J Vet Clin 27(2) : 136-141 (2010)

Journal of Veterinary Clinics
www.ksvc.or.kr

Effects of Pain Stimulation on EEG in Dogs Anesthetized with Medetomidine and Tiletamine/Zolazepam

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(Accepted: April 12, 2010)

Abstract : The aim of this study is to investigate whether medetomidine (MED) and tiletamine/zolazepam (ZT) combination in dogs provide the sufficient analgesia during the period of the stage of surgical anesthesia determined by the response to the noxious stimuli, which were evaluated by the change of electroencephalogram (EEG) and hemodynamic values. Seven clinically healthy, adult beagle dogs were used. They were used repeatedly at interval of a week, according to a randomized design. This study had 2 experimental groups. In Group 1, dogs received 30 μg/kg of medetomidine and 10 mg/kg of tiletamine/zolazepam. Both drugs were administered intramuscularly. In Group 2, dogs were medicated with the same method as in Group 1, except the pedal withdrawal reflex test was done. In Group 2, interdigital regions were grasped with a mosquito forceps for 30 seconds, every 5 min from 10 min to 45 min after ZT injection. During all recording stages, the power for each band, mean arterial pressure and heart rates were calculated. On EEG, no significant changes were observed between groups. Although mean arterial pressure and heart rate were increased 10 min after ZT injection, no significant differences were observed between groups. In conclusion, the MED and ZT anesthesia in dogs are seemed to provide a satisfactory analgesic effect during the period of surgical anesthesia based on EEG with pedal withdrawal reflex test.

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

Introduction

Pain is an unpleasant sensory and emotional experience (perception) associated with actual or potential tissue damage or is described in terms of such damage. Acute pain is the result of a traumatic, surgical, or infectious event that is abrupt in onset and relatively short in duration.

The prevention and control of surgical pain is essential to the practice of anesthesia. A decrease in the patient's intraoperative stress response is beneficial and may be represented by improved hemodynamic stability during the surgical procedure. Improved blood pressure control may decrease intraoperative bleeding that may prolong and complicate surgery.

The changes of hemodynamics, vital signs and electroencephalograms (EEG) were often used to evaluate the condition of anesthesia (3,4,5,6,9,14,15,17). Among them the quantitative EEG analysis has been proven to be a valuable and sensitive method in assessing the brain function in dogs during anesthesia, and comparison of anesthetic depth with EEG recordings during anesthesia demonstrated that the degree of central nervous depression could be more accurately expressed by alteration in the EEG pattern than by clinical signs (15,21).

Medetomidine is a selective and potent α_2-agonist which exerts marked sedative and analgesic effects in laboratory animals, cats and dogs (9,16,17,19,26). It is lipophilic, rapidly eliminated and it possesses more potency and efficacy than other α_2-agonists. Medetomidine is commonly used as a preanesthetic sedative prior to administration of ketamine, barbiturate, or mask induction with an inhalation anesthetic as well as prior to administration of local, regional, or epidural anesthesia (1,22,23,25). It has been used as sole agent for diagnostic and manipulative procedures (23).

Zoletil® (Virbac, France) is a 1:1 mixture by weight of tiletamine and zolazepam and a nonnarcotic, nonbarbiturate injectable anesthetic and immobilizing agent for intramuscular or intravenous use in dogs, cats, other domestic and wild animals (2,14,59).

Surgery in a inadequate anesthesia induce the insufficient muscle relaxation, the increase of the values of vital signs and the patient's movement, which were inhibit the surgical practice and may aggravate the condition of patient. In injectable anesthesia, especially, an inadequate analgesia shortens the duration of anesthesia, which causes the practitioners to administer additional anesthetics. An accurate evaluation of analgesic effect in anesthesia may help to surgical practice.

This study was carried out to investigate whether combination of medetomidine and tiletamine/zolazepam provide the sufficient analgesia during surgical anesthesia which was evaluated with EEG and hemodynamic values to noxious stimuli in dogs.

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Materials and Methods

Animals

Seven clinically healthy, adult beagle dogs of either sex (male: 6, female: 1) with a mean weight of 8.8 ± 1.4 kg (mean ± standard deviation) were used. All dogs were housed individually and fed commercial pelleted food (Biomill®, Woosung Feed Co Ltd., Korea) and water *ad libitum*. They were housed for at least 6 months before the experiment. Food, but not water, was withheld for at least 12 hour before the experiment. Seven beagle dogs were given both treatments at weekly intervals.

Procedures

This study had 2 experimental groups. In Group 1, dogs received 30 μg/kg of medetomidine (Domitor®, Orion Pharma, Finland) (MED) and 10 mg/kg of tiletamine/zolazepam (Zoletil®, Virbac, France) (ZT) at 15-min interval. Both were administered intramuscularly. In Group 2, dogs were medicated with the same manner as Group 1, and the pedal withdrawal reflex test were done. Interdigital regions were grasped with mosquito forceps to first ratchet for 30 sec, every 5 min from 10 min to 45 min after ZT injection.

At least 3 days before the beginning of the experiments, an arterial catheter was inserted into the right femoral artery and forwarded to the aorta about 5 cm under isoflurane/O_2 anesthesia for recording of the arterial blood pressure. The catheter was positiond through the tunnel in the subcutis to exit on the dorsal surface of the neck and filled with heparinized 0.9% saline (50 IU/ml). And the sites whereby needle electrodes would be inserted for EEG recording in the head and ears were clipped.

On the day of the experiment, an acclimation time of at least 3 hour was allowed in the experimental room. Then a 2% lidocaine was injected subcutaneously at the proper sites of the head and both ears. After that, the dogs were caged in a copper case, which was done for shielding electrically. All measurements were accomplished in a copper case. About 10 min after lidocaine injection, the EEG electrodes were inserted and the arterial catheter was connected to a polygraph (Model 7P1, Grass Instrument Co., USA). Arterial pressure and EEG signals were recorded continuously. MED was injected. About 5 min after MED injection, the dog was positioned dorsal recumbency.

Baseline values were established during 10 min before ZT injection. Fifteen min after MED injection, the dogs received ZT.

Electroencephalography

A one-channel system and platinum subdermal needle electrodes (Grass instrument division Astro-Med, Inc., USA) were used. The recording electrode was placed subcutaneously at Cz, which was according to the International 10-20 system. The reference and the ground electrodes were inserted subcutaneously in both ears. The electrodes were connected to a polygraph (Model 74K®, Grass instrument Co., U.S.A). The measured EEG was digitalized by an A/D converting interface at the speed of 200 Hz (Model MP100ACE, Biopac system. Inc., USA) synchronized with the EEG recordings. It was recorded on a hard disk using a data acquisition program (Acqknowledge 3.5, Biopac system, Inc. USA).

Test items

In Group 1, the results at the time of ZT injection and every 5 min from 10 min to 45 min after ZT administration were used for analysis.

In Group 2, the results at the time of ZT injection and the period of receiving pain stimulation were used for analysis.

EEG

Noise-free 30 seconds period of EEG data in each recording stage were used in analysis. During all recording stages, the power for each band(the band 1: 1-2.5 Hz, band 2: 2.5-4.5 Hz, band 3: 4.5-8 Hz, band 4: 8-13 Hz, band 5: 13-20 Hz, band 6: 20-30 Hz, band 7: 30-50 Hz, band 8: 1-50 Hz) was calculated with an analysis program (Matlab R11).

Mean arterial pressure (MAP)

Mean values for 3 sec in each recording stage were calculated.

Heart rates

It was calculated by the records of arterial pulse waves for 15 sec at the same time period of measuring MAP.

Mean arousal time (MAT)

Duration from the time of ZT injection to the time when the dog moved its head was measured.

Statistical analysis

All data were expressed as mean ± standard deviation (SD).

The significant differences between groups were $p < 0.05$ were considered significant.

EEG

The data were analyzed by one-way analysis of variance (ANOVA) and Student's *t*-test

MAP, heart rates and MAT

One-way ANOVA and Fisher's LSD test were used.

Results

In Group 2, no positive pain response to the pedal withdrawal reflex test was observed until 45 min after ZT injection.

EEG

In all recording times, the low frequency bands, bands 1 and 2, had the high powers, but, the high frequency bands, bands 6 and 7, had the low powers. The changes of each band

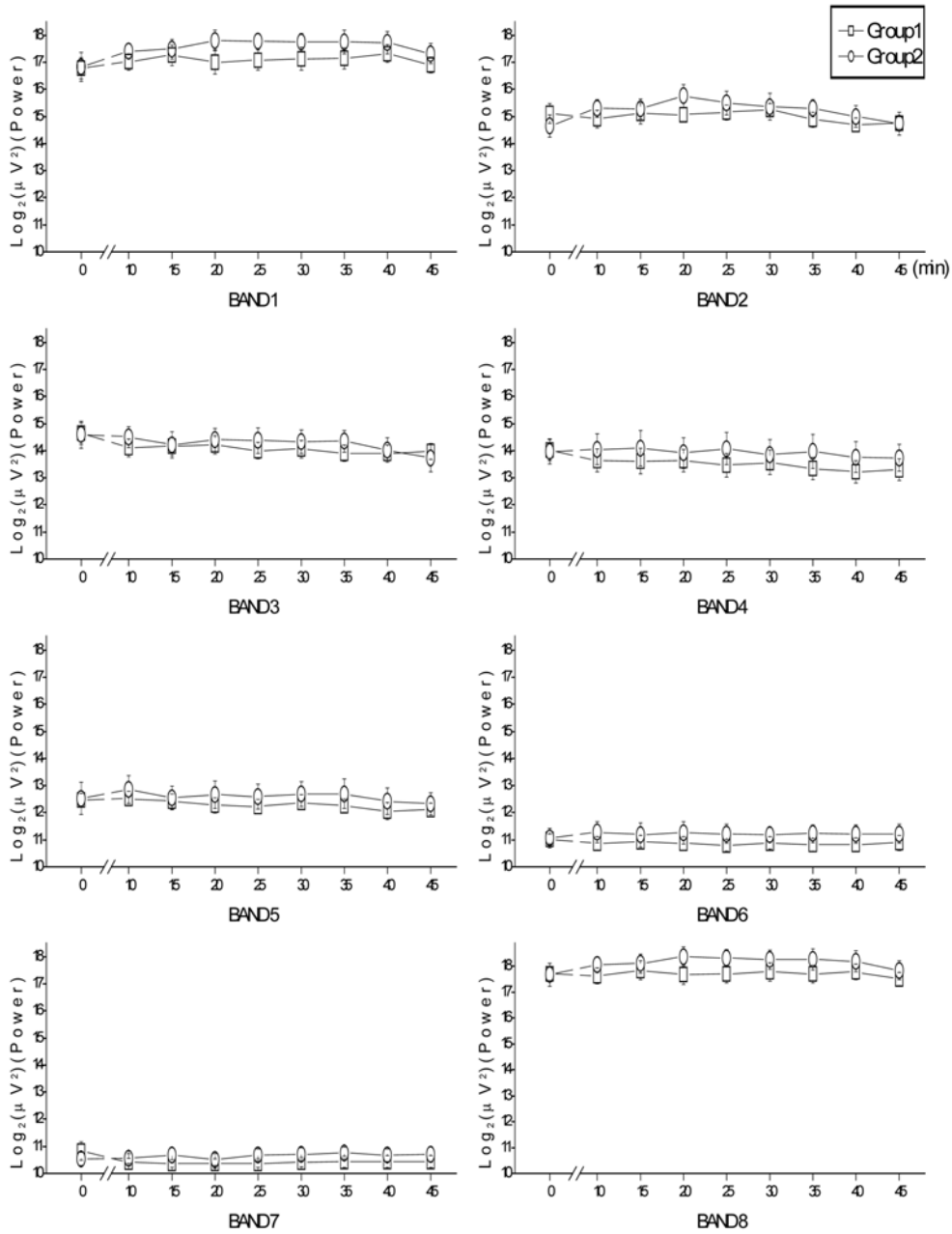

Fig 1. The mean band power versus time in dogs anesthetized with medetomdine (30 μg/kg intramuscularly (IM)) and tiletamine/zolazepam (ZT) (10 mg/kg IM). Dogs in Group 2 received the same drugs as in Group 1, but the pedal withdrawal reflex test was conducted at every 5 min from 10 min to 45 min after ZT injection. 0: ZT injection.

powers were little differences. No significant differences between groups were demonstrated (Fig 1.).

MAP

In both groups, MAPs were increased at 10 min after ZT injection, and then were gradually decreased. But, no significant differences between groups were observed (Fig 2). The differences of values at each recording times after ZT injection were 8.6 ± 9.9, 10.1 ± 12.4, 7.7 ± 10.7, 5.7 ± 9.7, 6.4 ± 11.2, 5.7 ± 11.2, 4.1 ± 5.4 and 2.4 ± 11.9.

Heart rates

In both groups, heart rates were increased at 10 min after ZT injection, then were gradually decreased. But, no significant differences between groups were observed (Fig 3). The differences of values at each recording times after ZT injection were 3.0 ± 4.62, 8.1 ± 8.2, 6.1 ± 9.2, 2.1 ± 4.4, 2.6 ± 3.8, 6.7 ± 9.6, 8.0 ± 9.7 and 7.4 ± 9.6.

MAT

MAT was 84.17 ± 6.79 min in Group 1 and 82.57 ± 5.47 min

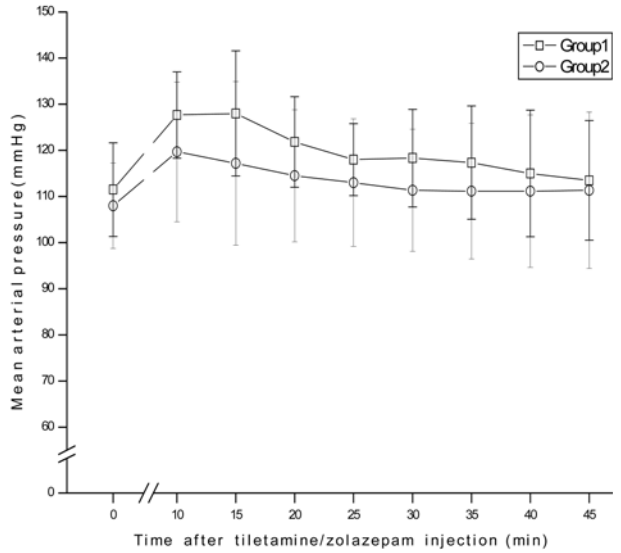

Fig 2. The mean arterial blood pressure versus time in dogs anesthetized with medetomdine (30 μg/kg intramuscularly (IM)) and tiletamine/zolazepam (ZT) (10 mg/kg IM). Dogs in Group 2 received the same drugs as in Group 1, but the pedal withdrawal reflex test was conducted at every 5 min from 10 min to 45 min after ZT injection. 0: ZT injection.

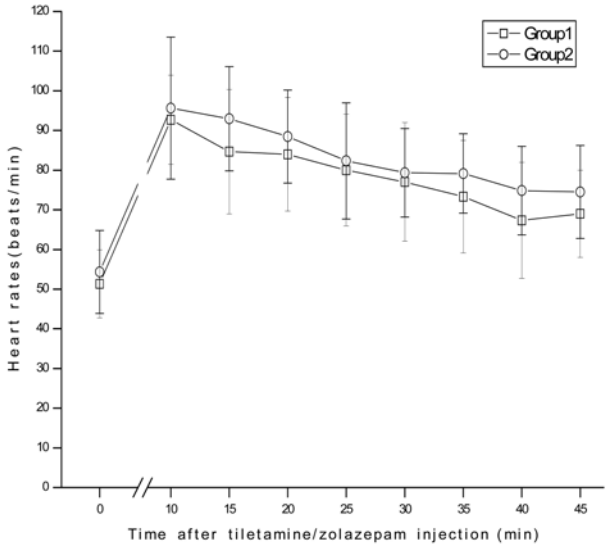

Fig 3. Mean heart rates versus time in dogs anesthetized with medetomdine (30 μg/kg intramuscularly (IM)) and tiletamine/zolazepam (ZT) (10 mg/kg IM). Dogs in Group 2 received the same drugs as in Group 1, but the pedal withdrawal reflex test was conducted at every 5 min from 10 min to 45 min after ZT injection. 0: ZT injection.

in Group 2. In Group 2, MAT was shortened compared with Group 1. But, no significant differences between groups were observed.

Discussion

In this study, the pain stimulation under the surgical anesthesia does not affect the period of anesthesia.

Pedal reflex, limb flexing in response to painful stimulation on the digits or interdigital region are useful guide to assess the depth of anesthesia in dogs (14). In this study, it was applied to painful stimulation. The application period of pedal withdrawal reflex test, from 10 min to 45 min after ZT injection, were decided with previous study (14).

Several reports have shown that surgical stimuli and their analgesic suppression affect EEG during anesthesia. One study reported that surgical stimuli shift the electroencephalographic signals recorded during desflurane anesthesia (20). Hodgson and Liu (8) reported that epidural lidocaine reduced the dose of sevoflurane required to maintain an adequate level of anesthesia as indicated by the Bispectral index (BIS). Guinard *et al.* (6) reported that remifentanil affected the BIS only when a painful stimulus was applied.

In previous study, no changes were observed in electroencephalographic bicoherence after incision when epidural anesthesia was applied before surgery, which indicated that adequate analgesia could block the influence of surgical stimuli on electroencephalographic bicoherence (7). In current study, the results of band powers indicate that the administrations of MED and ZT to dogs provide effective analgesic effect during the period of surgical anesthesia determined by a response to pedal withdrawal reflex test.

Previous study wrote that classical EEG analysis is usually performed in frequency band below 30 Hz, i.e. the delta, theta, alpha and beta bands. An increase of the lower part than the beta band (< 21 Hz) indicates an increasing probability of unresponsiveness, whereas an increase of the higher part than the beta band (> 21 Hz) indicates an increasing probability of awareness. Owing to this oppositional behavior it may be reasonable to split the beta band into two parts when analysing beta-band power (5). In current study, beta band, usually 10-30 Hz, were split two parts; band 5: 13-20 Hz, band 6: 20-30 Hz.

High-frequency bands were used to monitor the depth of anesthesia. The BIS components Beta Ratio and Sync Fast Slow use frequencies up to 47 Hz (18). Beta Ratio incorporates frequencies between 11 and 20 Hz (i.e. mainly beta activity) and between 30 and 47 Hz (i.e. gamma activity). These show that higher-frequency band may be useful for depth of anesthesia monitoring. In current study, the differences of band 5, 6 and 7 between groups were not significant. These were caused by no sensitization the nociception during MED and ZT anesthesia.

Generally, noxious stimuli change the EEG into a pattern with low-voltage and high-frequency components dominating, which results in the incresed high-frequency band power. In some situation, however, high-voltage and slow waves became dominant in the EEG by noxious stimuli. Kiyama and Takeda (11) reported that, during administration of 1.0% isoflurane and 66% nitrous oxide anesthesia, when epidural

anesthesia was not applied, SEF90 significantly decreased and blood pressure increased after incision. In their study, after incision, all patients without epidural anesthesia showed paradoxical arousal accompanied by significantly lower SEF90. Kochs *et al*. (12) reported that, during 1.2% isoflurane with 66% nitrous oxide, noxious stimuli prompted decreased alpha activity in 53% and increased delta activity in 44% of patients. These changes also seem to be paradoxical arousal (3). It was insisted that paradoxical arousal is more likely to be observed when intense noxious stimuli are added during moderate anesthesia (7). In current study, the changes of band 1 and 2 were not significant in all recording stages. When pedal withdrawal reflex test could be regarded as an intense noxious stimuli, MED and ZT combination in dogs is seemed to provide very effective analgesia.

In conclusion, the MED and ZT anesthesia in dogs is seemed to provide a satisfactory analgesic effect during the period of surgical anesthesia determined by pedal withdrawal reflex test.

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Medetomidine과 Tiletamine/Zolazepam을 병용마취한 개에서 통증자극이 뇌파 변화에 미치는 영향

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요 약 : 개에서 Medetomidine (MED)과 tiletamine/zolazepam (ZT) 병용마취시에 통증자극에 대한 반응으로 판단되는 외과적 마취기에 적절한 진통효과가 나타나는지를 확인하기 위해 뇌파를 이용하여 실험을 실시하였다. 임상적으로 건강한 비글견 7두를 이용하여 동일견을 대조군과 통증자극군에 이용하였다, 대조군은 MED 30 μg/kg 투여 후 15분에 ZT 10 mg/kg을 각각 근육주사하였으며, 통증자극군은 대조군과 동일한 방법으로 약물을 투여한 다음 ZT 투여 후 10분부터 45분까지 5분 간격으로 pedal withdrawal reflex test를 실시하였다. 각각의 기록시간대에서 뇌파의 band power, 평균동맥혈압과 심박수를 측정하여 실험군간 비교하였다. 뇌파 기록전극은 International 10-20 system을 이용하여 Cz에, 기준전극과 접지전극은 양쪽 귀에 장착하였다. 뇌파 분석상 저주파 band가 높은 power를 보이고 고주파 band가 낮은 power를 나타냈으나 군간 유의성 있는 차이는 발견할 수 없었다. 평균 동맥혈압과 심박수는 TZ 투여 10분 후 두 군 모두 상승하였으나 군간 유의성은 없었다. 본 실험 결과, 개에서 MED와 ZT 병용마취는 외과적 마취기에 우수한 진통효과를 제공하는 것으로 사료된다.

주요어 : 메데토미딘, 틸레타민/졸라제팜, 뇌파, 진통효과, 개.