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# Effects of Hemorrhage on the Electroencephalograms in Dogs Anesthetized with Ketamine, Propofol and Isoflurane

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**Abstract :** The effect of hemorrhage on the electroencephalogram(EEG) was investigated in fifteen mixed-breed dogs anesthetized with ketamine, propofol and isoflurane. Animals were randomly allocated to three groups (n = 5) by anesthetic agents; group 1 (ketamine 5 mg/kg, IV), group 2 (propofol 156 μg/kg/min, IV) and group 3 (isoflurane 2.0% end-tidal concentration). Medetomidine (40 μg/kg, IM) was used in all dogs as a preanesthetic agent. Recording electrode for EEG was positioned at CZ. EEG, heart rate, systolic/diastolic blood pressure, $pCO_2$, $pO_2$ and blood pH were measured before anesthesia, after anesthesia and after every bleedings. Three bleedings were accomplished by drawing blood through the femoral artery catheter at a rate of 7 ml/kg (10% of total blood volume) for 10 minutes. In the course of hemorrhage, a systolic/diastolic pressure continuously decreased in all groups. The $pCO_2$ values and heart rates were increased in all groups. The $pO_2$ values were most significantly increased in group 1 compared with those in other groups. The pH values were not significantly changed. On statistical analysis of EEG, there was no significant changes in group 1 and 3. But in group 2, band 3, 4 and 7 were significantly altered after 2nd and 3rd bleeding. Power alterations of band 3, 4 and 7 were thought to be related with hemorrhage over 20% of total blood volume in group 2. In conclusion, the regulation of infusion rate would be considered when a dog, anesthetized with propofol, bleed over 20% of total blood volume.

***Key words*** **:** hemorrhage, electroencephalogram, ketamine, propofol, isoflurane, dogs.

## Introduction

Hypovolemia or hemorrhage can increase morbidity and mortality rate associated with anesthesia in veterinary patients (23). Hemorrhage has been the subject of many investigations, most using one of the standard "shock" model (15,30), in which experimental animal were bled or maintained at a predetermined arterial blood pressure. Some investigations had used graded or measured hemorrhage in variety animals, such as dogs (1,23,34), rats (6,30) and pigs (8,15,21,33). Previous researchers have investigated how blood loss influences the pharmacologic aspects of several anesthetics, including opioids (8), sedative hypnotics (33), benzodiazepines (1) and inhalants (23,30). Their studies had demonstrated that blood loss alter the pharmacology of common anesthetic agents such that equivalent doing leads to higher drug concentrations in the setting of severe blood loss when compared with normovolemic, normotensive conditions. These findings are consistent with the clinical practice of reducing the dose of intravenous anesthetics for patients who have significant blood loss before or during surgery (15).

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In veterinary medicine, capillary refill time, heart rate, hematocrit value and blood pressure were used for assessment of a blood loss volume. But those values were not changed regularly according to the hemorrhagic volume. The one of sensitive organs to bleeding is the brain, which could induce a hypovolemic reflex of the central nervous system (CNS). Electroencephalogram (EEG) analysis is one of the most effective non-invasive methods for assessment a conditions of the brain. As the main site of action of sedative or anesthetic drugs is the CNS, there have been many studies on the relationship between anesthetic agents and EEG assessing level of sedation or anesthesia because of drug-specific alterations of EEG (5,13,25,27,31). Recently, computerized quantitative EEG analysis has been used to monitor the adequacy of anesthesia in both human (31) and veterinary medicine (25).

There were a few studies on the relationship between bleeding and EEG in anesthetized animals, being bled to and maintained at a predetermined arterial blood pressure or measured hemorrhage (5,6,23). Only one study was found to put a graded hemorrhage to pigs (21). Therefore, the purpose of the present study is to investigate the effects of graded hemorrhage on the EEG in dogs anesthetized with ketamine, propofol and isoflurane.

## Materials and Methods

### Animals

Fifteen healthy adult, mixed-breed dogs of either sex, weighing from 2.0 to 4.3 (3.2 ± 0.79 kg) were used in this study. They were fed a commercial dry food (Biomill®, Woosung Feed Co. Ltd., Korea) and free access to water. Food was withheld for 12 hours before anesthesia from all dogs. Fifteen dogs were randomly divided into 3 groups (n = 5, respectively) by anesthetic agent. Group 1 was anesthetized by ketamine (5 mg/kg, iv, Yuhan Ketamine 50 inj.®, Yuhan Co., Korea), group 2 was anesthetized by propofol (2 mg/kg, iv, followed by 156 μg/kg/min, iv infusion, Anepol inj.®, Hana Pharm. Co. Ltd., Korea) and group 3 was anesthetized by 2.0% end-tidal concentration of isoflurane (Choongwae Foran soln®., Choongwae Pharm. Co. Ltd., Korea).

### Procedure

Two days before the experiment, a catheter was inserted into the femoral artery for blood pressure measurement and collection of blood sample for arterial blood gas analysis and inducing bleed. A catheter was filled with heparine (Choongwae Heparine inj.®, Choongwae Pharm Co., Korea) diluted with saline per 50 iu/ml. A dog received an intravenous bolus dose of heparine (70 iu/kg) just before the experiment preventing blood coagulation during bleeding (14). The sites whereby needle electrodes would be inserted for electroencephalographic recording in the head and ears were clipped, then 2% lidocaine was injected subcutaneously at the site. The site of electrodes in head was CZ (the mid between inion and nasion). After that, the dog was caged in a copper cage with electrical sheilding. All dogs were given atropine (0.01 mg/kg, sc, Atropine Sulfate Inj.®, Dai Han Pharm. Co. Ltd., Korea) and

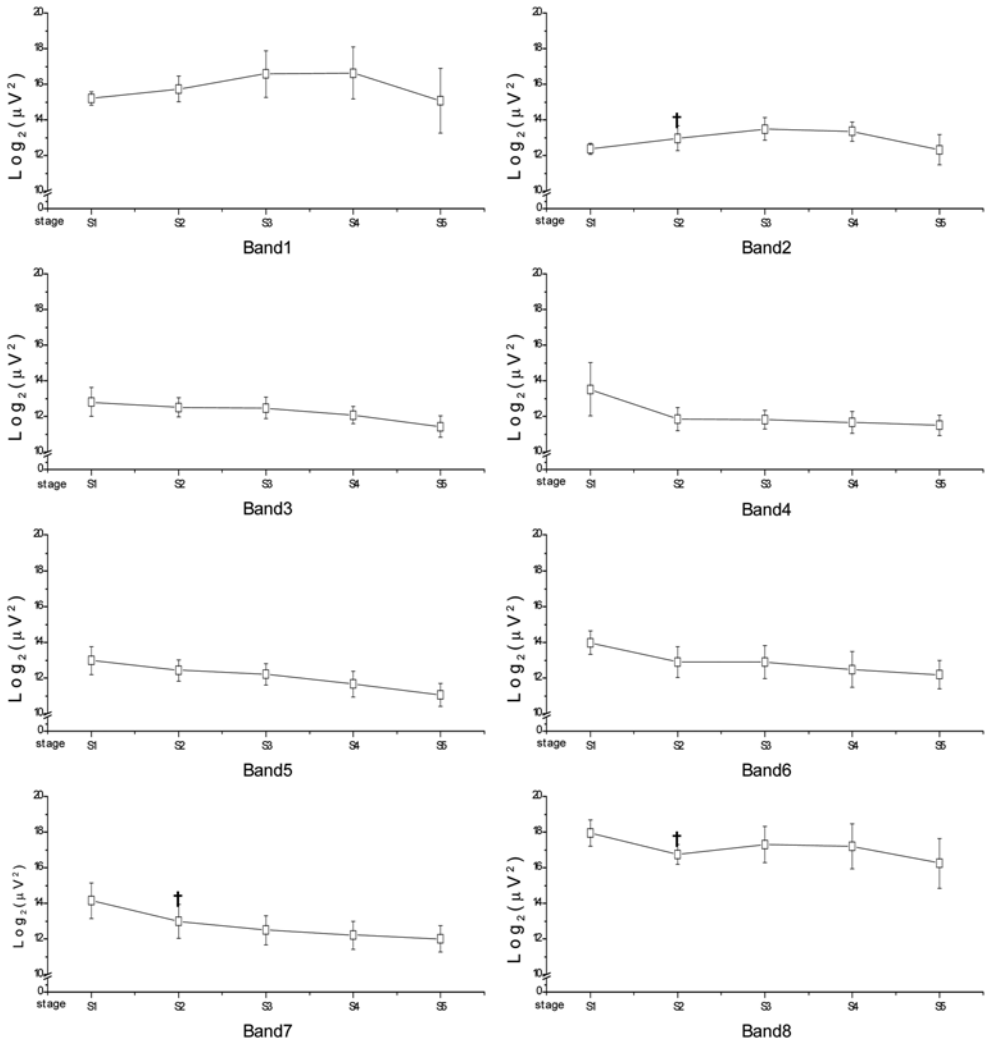


**Fig 1.** Mean band powers in dogs anesthetized with ketamine.
S1 : pre anesthesia, S2 : post anesthesia, S3 : after 1st bleeding (10% reduction of total blood volume as the result of bleeding), S4 : after 2rd bleeding (20% reduction of total blood volume as the result of bleeding), S5 : after 3rd bleeding (30% reduction of total blood volume as the result of bleeding)
†Significant changes between S1 and S2 mean band powers ($p < 0.05$).
*Significant changes between S2 and S3 and S4 and S5 mean band powers ($p < 0.05$).

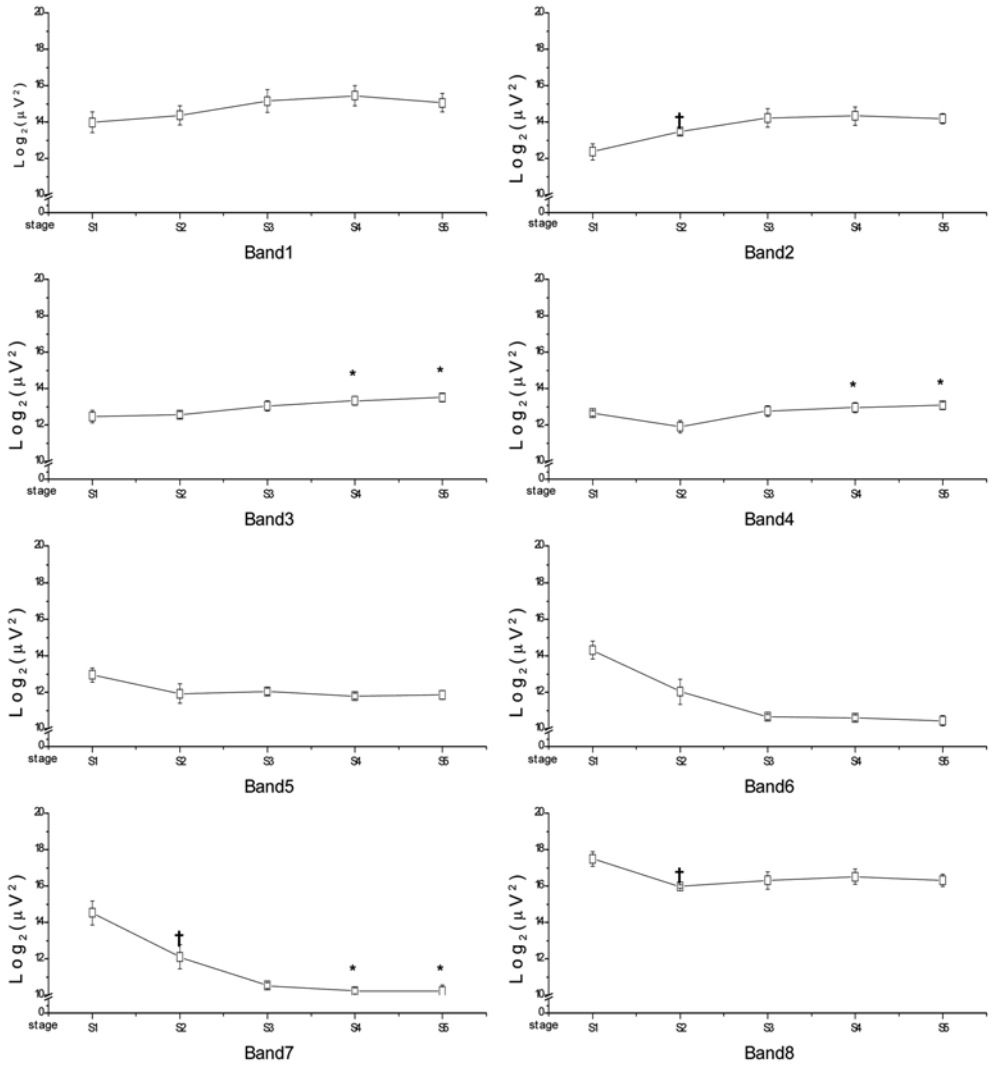


**Fig 2.** Mean band powers in dogs anesthetized with propofol. Keys see for Fig. 1.

medetomidine (40 μg/kg, im, Domitor®, Orion Pharm., Finland). Ten minutes after medetomidine injection, three groups were given anesthetics, ketamine, propofol and isoflurane respectively.

This experiment was divided into 5 stages (S1; pre anesthesia, S2; post anesthesia, S3; first hemorrhage, S4; second hemorrhage, S5; third hemorrhage). Each stage made up 15 minutes and consisted of an operation period (first 10 minutes) and a measurement period (last 5 minutes).

Bleeding was induced by drawing blood through the femoral artery catheter over an operation period of S3, S4 and S5 stage. Each hemorrhage volume was 10% of total blood volume (70 ml/kg) (34).

### Measurement items

#### EEG

A one channel system and platinum subdermal needle electrodes (Grass instrument division Astro-Med, Inc., USA) were used. The recording electrode was placed subcutaneous 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., USA). The measured EEG was digitalized by an A/D converting interface (Model MP100ACE, Biopac system. Inc., USA) synchronized with the EEG recording, which was accomplished at the speed of 200 Hz. It was recorded on a hard disk using a data acquisition program (Acqknowledge 3.5, Biopac system Inc., USA). The EEG was continuously recorded for whole experiment.

#### pH, $pO_2$ and $pCO_2$

During a measurement period of each stages, arterial blood sample collected through a femoral artery catheter. pH, $pO_2$ and $pCO_2$ were measured by an blood gas analyzer (i-STAT®1 Analyzer MN300, i-STAT Co. Ltd., USA).

#### Heart rate and systolic/diastolic pressure

Heart rate and systolic/diastolic pressure were measured by

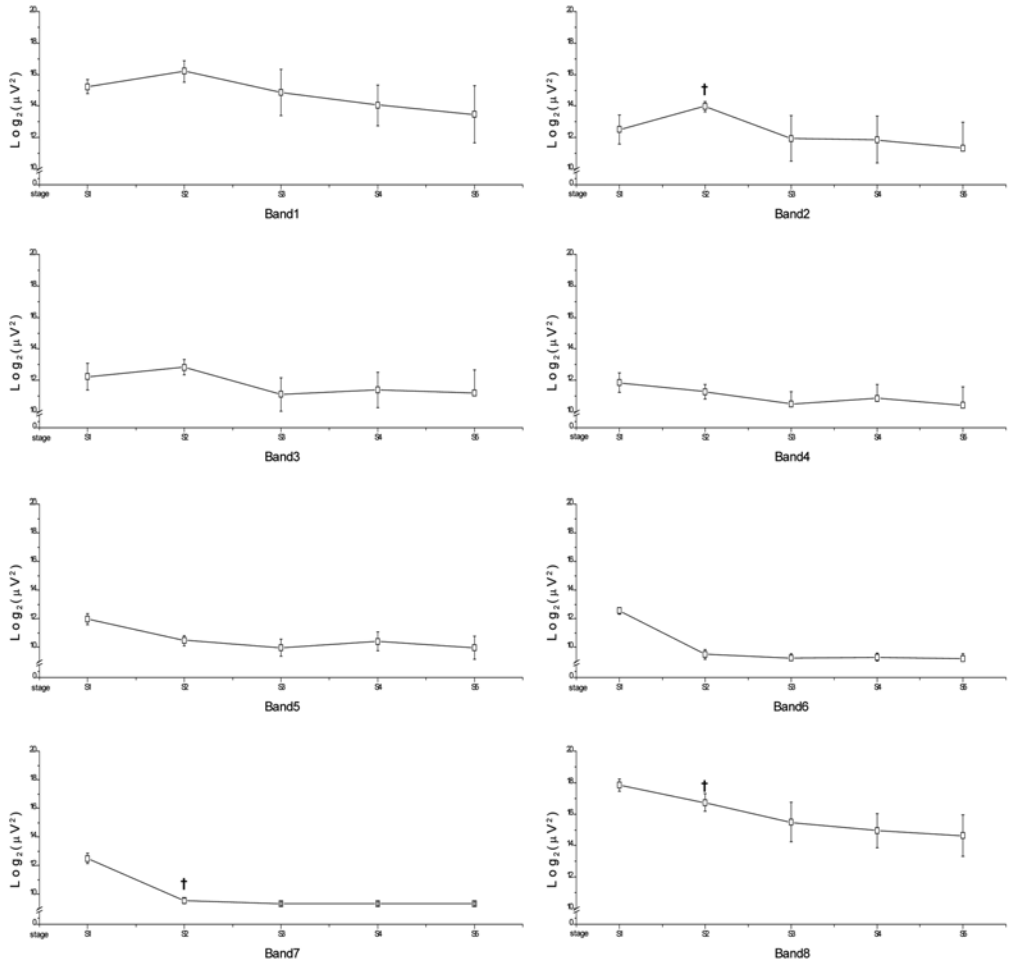


**Fig 3.** Mean band powers in dogs anesthetized with isoflurane. Keys see for Fig. 1.

a polygraph (Model 7P3, Grass instrument Co. USA). Heart rate was recorded at the speed of 100 mm/min. Systolic/diastolic pressure were measured through a femoral artery catheter.

Data analysis

A noise free 1 minute period for each stage of EEG data was used in statistical analysis. All data were analyzed by one-way analysis of student's t-test. The power of EEG bands (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) were calculated with analysis program (Matlab R11 version 6.0, The Mathwork Inc., USA). Significant differences were $p < 0.05$.

## Results

### EEG analysis

After anesthesia, there wer significant changes on the increase of band 2 and decrease of band 7 and 8 in all groups. In the course of hemorrhage, there was no significant alteration in group 1 (Fig 1) and 3 (Fig 3). In group 2, there were significant increase of band 3 and 4, and decrease of band 7 after S4 and S5 in comparison with those after S2 (Fig 2).

### Changes of pH, $pO_2$ and $pCO_2$

There was no significant alteration in the pH value (group 1; from 7.39 ± 0.02 to 7.35 ± 0.05, group 2; from 7.32 ± 0.01 to 7.33 ± 0.04, group 3; from 7.32 ± 0.08 to 7.08 ± 0.14). The $pO_2$ value was significantly increased at least more than once after bleeding. In group 1, the $pO_2$ value was increased after S5 (from 61.5 ± 3.14 mmHg to 81.5 ± 3.64 mmHg). In group 2, the $pO_2$ value was increased after S4 (from 84.0 ± 0.84 mmHg to 85.0 ± 2.23 mmHg) and after S5 (to 89.75 mmHg ± 3.64 mmHg). In group 3, the $pO_2$ value was increased after bleeding (S2; 514.2 ± 8.57 mmHg, S3; 628.2 ± 2.26 mmHg, S4; 633.7 ± 1.30 mmHg, S5; 546.0 ± 2.02 mmHg). The $pCO_2$ value was significantly increased (group 1; from 28.86 ± 1.06 mmHg to 27.43 mmHg, group 2; from 31.60 ± 1.30 mmHg to 33.07 ± 1.89 mmHg, group 3; from 64.90 ± 2.94 mmHg to 59.12 ± 7.68 mmHg) after bleeding in all groups (Table 1).

### Changes of heart rate and systolic/diastolic pressure

The heart rate was significantly decreased after anesthesia in all groups (group 1; from 140.00 ± 3.82 beat/min to 105.00 ± 5.73 beat/min, group 2; from 124.00 ± 32.80 beat/min to 52.00 ± 4.83 beat/min, group 3; from 120.00 ± 7.15 beat/min to 80.00

**Table 1.** Values of blood gas analysis pre- and post anesthesia and after bleeding

| | | S1 | S2 | S3 | S4 | S5 |
|---|---|---|---|---|---|---|
| pH | Group 1 | 7.39 ± 0.02 | 7.37 ± 0.04 | 7.355 ± 0.02 | 7.35 ± 0.02 | 7.35 ± 0.05 |
| | Group 2 | 7.32 ± 0.01 | 7.36 ± 0.02 | 7.34 ± 0.02 | 7.33 ± 0.02 | 7.33 ± 0.04 |
| | Group 3 | 7.32 ± 0.08 | 7.24 ± 0.05 | 7.16 ± 0.07 | 7.2 ± 0.04 | 7.08 ± 0.14 |
| $pO_2$ | Group 1 | 78.52 ± 2.25 | 61.50 ± 3.14 | 70.50 ± 3.94 | 77.00 ± 3.72 | 81.50 ± 3.64* |
| | Group 2 | 87.00 ± 0.85 | 84.00 ± 0.84 | 84.5 ± 2.43 | 85.00 ± 2.23* | 89.75 ± 1.81* |
| | Group 3 | 89.25 ± 0.77 | 514.20 ± 8.57 | 628.20 ± 2.26* | 633.70 ± 1.30* | 546.00 ± 2.02 |
| $pCO_2$ | Group 1 | 27.40 ± 11.53 | 29.23 ± 2.27 | 28.86 ± 1.06* | 28.66 ± 1.29* | 27.43 ± 0.98* |
| | Group 2 | 25.20 ± 1.53 | 23.52 ± 2.28 | 31.60 ± 1.30* | 32.70 ± 1.39* | 33.07 ± 1.89* |
| | Group 3 | 26.70 ± 1.56 | 39.47 ± 1.76 | 64.90 ± 2.94* | 58.35 ± 2.05* | 59.12 ± 7.68* |

pH : arterial blood pH
$pO_2$ : partial pressure of oxygen in arterial blood (mmHg)
$pCO_2$ : partial pressure of $CO_2$ in arterial blood (mmHg).
Values are means ± SE of five dogs. *Significant changes ($p < 0.05$) compared between S2 and after bleeding (S3, S4 and S5).

**Table 2.** Values of blood pressure pre- and post anesthesia and after bleeding

| | | S1 | S2 | S3 | S4 | S5 |
|---|---|---|---|---|---|---|
| HR | Group 1 | 140.00 ± 3.82 | 105.00 ± 5.73† | 85.00 ± 5.33 | 80.00 ± 2.69 | 90.00 ± 4.13 |
| | Group 2 | 124.00 ± 32.80 | 52.00 ± 4.83† | 52.00 ± 4.83 | 68.00 ± 2.59* | 80.00 ± 3.16* |
| | Group 3 | 120.00 ± 7.15 | 80.00 ± 4.38† | 80.00 ± 4.38 | 80.00 ± 4.18 | 93.30 ± 2.34* |
| SP | Group 1 | 137.57 ± 2.35 | 148.35 ± 4.01 | 120.50 ± 4.05 | 110.97 ± 1.99* | 103.70 ± 3.58* |
| | Group 2 | 159.02 ± 5.90 | 129.60 ± 3.21† | 114.45 ± 2.63 | 106.94 ± 3.87* | 99.70 ± 3.71* |
| | Group 3 | 156.76 ± 3.25 | 158.10 ± 2.49 | 107.86 ± 0.04 | 86.43 ± 1.99* | 86.66 ± 2.65* |
| DP | Group 1 | 97.93 ± 3.46 | 112.60 ± 4.27 | 99.16 ± 3.05* | 82.62 ± 2.95* | 78.1 ± 4.70* |
| | Group 2 | 106.94 ± 6.09 | 71.26 ± 1.67† | 69.21 ± 2.28 | 68.16 ± 2.79 | 66.70 ± 4.07 |
| | Group 3 | 115.6 ± 3.27 | 120.85 ± 2.05 | 74.20 ± 2.67* | 72.83 ± 6.37* | 62.66 ± 2.90* |

HR : heart rate (beat/min)
SP : systolic blood pressure of artery (mmHg)
DP : diastolic blood pressure of artery (mmHg)
†Significant changes between S1 and S2 in heart beat rates ($p < 0.05$).
*Significant changes ($p < 0.05$) compared between S2 and after bleeding (S3, S4 and S5)

± 4.38 beat/min). There was no significant alteration in group 1 during S3, S4 and S5 (S3; 85.00 ± 5.33 beat/min, S4; 80.00 ± 2.69 beat/min, S5; 90.00 ± 4.13 beat/min). In group 2, the heart rate was significantly decreased (from 52.0 ± 4.83 beat/min to 68.0 ± 2.59 beat/min) after S4. In group 2 and 3, the heart rate was significantly decreased (group 2; from 52.0 ± 4.83 beat/min to 80.0 ± 3.16 beat/min, group 3; from 80.0 ± 4.38 beat/min to 93.3 ± 2.34 beat/min) after S5.

The systolic pressure was significantly decreased (from 159.02 ± 5.90 mmHg to 129.60 ± 3.21 mmHg) after anesthesia in group 2. Systolic pressure was significantly decreased in all groups (group 1; from 120.50 ± 4.05 mmHg to 110.97 ± 1.99 mmHg, group 2; from 114.45 ± 2.63 mmHg to 106.94 ± 3.87 mmHg, group 3; from 107.86 ± 0.04 mmHg to 86.43 ± 1.99 mmHg) after S4. The diastolic pressure was significantly decreased (from 106.94 ± 6.09 mmHg to 71.26 ± 1.67 mmHg) in group 2 after anesthesia. In group 1 and 3, the diastolic pressures was continuously decreased significantly (group 1; from 99.16 ± 3.05 mmHg to 78.10 ± 4.70 mmHg, group 3; from 74.20 ± 2.67 mmHg to 62.66 ± 2.90 mmHg) after S3. There was no significant alteration in group 2 (Table 2).

## Discussion

The purpose of this study is to investigate the effects of hemorrhage on the EEG in dogs anesthetized with ketamine, propofol and isoflurane. As a result of hemorrhage, 30% of total blood volume was removed in anesthetized dogs. Removal of 30% of the estimated blood volume is considered as moderate hypovolemia and reduction of more 30% without fluid infusion could induce a circulatory collapse in animals (17). This hemorrhage model was described by Weiskopf *et al* (34). This study's anesthesia regimens were previously reported (19,20,32). In comparison of awakening and anesthesia, the alterations of hemodynamics and EEG were similar to previous reports (10,14,19,20,32). Apnea and cyanosis (24) had not been observed in this study during induction of anesthesia with propofol. In ketamine anesthesia, the additional injec-

tion of ketamine was done once on average in 35 to 40 minutes after induction of anesthesia.

The influence of blood loss on the pharmacologic and hemodynamic properties of several anesthetics has been reported by many previous studies (1,4-6,8,11,12,15,18). Those reports have demonstrated that blood loss resulted in a decrease of central compartment volume, central compartment clearance, or both. And hemorrhage leads to a pathophysiological change. Pathophysiological change during hemorrhage might alter the effects of analgesic or anesthetic agents by influencing the pharmacokinetics. These pharmacokinetics changes account for the difference observed in hemorrhagic and normovolemic animals (1,6,8,15,21,23,30,33,34).

On statistical analysis of EEG there was no significant change in group 1 and 3. Some band powers in group 2 were significantly altered. Those alterations were the increase of band 3 and 4 and the decrease of band 7. As previously stated, the blood loss influenced pharmacologic properties of variety anesthetics. These pharmacokinetic changes often account for the large difference observed in blood concentrations after equivalent dosing in hemorrhagic and normovolemic animals. In study on the influence of blood loss on the pharmacokinetics and pharmacodynamics of propofol, de Paepe *et al* (5,6) have demonstrated that moderate blood loss (18 ml/kg) results in a decrease in central compartment clearance and volume and an increase in end-organ sensitivity in the rat. These pharmacologic changes required a 2.5 fold reduction in dose via continuous infusion to achieve the same drug effect. Johnson *et al* (15) have also demonstrated that hemorrhagic shock shift the concentration-effect relation to the left, in a study investigating the influence of more severe hemorrhage (30 ml/kg) on the pharmacokinetics and pharmacodynamics of propofol in which a 2.7 fold decrease in the effect site concentration was required to achieve 50% of maximal effect in the electroencephalogram. In inhalant anesthesia, hemorrhage should influence the uptake and distribution of anesthetics. Anesthetic uptake itself is the product of three factor: solubility, cardiac output and the difference in the alveolar and venous partial pressures (29). Among these three factors, hemorrhage clearly decreased cardiac output, and a reduce passage of blood through the lungs is expected to decrease uptake and increase the alveolar concentration. de Paepe *et al* (5) have illustrated that the blood concentration was not changed under bleeding in a bolus intravenous injection of etomidate. According to previous explain, it seems likely that a hemorrhage did not influence on the blood concentration in a bolus intravenous injection of ketamine and inhalant anesthesia of isoflurane. The relation between the change of EEG and the concentration of anesthetics in blood was examined by Dutta *et al* (7) and Jang *et al* (14). In accordance with above whole explains, the cause of the alteration of EEG is hemorrhage, over 20% of total blood volume in dogs anesthetized with propofol infusion, especially a significant alteration of band 3, 4 and 7.

In spite of hemorrhage, the pH value has not been changed significantly in all groups. Accordong to the previous reports (5,6), the pH value was well maintained in the hemorrhage animals as the decrease in $HCO_3^-$ was compensated by a decrease in $CO_2$ partial pressure caused by hyperventilation, resulting in an increase of $O_2$ partial pressure. In this study, respiratory rate was not measured. The $pO_2$ value was similar to the study of Weiskopf *et al* (34) and Ko *et al* (20), which explained that $pO_2$ value increased, in general, during bleeding. The $pO_2$ value was increased remarkably in group 3 after anesthesia. We thought that the reason was $O_2$-supply through a endotracheal tube for inhalant anesthesia. The $pCO_2$ value was higher in group 3 than in group 1 and 2. According to Weiskopf *et al* (34), the cause of this result was the increase of total body oxygen consumption in inhalant anesthesia.

There were various opinions of heart rate alteration during bleeding (3,9,10,26,28). Cunningham *et al* (3) asserted that heart rate response to hemorrhage was somewhat variable. they found that, when heart rate was initially below 100 beats per minute, it increases in response to hemorrhage; that when it was initially 150 beats per minute or more, it tended to decrease in response to hemorrhage. Additionally, Skinner *et al* (28) described that the change of heart rate appeared as non-liner change in hemorrhage. According to them the reason of that change was the autonomic nervous system self organization to change a physiologic function that will lead to survival. And Haskin *et al* (9) found that heart rate was not increased in spite of hemorrhage in ketamine-anesthetized dogs. In group 1, heart rate was not changed significantly, being similar to that in the study of Cunningham *et al* (3). In group 2 and 3, they were increased significantly during bleeding, being similar to those in reports by Robert *et al* (26) and Horan *et al* (10).

According to previous reports, the mean arterial pressure was decreased in propofol and isoflurane anesthetized dogs (9,22), it was, however, increased or not changed in ketamine anesthetized dog (9,22). In our study, the systolic/diastolic pressures of all groups were continuously decreased during hemorrhage. Such differences between group 1 and previous report (9) might be due to the differences in species and/or experimental protocol.

As shown in this study, the significant change of EEG was observed only in propofol infusion anesthesia. It was supposed that power alterations of band 3, 4 and 7 were related with hemorrhage over 20% of total blood volume in dogs anesthetized with propofol infusion. In conclusion, the regulation of infusion rate would be considered when a dog, anesthetized with propofol, bleed over 20% of total blood volume.

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# 출혈이 Ketamine, Propofol, Isoflurane 마취견의 뇌파에 미치는 영향

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**요 약** : 잡종견 15마리를 이용하여 ketamine, propofol 및 isoflurane 마취견에서 실험적 출혈이 뇌파에 미치는 영향을 평가하였다. 실험견은 마취제의 종류에 따라 군당 5마리씩, 3개 실험군으로 분류하였다 (1군: ketamine 5 mg/kg, IV, 2군: propofol 156 μg/kg/min, IV, 3군: 2.0% end-tidal concentration of isoflurane). 모든 군에 전마취제로 Medetomidine (40 μg/kg, IM)을 투여하였다. 뇌파기록전극은 Cz 위치에서 피하에 장착하였다. 뇌파, 심박수, 수축기/이완기 동맥혈압, $pO_2$, $pCO_2$ 및 혈액 pH를 마취 전, 마취 후, 매 출혈 후에 각각 측정하였다. 대퇴동맥에 삽관한 카테타를 통해 총 혈액량의 10%인 7 ml/kg을 10분동안 출혈시켰으며, 총 3회 실시하였다. 출혈기동안 수축기 및 이완기 동맥혈압은 모든 군에서 지속적으로 감소하였다. $pCO_2$ 농도와 심박수는 모든 군에서 증가하였다. $pO_2$ 농도는 다른 군과 비교하여 1군에서 가장 유의적으로 증가하였다. 혈액 pH의 유의적인 변화는 없었다. 뇌파 분석결과 1군과 3군에서는 유의적인 변화는 없었다. 2군의 band 3, 4 및 7은 2번째 및 3번째 출혈 후에 유의성있게 변화하였다. 이와 같은 변화는 propofol 점적 유지마취에서 총 혈액량의 20% 이상 출혈과 관계되는 것으로 사료된다. 따라서, Propofol 마취견이 총 혈액량의 20% 이상 출혈할 경우 propofol 점적 투여율의 조절이 고려되어야 한다.

**주요어** : 출혈, 뇌전도, ketamine, propofol, isoflurane, 개.