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Prediction of Surgical Anesthesia in Medetomidine/Tiletamine/ Zolazepam Anesthetized Dogs using Electroencephalography

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Abstract : Changes of electroencephalogram (EEG), mean arterial blood pressure (MAP) and heart rate under surgical anesthesia were investigated in medetomidine (MED) and tiletamine/zolazepam (ZT)-anesthetized dogs. To determine the level of surgical anesthesia, pedal withdrawal reflex was regularly tested after ZT injection. The first time point without pain response was regarded as the beginning of surgical anesthesia (SSA). After SSA, the first time point showing positive pain response was considered the end of surgical anesthesia (ESA). Comparing the control, an additional significant decrease of δ2 and α2 was observed at SSA. Comparing the control, δ2 was significantly decreased at ESA. Significant reductions of MAP were observed at pre-ESA and ESA. Heart rate significantly decreased in all stages. These results suggest that δ2 band power is a valuable parameter for correlating surgical anesthesia in dogs anesthetized with MED and ZT.

***Key words* :** surgical anesthesia, EEG, medetomidine, tiletamine/zolazepam, dog.

Introduction

The purpose of anesthesia is to allow the execution of surgical practice without recognition of pain, life-threatening problems or eventful recovery. Surgical practice under light anesthesia increases patient movements, which prolongs surgical operations and leads to greater complications.

Vital signs and electroencephalograms (EEG) are often used to evaluate the quality of anesthesia (8,11,12,16). Quantitative EEG analysis is a valuable and sensitive method for assessing brain function in dogs during anesthesia, and comparison of EEG during anesthesia demonstrated that the degree of central nervous depression could be more accurately assessed by EEG patterns during anesthesia than by clinical signs (12,22). During anesthesia, quantitative EEG has been used to predict patient movement and to assess anesthetic depth in various surgical circumstances (1,3,9,10). However, some studies have demonstrated that EEG does not predict movement responses to noxious stimuli (7,18).

Medetomidine (MED) is a selective and potent α_2-agonist that exerts marked sedative and analgesic effects in cats and dogs (15,16,19). MED is commonly used as a pre-anesthetic sedative, and it has been used as the sole agent for diagnostic and manipulative procedures (2,23,24). Zoletil® (ZT) (Virvac, France) is a 1:1 mixture by weight of tiletamine and zolazepam, and is a non-narcotic, non-barbiturate injectable anesthetic and immobilizing agent for intramuscular or intravenous use in dogs (5,6).

The aim of the present study was to determine whether changes of band power, arterial blood pressure or heart rate could predict the level of surgical anesthesia as determined by response to noxious stimuli in MED and ZT-anesthetized dogs.

Materials and Methods

Animals

Seven vaccinated, clinically healthy, adult mongrel dogs (male, 5; female, 2) with a mean weight of 5.26 ± 0.99 kg (mean ± SD) were used. The dogs were individually housed and fed commercial dry pellet food and water *ad libitum*. Food, but not water, was withheld for at least 12 hours before the experiments. The experiments were approved by the Kyungpook National University Institutional Animal Care and Use Committee.

Procedures

Three days before the experiments, an arterial catheter, for recording of arterial blood pressure, was inserted into the right femoral artery and advanced about 5 cm from the insertion site under isoflurane/O_2 anesthesia. The catheter was tunneled subcutaneously to exit on the dorsal surface of the neck, and was

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filled with heparinized normal saline (50 IU/ml). Sites on the head and ears where needle electrodes would be inserted for EEG recording were clipped. The femoral artery catheter was flushed with heparinized normal saline two times a day.

On the day of the experiment, the dogs were acclimatized for at least 3-hours in the experimental room. Then 2% lidocaine was injected subcutaneously at sites on the head (1 ml) and both ears (0.5 ml of each). Five minutes after lidocaine injection, EEG electrodes were inserted and an arterial catheter was connected to a polygraph (Model 7P1, Grass Instrument Co., USA). A recording electrode was placed subcutaneously at Cz, a midpoint between nasion and inion, for use with the International 10-20 system; the electrode was sutured at the scalp with 4-0 nylon to prevent removal. Reference and ground electrodes were inserted subcutaneously in both pinnas and were affixed with surgical tape. Arterial pressure and EEG signals were recorded continuously throughout the experiment. Baseline values of EEG and blood pressure were established for 5 min in a standing or sitting position without drug administration. After baseline measurements, the dogs were medicated with atropine (Atropine sulfate®, Dong-A Pharma Co. Ltd., Korea, 0.04 mg/kg subcutaneously), MED [Domitor®, Orion Pharma, Finland, 30 μg/kg intramuscularly (IM)] and ZT (10 mg/kg IM) at a 10-minute interval. Throughout the study, the dogs were in an electrically-shielded recording box, and a heating pad (fixed at 37°C) was applied after medetomidine administration.

After ZT administration, pedal withdrawal reflex was measured to determine the clinical level of surgical anesthesia. Interdigital regions in the hindlimbs were alternately pinched with mosquito forceps to the first ratchet for 10 seconds at 3, 5, 7, 10, 13, 15, 17, 20, 23, 25, 27, 30, 33, 35, 37, 40, 43, 45, and 47 min from ZT injection. The pedal withdrawal reflex test was stopped if the dog showed a positive response. Positive response was judged by head and body movements, including those of the extremities.

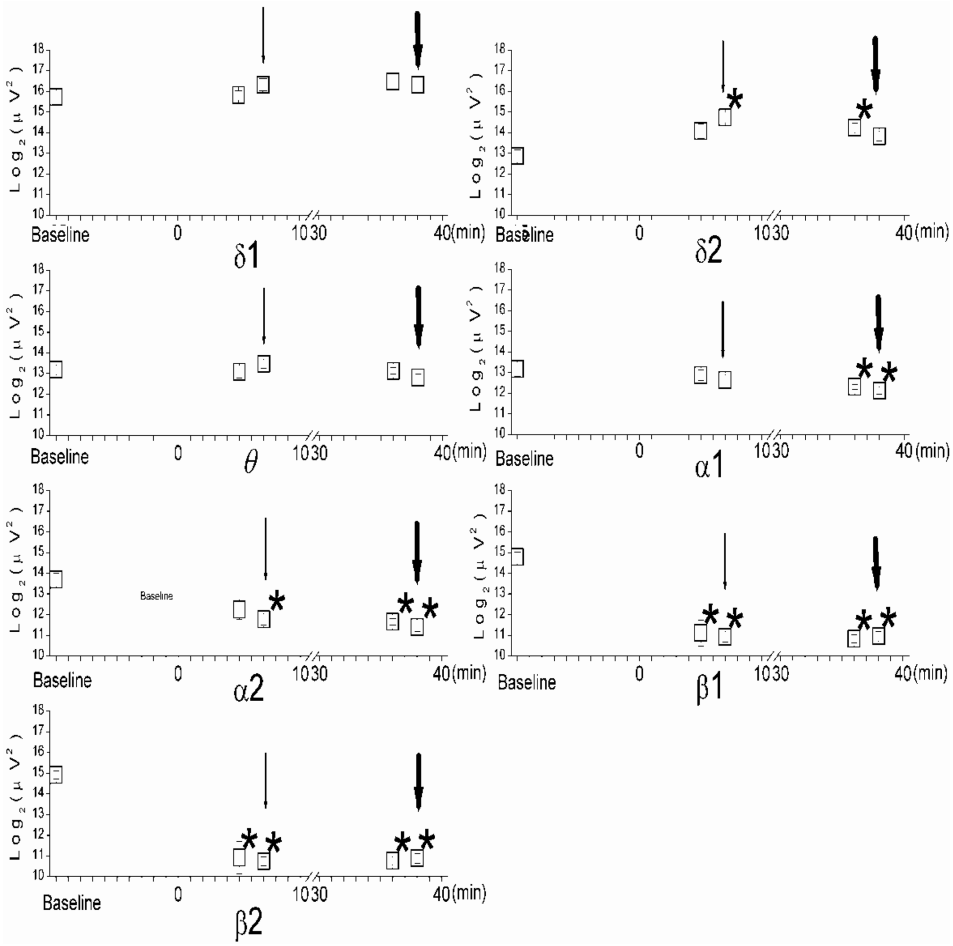

Fig 1. Band powers (mean ± s.d.) at baseline, immediately before starting-point of surgical anesthesia (SSA), at SSA, immediately before end-point of surgical anesthesia (ESA) and at ESA in dogs ($n = 7$) anesthetized with medetomidine (30 μg/kg body weight intramuscularly) and tiletamine/zolazepam (ZT) (10 mg/kg body weight intramuscularly). Surgical anesthesia was judged by lack of response to toe-web clamping. Mean values of SSA (thin arrow) and ESA (thick arrow) from ZT injection at 0 min were 6.86 ± 1.7 and 38.15 ± 6.2 min, respectively. The data were analyzed by one-way ANOVA followed by a Fisher's LSD test. *$p < 0.01$, *vs.* baseline values.

EEG

A one-channel system with platinum subdermal needle electrodes (Grass Instrument Division Astro-Med, Inc., USA) was used. Electrodes were connected to a polygraph (Model 74K, Grass Instrument Co., USA). The signals were amplified × 1,000 and filtered over a range of 1 to 35 Hz. Monopolar EEG measurements were digitalized at a 200-Hz sampling rate by an A/D converting interface (Model MP100ACE, Biopac System, Inc., USA) and simultaneously recorded on a hard disk using a data acquisition program (Acqknowledge 3.5, Biopac System, Inc., USA). In off-line analysis, the raw EEG signal was visually inspected prior to analysis, and any sections with artifacts were removed. Artifact-free 30-second EEG data at baseline (control) and each analysis state were used to quantify the EEG. The 2.5-second epochs (Hanning window and 1.25-second overlap) were converted to power spectra using a fast Fourier transform (FFT) algorithm and then averaged.

Test items

Band power, mean arterial pressure and heart rates were measured immediately before the pedal withdrawal reflex test.

1) Determinations of starting-point (SSA) and end-point of surgical anesthesia (ESA): After ZT injection, the time at loss of the pedal withdrawal response on interdigital pinching was regarded as SSA. The time at which this response returned was considered ESA. Ten-s EEG periods at baseline (control), immediately before SSA, at SSA, immediately before ESA, and at ESA were analyzed.

The absolute power of each band (δ1, 1-2.5 Hz; δ2, 2.5-4.5 Hz; θ, 4.5-7 Hz; α1, 7-10 Hz; α2, 10-14 Hz; β1, 14-22 Hz; and β2, 22-34 Hz) was calculated with an analysis program (Matlab R12 version 6.0).

2) Mean arterial pressure (MAP) was measured in the same periods, and 3-second mean values in each period were calculated.

3) Heart rates were calculated from 15-second arterial pulse wave records from the same time periods.

Statistical analysis

All data were expressed as mean ± SD. The comparisons for statistical significance of band powers, MAP and heart rates between the control and each period were performed in a one-way repeated measures ANOVA followed by a Fisher's LSD test (SPSS 12.0K; Datasolution, Seoul, Korea) was used to identify the differences between the means. Values of $p < 0.01$ were considered significant.

Results

SSA and ESA

Mean times to SSA and ESA from ZT injection were 6.86 ± 1.7 minutes and 38.15 ± 6.2 minutes, respectively.

Band powers

Immediately before SSA, β1 and β2 powers significantly decreased. At SSA, δ2 power increased significantly and the powers of α2, β1 and β2 decreased significantly. Immediately before ESA, the powers of δ2, α1, α2, β1 and β2 changed significantly. At ESA, powers of α1, α2, β1 and β2 decreased significantly (Fig 1).

MAP

Immediately before SSA and at SSA, MAP changes were not significant. Significant reductions were observed both immediately before ESA and at ESA (Fig 2).

Heart rates

Heart rates were significantly decreased in all recording periods (Fig 3).

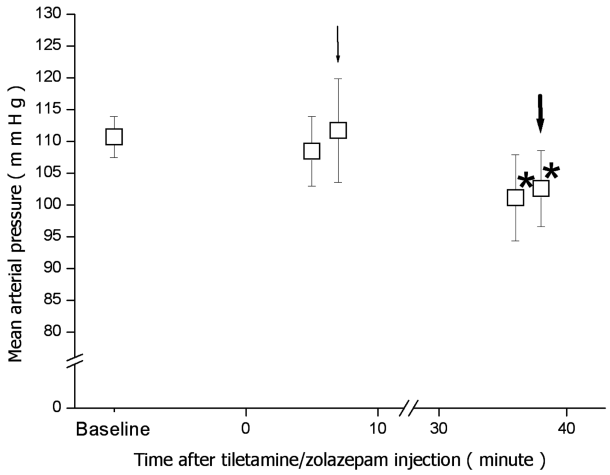

Fig 2. Mean arterial blood pressure (MAP; mean ± s.d.) in dogs ($n = 7$) anesthetized with medetomidine (30 μg/kg body weight intramuscularly) and tiletamine/zolazepam (ZT) (10 mg/kg body weight intramuscularly). See Fig 1 for details.

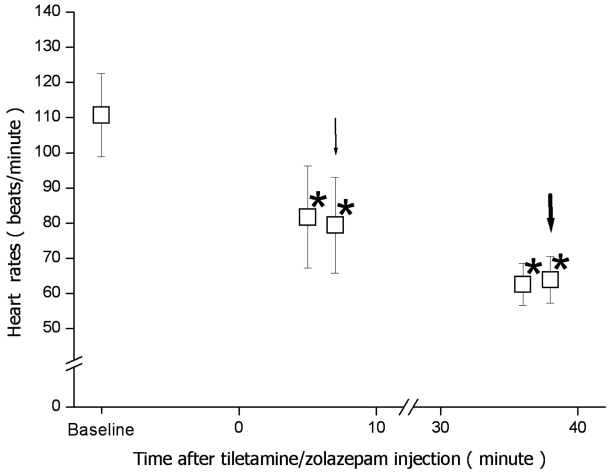

Fig 3. Heart rates (mean ± s.d.) in dogs ($n = 7$) anesthetized with medetomidine (30 μg/kg body weight intramuscularly) and tiletamine/zolazepam (ZT) (10 mg/kg body weight intramuscularly). See Fig 1 for details.

Discussion

The present results demonstrate that only δ2 band power could predict both the beginning and end of surgical anesthesia in dogs anesthetized with medetomidine-tiletamine/zolazepam.

Previous results revealed that no EEG parameter, including spectral edge frequencies (SEF), was a reliable indicator of anesthetic depth, and that EEG changes were only a trend rather than an accurate prediction of anesthetic depth (7,17, 18,21). Schraag and co-workers (21) demonstrated the single EEG parameters, such as SEF and median frequency (MF), were poor indicators for predicting the response of individual patients during total intravenous anesthesia, and combined anesthetic drugs could probably alter the predictive probability. Although Dwyer and co-workers (7) also failed to demonstrate that EEG might distinguish different clinical measures of depth, they wrote that δ-band (< 4 Hz) power or α-band (8-16 Hz) power may be useful in predicting whether subjects retain the ability to respond purposefully to verbal command or to retain verbal information in memory, but that utility is no greater than that provided by measuring the end-tidal concentration of anesthetic. In the present study, we did not apply the spectral edge frequencies or median power. Based on the results mentioned above, however, these EEG parameters might have been unrelated to depth of anesthesia in the present study. In contrast, polypharmacy in the present study could change EEG in different ways and make δ2 band power a reliable indicator for predicting patient movement during MED and ZT anesthesia.

In the present study, various anesthetic drugs as well as atropine were used; all these drugs pass the blood-brain barrier, and, of course, influence EEG changes. Most clinically-applied anesthetic methods are a balanced anesthesia. In the present study, we tried to find an indicator for determining the level of surgical anesthesia in clinically-applied balanced anesthesia, and one anesthetic protocol, which is used routinely in our laboratory, was performed.

Bischoff and co-workers (4) reported that clonidine application in humans resulted in electrophysiological sedation represented by the suppression of a dominant alpha rhythm (8-12 Hz) and increases in slow delta waves (0.5-4 Hz). In addition, there was a relationship between clonidine-related EEG changes (alpha suppression and increases in slow waves) and the observed pain relief. During clonidine application, mean arterial pressure did not change from baseline values during the observation periods. Heart rate was statistically affected, exhibiting a slight initial increase and a slight decrease without clinical effect at the end of the observation period. In the present study, changes in δ2, α1, α2, β1 and β2 bands were significant, and changes in δ2 and α2 bands were related to the induction of surgical anesthesia, but α2 was unrelated to the end of surgical anesthesia. Change in δ2 was closely related to nociceptive response. Loss of response was related to a significant increase in δ2, and regaining of nociceptive response was also related to the disappearance of the significance of δ2. The pedal withdrawal reflex test is very painful, so a positive pain response to this test is regarded as a very early sign of the end of surgical anesthesia. Delta2 band power may therefore be a sensitive parameter to predict surgical anesthesia and movement of the patient in response to surgical pain stimuli.

Previous studies reported limitations of EEG variables to represent the analgesic potency of remifentanil during propofol infusion (8,20). Guignard and co-workers (8) hypothesized that the reason for the unsatisfying indication of analgesic degree by BIS™ in orotracheal intubation was due to components of the analgesic effect mediated in subcortical brain structures and at the level of the spinal cord that cannot be detected by EEG registration from the scalp. But, the present results empirically demonstrate that δ2 was related to the loss of a pain response, which was caused by use of different parameters of band power subdivided into eight bands.

In previous studies, hemodynamic and EEG responses to various noxious surgical stimuli were investigated (3,9,13). Unlike the significant changes in arterial blood pressure, the heart rate response to surgical stimulation was less pronounced and inconsistent, and the reason for the less pronounced heart rate response is unknown (13). Also, heart rate response to noxious stimulus was surmised to be a less specific indicator of adequate surgical anesthesia than arterial blood pressure. Although heart rates in the present study were significantly decreased over recording stages, they were not useful to assess the depth of anesthesia because the variation did not correlate with the level of anesthesia. MAP slightly increased at SSA, but it was not significant. Changes in MAP immediately before ESA and at ESA were significant, so it was not useful for predicting this movement. Thus, the changes of MAP under periodic noxious stimulation were less sensitive to the level of anesthesia.

Various pain stimuli will accompany surgical practices. The present experiment was done under the application of periodic pain stimulation, which might simulate surgical conditions. Changes in EEG and biochemical values in this study might therefore be helpful in evaluating the anesthetic condition of patients during surgery.

In the present study, a subcutaneous electrode was fixed by suturing in order to avoid electrical noises produced by rolling of electrodes due to the neck, eye or ear movements. Additionally, line movements also caused empirical EEG artifacts, mainly within low frequency bands. However, δ1 power was high even in the un-medicated state, which might be caused by eye, palpebrae and head movement. Otto and Short (14) observed a distribution of electrical activity mainly in the δ and β frequency bands and only minor activity in the θ and α frequency ranges during a power spectrum analysis to monitor anesthetic depth with a needle electrode in horses; those were caused by electromyographic artifacts.

In conclusion, the power of δ2 was a valuable parameter for assessing the level of surgical anesthesia in dogs anesthetized with MED and ZT.

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Medetomidine/Tiletamine/Zolazepam 마취견에서 뇌전도를 이용한 외과마취의 평가

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요 약 : Medetomidine (MED)과 tiletamine/zolazepam (ZT)으로 마취한 개에서 외과 마취 상태 하에서의 뇌전도, 혈압 및 심박수 변화를 조사하였다. 외과 마취 수준을 결정하기 위해 ZT 주사 후, pedal withdrawal reflex를 규칙적으로 평가하였다. 통증반응을 보이지 않은 최초 시간은 외과마취 개시기로 결정하였다. 외과마취 개시기 후 처음으로 통증에 양성반응을 보이는 시간을 외과마취 종료기로 하였다. 대조군과 비교할 때 외과마취 개시기에 δ2와 α2의 유의적인 감소가 나타났으며 외과마취 종료기에, δ2의 유의적인 변화가 관찰되었다. 외과마취 종료기 직전과 외과마취 종료기에 혈압이 유의적으로 감소하였다. 심박수는 전실험기간 유의적인 감소를 보였다. 이런 결과로 미루어 δ2 band power는 MED와 ZT로 마취한 개에서 외과마취와 관련된 가치있는 지표로 판단되었다.

주요어 : 외과마취, 뇌전도, medetomidine, tiletamine/zolazepam, 개