values. So, we propose that tramadol can be safely administered as an immediate postoperative analgesia without concern about intra-operative awareness. (Korean J Anesthesiol 2009; 56: 375–80)

Key Words: Bispectral index, Desflurane, Tramadol.

INTRODUCTION

Tramadol, a central acting opioid agonist, has been frequently used for pain control during administration of inhaled anesthesia as it prevents severe postoperative pain and reduces the demand for opioid analgesics significantly [1-3]. However, it has been hypothesized that it may increase the risk of intra-operative awareness through excitatory activation of electroencephalogram (EEG) in a dose-dependent manner, which has been a very important drawback of tramadol [3-5].

Bispectral index (BIS) is a useful monitoring device designed to reduce and prevent the risk and development of awareness during anesthesia by measuring depth of anesthesia [6,7], and to measure the degree of sedation and hypnosis by analyzing and digitizing electroencephalograms, which are known to reflect hypnotic states by intravenous or inhaled anesthetics [8].

Though there is a risk of intra-operative awareness associated with tramadol, research is still limited. This study aim to identify the effect of tramadol on the BIS and hemodynamic changes during general inhalational anesthesia using desflurane.

MATERIALS AND METHODS

This study targeted 150 male and female patients (ASA class 1, 2) who had surgery under general anesthesia and their ages ranged from 15 to 65. We explained the aim and methods of our study to the patients upon admission and got in-
formed consent before surgery. However, we excluded those patients who had central nervous system diseases, hemodynamic instability, ischemic heart disease, liver and kidney disease, and those who used medications that may affect the activity of the EEG. We also received hospital ethics committee’s approval. There was no significant difference in age, sex, weight, height and ASA class among the different groups (Fig. 1).

None of the patients were premedicated for preoperative sedation and hypnosis, and after they arrived at the operating room, we monitored their electrocardiograms, non-invasive blood pressure and peripheral oxygen saturation (SpO₂). We attached the BIS (BIS A-2000, software version 3.30, Aspect Medical Systems, USA) at the frontal area of head according to the way recommended by the manufacturing company and with more than 95 on the signal quality index (SQI), we measured and recorded BIS values. We introduced a general anesthesia with propofol 2 mg/kg, rocuronium bromide 0.9 mg/kg and lidocaine 1 mg/kg, and manually ventilated with desflurane 6 vol%, O₂ 1.5 L/min and air 2.0 L/min. Then we checked the patient’s degree of muscle relaxation and then the patients were intubated. We adjusted the concentration of desflurane to achieve BIS values within 50–60 and monitored the changes of end-tidal PCO₂ (ETCO₂).

The subjects were randomly categorized into the groups of normal saline (C), tramadol 1.5 mg/kg (T1) and tramadol 3.0 mg/kg (T2), to whom a total volume of 5 ml with normal saline was administered 40 minutes before the expected completion of the surgery. We observed systolic and diastolic arterial blood pressure (SBP and DBP), heart rate (HR), BIS value, ETCO₂ (mmHg) and SpO₂ before and 5, 10, 15, 20, 25, 30, 35 minutes after administration, and at this time, the concentration of inhaled anesthetics was not adjusted. In the recovery room just before transfer to the ward, the patients were interviewed using a modified Brice interview to evaluate the possible occurrence of awareness [9].

For statistical data, we used SPSS (version 12.0, SPSS Inc, Chicago, USA) and the results were expressed as mean ± standard deviation. We analyzed sex using chi-square test and age, weight and height using one-way ANOVA. The change of each variable in each group according to time was analyzed with repeated measures ANOVA and for Post-hoc Comparison, Bonferroni was used. We judged statistically significant when \( P < 0.05 \).

**RESULTS**

There was no significant difference in systolic and diastolic arterial blood pressures, heart rates, BIS values, ETCO₂ and SPO₂ between groups before tramadol was injected (Fig. 2).

Group T1 and Group T2 showed a significant, time dependent difference in systolic blood pressure and diastolic blood pressure after tramadol was administered, but Group C did not. We found there was a significant differences in Group T1 and T2 compared to group C 5 minutes after tramadol was administered, but there was no significant difference after 10, 15, 20, 25, 30, 35 minutes. There was no significant difference in heart rate, ETCO₂ and SPO₂ according to the time after tramadol was administered in each group. BIS values did not show significant difference in each group after tramadol was administered according to time lapse (Fig. 2).

No patients had explicit recall of events during the operation, as assessed by the Brice interview in the recovery room.

**DISCUSSION**

For postoperative pain control, pre-emptive analgesia, preventive analgesia, have been frequently used to reduce post-operative pain and the demand of opioid analgesics by administering it before the surgery is completed [1]. Of the drugs used for pain control, tramadol is ten times weaker than morphine, but it is classified as an opioid analgesic with weak affinity in \( \mu \)-receptor with analgesic potency similar to pethidine

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**Fig. 1.** Demographic Data. Height, weight and age are presented as mean ± SD, sex (female and male) and ASA (1, 2) are presented as number of patients. There are no differences in demographic data among the three groups. C: group with normal saline, T1: group with tramadol 1.5 mg/kg, T2: group with tramadol 3.0 mg/kg intravenously.
Fig. 2. Changes of systolic (A) and diastolic (B) arterial blood pressure, bispectral index (C), heart rate (D), SPO₂ (E) and EtCO₂ (F) among the three groups. All data are presented as mean ± SD. There are no differences among the three groups at each time intervals except slightly increased systolic and diastolic arterial blood pressure after 5 minute (A, B). C: group with normal saline, T1: group with tramadol 1.5 mg/kg, T2: group with tramadol 3.0 mg/kg intravenously. *P < 0.05 compared to the group C.
and is known as having little complications common to most opioids [10]. However, previous studies did not recommend its use during surgery under general anesthesia as it may induce awareness through activation of EEG [4,11-13].

Intra-operative awareness is an unpleasant experience and may result in sleep disorders, nightmares, anxiety and recall after surgery in addition to intra-operative pain or fear of no movement during surgery. Because of these issues, it is very important to properly monitor patients to prevent them [14,15]. In the past, to predict awareness and anesthetic depth, we used hemodynamic changes, movement, change of respiration and pupil size [15,16]. However, after a muscle relaxant was widely used clinically, it was hard to find such typical symptoms, and to use them to predict the risk of intra-operative awareness and light anesthetic state [15]. Due to such reasons, many devices to monitor intra-operative awareness and anesthetic depth were developed and introduced, and among them, the BIS is known to be very useful to analyze the EEG of cerebral cortex and monitor sedation and unconsciousness of the patients [17-19]. This study used the BIS to monitor the effect of tramadol on the changes in awareness in EEG.

Though intra-operative awareness is problematic, tramadol, which may cause such problems during surgery, has been used to control pain before and after surgery. There have been many studies on tramadol’s advantages, but few on the risk of awareness and a few intermittent studies on the effects of tramadol on EEG during general anesthesia [20-24]. Coetzee et al. reported that in anesthesia using isoflurane and nitrous oxide, tramadol induced dose-dependent activation of EEG, but such change was not enough to induce awareness and there was no movement in skin incision or postoperative recall [11]. Vaughan et al. reported that tramadol changed EEG activity in a dose-dependent manner, but when anesthetic depth using auditory evoked potential (AEP) was measured, it did not antagonize the hypnotic effect of inhalation anesthetics [12]. According to the previous studies, it was confirmed that tramadol did not antagonize the hypnotic effect of inhalation anesthetics but it affected the EEG in a dose-dependent manner. We believe a few factors are associated with this activation. The most peculiar things were the use of low concentration below 1 MAC of inhalation anesthetics and above 50% of N₂O [4,12]. In particular, the fact that British National Formulary do not recommend the use of tramadol under light anesthetic state indicates that tramadol may affect EEG according to concentrations of inhalation anesthetics [4,12,13]. Coetzee et al. administered 200 mg tramadol under stable anesthesia at 0.7 vol% isoflurane and 66% N₂O and Vaughan et al. administered tramadol under anesthesia at 0.6 MAC isoflurane – 50% N₂O [4,12]. These studies reported that tramadol activated EEG when the concentration of inhaled anesthetic was less than 1 MAC, it also decreased the heart rate and increased systolic arterial blood pressure significantly [12]. Cuvas et al. reported that when 100 g of tramadol was administered under general anesthesia with sevoflurane – 50% N₂O, the mean arterial blood pressure increased for the initial 5 minutes and then decreased, and heart rate decreased for 35 minutes, but it did not influence anesthetic depth [25]. However, recently, studies by Fodale et al. reported that 1.5 mg/kg of tramadol used during general anesthesia of 1.5 vol% sevoflurane did not influence BIS values as well as blood pressure and heart rate and reported that it can be safely used for pre-emptive and preventive analgesia [26]. When BIS value was kept between 50–60 in our study, the concentration of desflurane was maintained at less than 1 MAC. We observed that the BIS values did not change except for the early increase of systolic and diastolic blood pressure after tramadol injection in this condition; hence we concluded that it did not influence EEG under inhalation anesthetics below 1 MAC. We assumed that early increase of blood pressure after injection resulted from the enhancement of noradrenaline (NA) and serotonin (5-HT) concentrations by interfering with their reuptake and release mechanisms [10].

N₂O also may have an important influence on EEG activation of tramadol. In an animal study by Roald et al. [27], when N₂O is added to low concentration of isoflurane, it activates EEG, but when air is substituted for N₂O under anesthesia with 1.9 vol% isoflurane [28], the inhibition of EEG increased. Hans et al. reported that N₂O inhibits activity of EEG under 2.0 vol% end-tidal sevoflurane and very harmful stimulus such as endotracheal intubation or skin incision excite sympathetic nerve and increase BIS values, but when N₂O is added, it may decrease [29]. Thus, as diverse effects of N₂O on EEG independent of other inhaled anesthetics may occur, this study used air rather than N₂O and administered the medication before completion of the surgery, with less harmful stimuli, to minimize increase of BIS values from the stimulus.

Finally, the dose of tramadol plays an important role and previous studies reported that the excitatory effect of central nervous system was observed when more than the therapeutic dose was administered [30]. As many previous studies used
100 mg or 200 mg of tramadol rather than doses at an appreciable ratio to the patient’s body weight [4,12,20,25], EEG was activated, but it was not resulted in awareness. As it is thought that higher doses may affect EEG, this study used 1.5 mg/kg and 3.0 mg/kg tramadol, clinically allowed doses, to examine its effect on the BIS and confirmed that it did not influence the BIS values at those doses.

In conclusion, clinical doses of tramadol under general anesthesia using desflurane when BIS is kept below 60, may be safe for intra-operative use for postoperative pain control as it does not cause awareness by changing BIS values, but as it may increase mild systolic and diastolic blood pressure during operation, it is suggested that more serious care should be paid to its use to patients who may have hypertension or a risk of increased blood pressure, and further studies should be developed.

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REFERENCES


