EFFECT OF TRAMADOL ON BISPECTRAL INDEX DURING ANESTHESIA WITH SEVOFLURANE AND N2O

Orıgınal Artıcle

SEVOFLURAN VE N2O İLE UYGULANAN GENEL ANESTEZİ SIRASINDA TRAMADOL'ÜN BİSPEKTRAL İNDEKS ÜZERİNE ETKİSİ

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ABSTRACT

Purpose: This prospective, randomized, double-blind, controlled study was designed to investigate the effects of tramadol on the bispectral index (BIS) during anesthesia with sevoflurane and N2O.

Methods: 60 ASA class 1 and 2 patients, scheduled for elective lumbar microdiscectomy operation under general anesthesia, were included in this study. None of the patients were premedicated; anesthesia was induced with thiopental 5 mg.kg-1 and rocuronium 0,6 mg.kg-1, and maintained with 40% N2O-O2 mixture and sevoflurane. At induction of anesthesia, subjects were randomly allocated into 2 groups to receive either saline (control group), or tramadol 2 mg kg-1 (T group) intravenously. Hemodynamic data and BIS values were then recorded until the completion of the operation, during which time the concentrations of sevoflurane were not modified.

Results: The BIS values were significantly different between groups throughout the operation. No significant changes in the hemodynamics were noted, except mean arterial blood pressure in the T group which was significantly high in the first 5 minutes of entubation.

Conclusıons: There were no patients that has BİS values more than 60 or who presented explicit recall of events under anesthesia. Tramadol didn't seem to cause a problem with respect to depth of anesthesia and can be safely administered perioperatively.

Key Words: *bispectral index; awareness; general anesthesia; sevoflurane; tramadol.*

ÖZET

Amaç: Bu prospektif, randomize, çift-kör, kontrollü çalışmada sevofluran ve N20 ile uygulanan genel anestezi sırasında kullanılan tramadolün bispektral indekse olan etkisi araştırıldı.

Method: Çalışmaya genel anestezi altında mikrodiskektomi operasyonu geçirecek ASA grup 1 ve 2 olan 60 hasta dahil edildi. Hiçbir hastaya premedikasyon uygulanmadı, anestezi indüksiyonu 5 mg kg-1 tiopental ile yapıldı, kas gevşetici olarak rokuronyum uygulandı; idame N2O-O2 ve sevofloran ile sağlandı. İndüksiyonda hastalar rastgele iki gruba ayrıldı: tramadol grubuna (T grup) 2 mg kg-1 tramadol, kontrol grubuna ise serum fizyolojik uygulandı. Hemodinamik ve BİS değerleri operasyon boyunca kayıt edildi, bu sırada sevofluran değerleri değiştirilmedi.

Bulgular: Operasyon boyunca BİS değerleri tramadol grubunda kontrol grubundan farklı bulundu. Hemodinamik parametrelerde önemli değişiklikler gözlenmedi, yalnızca entübasyon sonrası ilk 5 dakikada ortalama arter basıncı T grubunda yüksek seyretti.

Sonuç: Hiçbir hasta intraoperatif olayları hatırladığını belirtmedi ve hiçbirinin BİS değerleri 60'ın üzerinde gözlenmedi. Tramadolün anestezi derinliği açısından sorun yaratmayacağı ve güvenli olarak pre ve intraoperatif olarak uygulanabileceği sonucuna varıldı.

Anahtar kelimeler: *Bispektral indeks; farkındalık; genel anestezi; sevofluran; tramadol.*

INTRODUCTION

Tramadol is a synthetic, centrally acting opioid analgesic with a potent opioid metabolite (1).

It has been frequently used for pain control during administration of inhaled anesthesia as it prevents severe postoperative pain and reduces the demand for opioid analgesic significantly (2-4). Hovewer intraoperative administration of tramadol was reported to cause dose-dependent activation of the electroencephalogram (EEG) during volatile anaesthesia (5). For this reason, it has been suggested that the use of tramadol could increase the risk of awareness (5,6).

Bispectral index (BIS) provides a continuous age-independent monitoring of hypnotic state induced by the most widely used sedative-hypnotic agent and has been used to asess the induction quality, depth of anesthesia, intraopertive requirement of anesthetics, postoperative recovery, and to reduce the intraoperative recall awareness. BIS value of 0 represents an isoelectric electroencephalogram and 100 represents an awake state, whereas 40 to 60 reflect adequate hypnotic effect for general anesthesia (7-9).

Tramadol has a risk of intra-operative awareness but there are limited data on this issue. This study aim to identify the effects of tramadol on the BIS and hemodynamic changes during general inhalational anesthesia using sevoflurane.

METHODS

After obtaining approval from the Institutional Ethics Committee (Date: 11.01.2011 Chairperson: Ahmet Göçmen, MD) and written informed consent, a total of 60 adults, 18 to 65 years ofage, physical status ASA (American Society of Anesthesiologists) I and II, scheduled for an elective single space lumbar disc surgery under general anesthesia were included in this study. All of the surgical procedures were performed by the same surgical team. The demographic data of

the patients and their ASA values were recorded.

Exclusion criteria were history of hearing loss, language or communication difficulties, chronic pain on analgesic medications, allergy to any drugs used in the study, central nervous system diseases, hemodynamic instability, ischemic heart diseases, renal or hepatic failure, therapies with drugs affecting EEG activity, body mass index>35kg m^{-2}. In the preoperative stage, all patients were informed about visual analog scale (VAS) (0=no pain at all to 10=intolerable pain). All enrolled patients were randomly divided into group C (controle), or group T (tramadol) (n=30 in each group) according to SNOSE way (10). At the induction of anesthesia before intratracheal intubation, one of two study solutions was slowly given to patients by the first author of this study according to a randomised, double-blinded and placebo-controlled protocol. The study solutions (C, T) were prepared by hospital pharmacist within two 10 ml syringes, so that C, T syringes contained 10 ml serum physiologic as placebo, 20 mg ml^{-1} tramadol respectively. The syringes were marked only with a coded label to maintain the double-blind nature of the study. Thus, while 30 patients in group-C received 1ml saline per 10 kg, and 30 patients in group-T received 1ml tramadol per 10 kg (2 mg kg^{-1}); these syringes were consecutively used. Injection of these solutions was done within at least 3 min advocated by Radburch et al (11).

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 (SpO_2). 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), BIS values were measured and recorded. After 5 minutes of preoxygenation with 100% O_2, anesthesia was induced with thiopental sodium 5 $mgkg^{-1}$and rocuronium 0,6 $mgkg^{-1}$ was given as muscle relaxant. Manual ventilation was done with sevoflurane 2 vol %, O_2 1,5 L min^{-1}, N_2O 2 L min^{-1}. After 3 minutes larngoscopy was done with Magill laryngoscope blade and trachea was intubated with cuffed polyvinyl chloride tube size 7,5 mm for female and 8,0 mm internal diameter for male. Controlled ventilation was adjusted to maintain normocapnia. Anesthesia was maintaned with 66% nitrous oxide in oxygen and the sevoflurane vaporizer was adjusted to maintain an end-expired sevoflurane concentration of 1,7%. During intraoperative stage, muscle relaxation was maintained with 10 mg rocuronium. In addition, a 2 µg kg^{-1} fentanyl bolus was planned for use in cases when the mean arterial pressure and heart rate rose 20% above basal values. All hemodynamic and BİS variables, $ETCO_2$ (mmHg), SpO_2, were recorded at following time interval: at baseline and 1,3,5,15,30,45,60,90 minutes after intubation; at this time, the concentration of inhaled anesthetics was not adjusted. At the termination of surgery, sevoflurane and N_20 were discontinued and the residual neuromuscular block was reversed and extubation was done when patients were awake and respiration was regular and adequate.

In the recovery area, all patients received 35% oxygen by mask. Pain intensity was assessed by the patient and anesthesist on arrival recovery room and every 15 minutes thereafter using a visual analogue scale. In addition, the presence of nausea and vomiting was recorded and the success of antiemetic therapy noted. Patients who requested additional pain relief were given meperidine 0,5 mg kg^{-1}i.v. Nausea was treated with ondansetron 4 mg i.v. Data were recorded for 90 minutes min in the recovery area or until patients received additional analgesia.

In the postanesthesia care unit just before transfer to the ward, the patients were interviewed using modified Brice interview (12); this aims to evaluate the possible occurrence of awareness.

STATISTICS

For statistical data, we used NCSS (Number Cruncher Statistical System) 2007 & PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) and the results were expressed as mean ± standard deviation. We analyzed sex using chi-square test and age, body mass index using one-way ANOVA. The chance of each variable in each group according to time was analyzed with repeated measures ANOVA and Post-hoc Comparison, Bonterroni was used. We judged statistically significant when $P<0.05$.

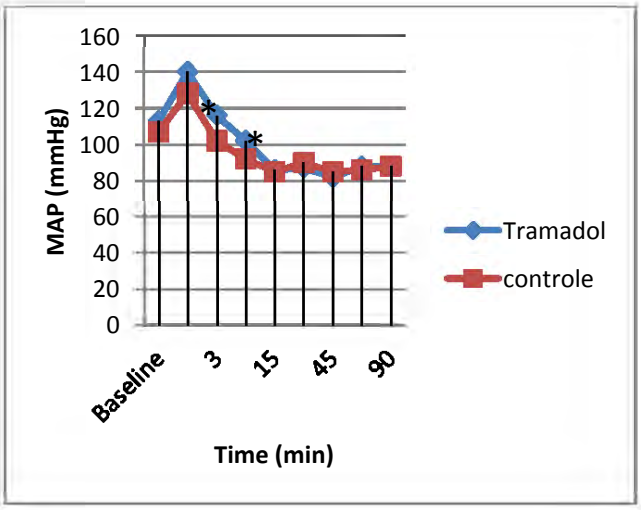
RESULTS

The two groups were similar in relation to age, sex, weight, duration of surgery, and baseline Bispectral Index (**Table 1**).

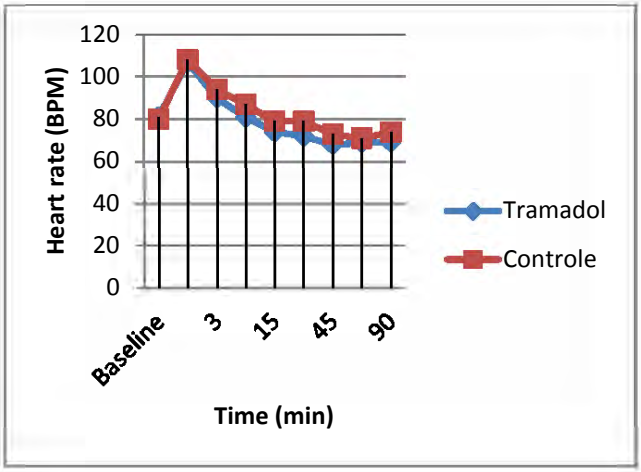
	Controle group	Tramadol group
Patients (number)	30	30
Gender (Male/Female)	18/12	16/14
Age (years)	48±8	46±11
ASA phsical status I/II (n)	14/16	15/15
BMI	28±31	28±3
Duration of surgery (min)	107±22	111±20
Baseline Bispectral index	98±1	97±1

Table-1: *Demographic variables of patients involved in the study, duration of surgery and baseline Bispectral index values.*

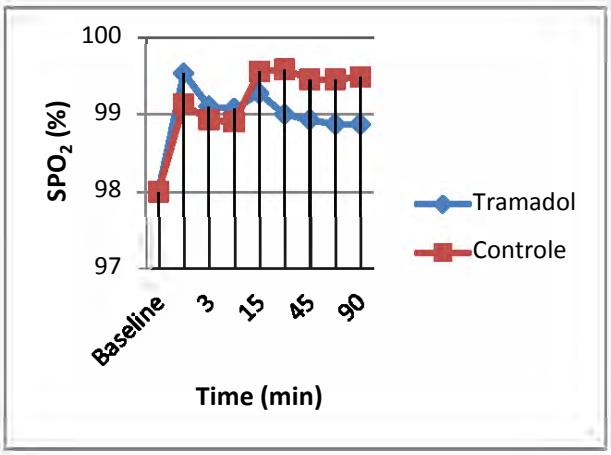
A)



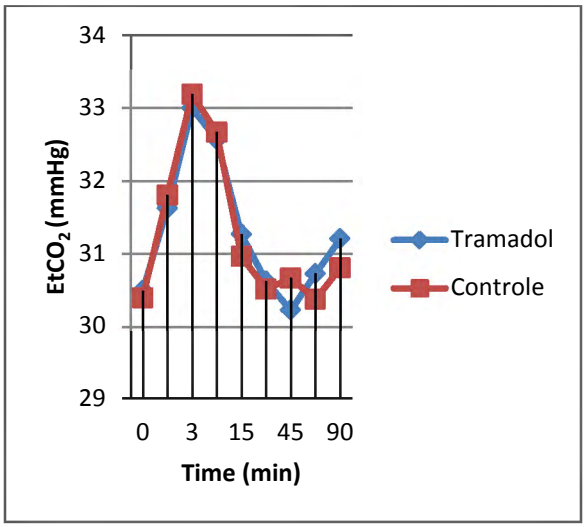
B)



C)



D)



E)

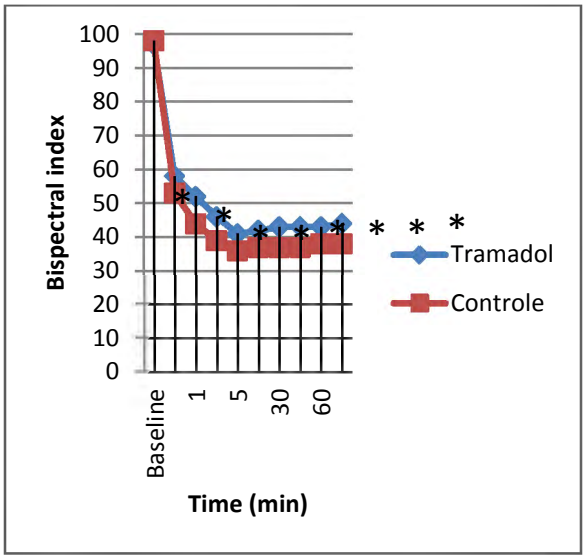


Fig. 1. *Changes of mean arterial blood pressure (A), heart rate (B), SPO2 (C), EtCO2 (D), bispectral index (E) among the two groups. All data are presented as mean ± SD. *p<0,05 **p<0,01 compared to the control group.*

There were no significant changes in SpO2, EtCO2, heart rate. Mean arterial pressure at third and fifth minutes and BIS values throughout the anesthesia were significantly higher in tramadol group compared with the control group. There were no patients in whom BIS values were more than 60 or who presented explicit recall of events under anesthesia, as assessed by the Brice interview in the recovery room (Figure-1) Opioid requirements in the operation and early postoperative period were significantly lower in patients with tramadol group as compared with the control group (p< 0,01). 12 patients (40%) in the tramadol group and 28 patients (93,3%) in the control group required supplementary analgesia in the recovery room (p=0,001). Eight and seven patients suffered nausea and vomiting (N/V) in the tramadol and controle groups, respectively (p=0,76). (**Table 2**)

	Tramadol	Control	P-value
Intraoperative fentanyl need	0 (0%)	4 (12.9 %)	0.038
Postoperative meperidine need	12 (40%)	28 (93.3%)	0.001
PONV	8 (25.8%)	7 (23.1%)	0.766

Table-2: *The analgesic requirement and postoperative N/V incidence.*

DISCUSSION

Tramadol is a central acting opioid agonist widely used in anesthesiology and suitable for preventive analgesia due to its unusual mode of action (1,2,4). Tramadol has lower affinity for the μ-opioid receptor than morphine resulting in analgesic

potency which is 10 times weaker than morphine. However, only 40% of the analgesic effect of tramadol is antagonized by naloxone, pointing to an additional non-opioid mechanism which contributes to tramadol's analgesic activity. This second mechanism is related to the activation of the descending antinociceptive system and consists in both inhibition of the reuptake of noradrenaline, serotonin and an increased release of serotonin. Houmes et al. showed that tramadol seems to be as effective and safe as morphine for treatment of postoperative pain (13). Potential advantages of administering tramadol for postoperative pain relief include long duration of action and limited respiratory depressing effects (13-15). Maximum analgesia occurs 1-2 hours after intravenous administration, therefore tramadol should be given during operation because administration after inhalation anesthesia has been shown to provide inadequate postoperative pain relief (14,16). However, it has been hypothesized that the use of tramadol could increase the risk of awareness during anesthesia (5,6).

Intraoperative 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. Therefore it is very important to monitor depth of anesthesia. ~~to~~ (17,18). In the past, variables used to predict awareness and anesthetic depth, were hemodynamic changes, movement, respiratory effort and pupil size (18,19). However, after a muscle relaxant was widely used clinically, it is hard to evaluate such ~~s~~symptoms along with a muscle relaxant, and to use them to predict the risk of intra-operative awareness and light anesthetic state (18). Due to such reasons, devices to monitor intra-operative awareness and anesthetic depth is developed and introduced into clinical practice. Among them, the BIS is shown to be very useful to analyze the EEG of cerebral cortex, monitor sedation and depth of anesthesia (20-22). This study used the BIS to monitor the effect of tramadol on the changes in awareness in EEG.

Previous studies have speculated on the intraoperative effects of tramadol on EEG activity. Coetze et al. reported that, during anesthesia with isoflurane and nitrous oxide, tramadol caused dose dependent activation of the EEG, but such change was not enough to induce awareness and there was no movement in response to skin incision or no postoperative recall (23). Later, Coetz et al. confirmed that tramadol did not antagonize the hypnotic effect of inhalation anesthetics, but it may cause awareness and EEG activation during anesthesia (6). Vaughan et al. reported that tramadol changed EEG activity in a dose-dependent manner during anesthesia with isoflurane and nitrous oxide (5). However when anesthetic depth was measured by using auditory evoked potential, it does not antagonize the hypnotic effect of inhalation anesthetic (5). Our study results confirm the findings of the previous studies, and show that BIS values were significantly higher in tramadol group troughout the anesthesia period. None of the patients participating in the study had BIS values higher than 60, or explicit recall of events under anesthesia.

Cuvas et al. reported that when 100 mg of tramadol was administered under general anesthesia, the mean arterial pressure increased for the initial 5 minutes and then decreased, and heart rate decreased for 35 minutes, but it did not influence anesthetic depth (24). We observed that mean arterial pressure significantly higher in tramadol group at 3, 5 minutes during the operation. We assumed that early increase of blood pressure was resulted from the enhancement of noradrenalin and serotonin concentration due to interfering with their reuptake and release mechanisms.

Also, the presence of nitrous oxide could play a role in the excitatory property of tramadol. In an animal study, an increase in EEG activity has been shown when nitrous oxide is added to low concentrations of isoflurane (25). Hovewer when air is substituted for nitrous oxide under anesthesia with 1,9 vol% isoflurane, the inhibition of EEG is increased (26).

In conclusion, clinical doses of tramadol under general anesthesia with sevoflurane and nitrous oxide showed no clinically significant effects of depth of anesthesia and can be safely used for perioperative pain control. It may lead to mild increase in systolic and diastolic blood pressures during operation and close monitorization is suggested for patients who have hypertension.

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