치의학석사 학위논문

Changes in Information Processing in Propofol-Induced Deep Sedation in Volunteers Using Electroencephalography

뇌파를 이용한 자원자에서 Propofol으로 유도된 깊은 진정상태에서 정보자극 처리의 변화에 관한 연구

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ABSTRACT

Changes in Information Processing in Propofol-Induced Deep Sedation in Volunteers Using Electroencephalography

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We analyzed the effects of deep sedation with propofol on long latency components of the auditory event-related potential (ERP) in 20 normal volunteers (aged 26-30yr).

ERP was elected though auditory passive odd pall paradigm in both the arousal and the sedative states for each volunteer. Electroencephalography (EEG) was recorded from 32 electrodes placed in the standard 10-20 International placement. To simulate the auditory passive odd ball paradigm, two different computer-generated auditory tones, an inter-stimulus of standard stimuli (p=0.8, n=400, 1000Hz) and a target oddball stimuli (p=0.2, n=100, 1200Hz) was presented via earphone. Sedative state was induced by intravenous propofol injection with a target controlled infusion syringe pump utilizing the Schnider model. Initial propofol concentration was 2.5 mg.kg-1. Propofol concentration was adjusted to maintain the bispectral index (BIS) value around 60.

Acquired EEG data were categorized according to arousal and sedative state. Each epoched signals were averaged to individual ERPs. Two-dimensional topographic map was generated to visualize the differences. Channels within the regions showing statistically significant differences were selected for further analysis in temporal changes.

In our study, we were able to verify a specific peak potential in the range of 320-360-ms, and 360-400-ms latency This peak signifies P300, an ERP component often elicited during simple discrimination tasks. P300 were especially evident in frontal and parietal areas. P300 signals showed statistically significant decrease after sedation. We conclude that P300 amplitude was profoundly affected by propofol given in sedative concentrations.

Keywords: Consciousness; Electroencephalography; Event-related potential; Propofol; Sedation

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I. Introduction

Drug induced sedation is an effective adjunctive measure for dental treatment, especially for patients with high anxiety. Currently, most of the sedative procedures in the field of dentistry are done as a form of minimal or moderate sedation (hereafter conscious sedation)(Peden, Cook et al. 2014). However, conscious sedation has a rather unpredictable sedative efficiency, showing high variance between patients. As an alternative, deep sedation has been suggested as an sedative measure for dental practice(Fukayama 1995). Unlike conscious sedation, deep sedation wields several risks such as inadequate airway patency and ventilation(McIntosh and Mierzwinski-Urban 2017). Thus, it is mostly utilized in hospital-based dental setting where trained specialists are available for emergency care. Recently, the application of deep sedation for dental procedures is increasing.

Deep sedation is described by American Society of Anesthesiologists(ASA) as a 'drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully to repeated or painful stimulation(Anesthesiologists 2004). Sedation is a continuum, and thus deep sedation can be understood as a borderline state between sedation and general anesthesia. Understanding the mechanism of deep sedation could help in better understanding the process of loss and recovery of consciousness. However, while the effects of anesthetic drugs upon cognitive function during perioperative periods are quietly well established(Mason, Noel-Storr et al. 2010),

only a few studies exist regarding the changes in cognitive function during deep sedation.

Oddball paradigm is an experimental method commonly used in studies utilizing event-related potentials(ERPs)(Patel and Azzam 2005). This method presents random sequences of two distinct stimuli; one standard stimulus is frequently repeated and the other target stimulus is infrequent and deviant, hence given its name 'oddball. Subjects could be asked to respond to the deviant signal (active oddball task), or to be uninvolved in the response process, only to record the changes in brain activities (passive oddball task)(Marshall, Mölle et al. 1996). In either case, subjects are required to utilize cognitive function. This elicits specific type of ERP. P300 is one of the best documented ERP of this kind, elicited after a certain time period (approximately 300-400 ms) following the introduction of a stimulus(Squires, Squires et al. 1975). P300 is thought to be activated as a result of attention-dependent cognitive task. Therefore, changes in the P300 is expected to reflect changes in the level of consciousness and attention(Sokhadze, Casanova et al. 2017). In fact, Reinsel et al have previously documented changes in P300 during propofol induced conscious sedation, suggesting that this could reflect cognitive impairment during the sedative state(Reinsel, Veselis et al. 1995).

In the present study, we analyzed the changes in ERP, most notably P300, in an auditory passive oddball paradigm in propofol induced deep sedation. We aimed to investigate how cortical and cognitive activity is altered in a borderline state between sedation

and anesthesia. We have used propofol as a sedative agent for the following reasons: (1) It is a commonly used sedative agent for deep sedation. (2) Due to its properties such as fast recovery and high patient compliance, use of propofol in dental anesthesia is of rising interest(Yokoe, Hanamoto et al. 2015). (3) Propofol is suspected to work on $GABA_A$ receptors(Maldifassi, Baur et al. 2016). Because many anesthetic agents tend to target $GABA_A$ receptors, results produced by propofol acting on this receptor can be expected to reflect the sedative process induced by other medications as well.

II. Material and Methods

II-1 Volunteer recruitment

Twenty volunteers (10 females and 10 males) ranged from 20 to 40 years old were recruited. Each volunteer were provided with informed consent. Experimental methods were approved by the institutional review board (IRB No. CME17001) prior to conducting experiments on volunteers. Volunteers who had significant medical diseases and laboratory abnormalities were excluded from the study. Each volunteer were instructed to fast for at least 8 hours before the experiment.

II-2 EEG acquisition

EEG cap was selected to match the head circumference of each volunteer. After seating the EEG cap, 32 electrodes in the standard 10-20 International placement were placed. (Fp1, AF3, F7, F3, FC1, FC5, T7, C3, CP1, CP5, P7, P3, Pz, PO3, O1, Oz, O2, PO4, P4, P8, CP6, CP2, C4, T8, FC6, FC2, F4, F8, AF4, Fp2, Fz, Cz). One additional electromyography (EMG) channel was placed on the right outer canthus to remove muscle artifacts. EEG was recorded referenced to the average EEG while keeping impedances at all electrodes below 5 kU. EEG was sampled using custom-made software, at a sampling rate of 2048 Hz. The data were downsampled at 128 Hz with 60-Hz notch filter. To evaluate sedation depth objectively, a bispectral index (BIS) sensor was also applied to the forehead and measured during EEG acquisition.

II-3 Auditory passive oddball paradigm.

EEG recording was performed on each subject under computer generated auditory stimuli. Two different auditory tone sequences were randomly delivered through earphones; A 1000 Hz standard tone and a 1200 Hz infrequent distractor tone. The ratio of standard tone (p=0.8, n=400) to distractor tone (p=0.2, n=100) was 4. The auditory stimulation time of each tone was 50 ms, with a rise and fall time of 10 ms. The time interval between each tone was 800 ms The auditory oddball task consisted of a mixture of 500 tones.

II-4 Propofol administration

Sedative state was induced by intravenous propofol administration with a target controlled infusion syringe pump utilizing the Schnider model. Initial effect site concentration of propofol was 2.5 mcg/ml. Effect site propofol concentrations were changed to maintain the BIS value around 60. During propofol infusion, a nasal cannula with oxygen concentration of 100% was administered to the subjects. Cuff blood pressure, electrocardiogram, pulse-oximetry, and capnography were monitored under a supervision of anesthesiologist. We instructed the volunteer to keep their eyes closed during the entire experiment; we defined loss of consciousness as loss of response to a verbal request to raise the index finger. After performing the oddball task, we stopped the administration of propofol infusion. Recovery of consciousness after discontinuing propofol administration was evaluated as a positive response to raise the index finger upon the verbal request. EEG was continuously recorded until volunteer gained full consciousness. This was also evaluated by checking the BIS value, and a positive response to the question "Do you feel the same compared to first sitting on the dental chair before sedation"

II-5 EEG preprocessing and statistical analysis

Through Matlab 2017b (MathWorks, Natick, MA, USA), detrend

function was used to remove each channel's linear trend in the acquired EEG signals. Detrended signals were filtered with a bandpass filter between 1 Hz and 30 Hz. The bandpassed EEG signals were then collected with epoch from −100 to 800 ms from sound onset. Next, starting 100 ms prior to onset stimulus, the continuous signal with a 800−ms time−window onset was epoched. The average amplitude in each epoch's 100−ms window prior to stimulus onset was subtracted for baseline correction of each epoch. To exclude artifacts such as EMG or ECG, each epoched signal was manually inspected by the researchers. For each participant, all epoched signals were averaged to obtain ERPs.

The two−dimensional topographic map of a scalp data field was generated with 40 ms window to average out each channels voltage in awake and sedation states. Each channel's ratio which had statistical significance in all moments were plotted using the topoplot function in EEGLAB (Swartz Center for Computational Neuroscience, UC San Diego, La Jolla, CA, USA). The maximum and minimum EEG voltages between 250 and 500 ms from stimulus onset were obtained as P300's peak of each channel.

II−6 Statistical analysis

The time between the awake and sedation states, the peak voltage between each state, the peak voltage and the voltage at that time of another condition (such as the sedation voltage at awake peak time) were compared using the paired T test. In all statistical analyses, a P value less than 0.05 was considered statistically

significant. The signal' s plot with the statistically significant window was plotted with a green window in each channel, in order to illustrate the signals of each channel.

III. Result

III-1. Topographic distributions of ERP

Topographic distribution of ERP amplitude in both 320-360-ms and 360-400-ms latency range are illustrated in Figure 1 and 2, respectively. Strong positive-going ERPs were observed in the arousal 320-360-ms and 360-400-ms latency range in response to both standard and target stimuli (Figure 1(a) and Figure 2(a)). The peak amplitude of the ERPs observed in 320-360-ms latency was mainly distributed in the central area, whereas in 360-400-ms latency, it was mainly visible in the parietal area. Figure 1(b) and Figure 2(b) shows a marked reduction of ERP amplitude in sedative states. P-value distribution in Figure 1(c) and Figure 2(c) signifies the statistically different ERP amplitude region between the awake and sedative states. Theses result suggest a spatio-temporal change in eliciting ERP response; ERPs were mainly elicited in the central(fronto-parietal) area with both the standard and target stimuli in 320-360-ms latency, whereas parietal distribution was evident in 360-400-ms latency.

III-2. Temporal changes of ERP in channel views

Based on the above results, electrodes, Fc1, Fc2, C3, Cz, from central and parietal region were selected to observe the temporal changes in ERP. The results are depicted through Figure 3 and Figure 4. Figure 3(a) shows the average time-domain graphs of ERPs measured with the Fc1 electrode. Positive-going ERPs were observed in the latency range of 300-400 ms. ERP amplitude was greater under target stimuli than standard stimuli. These ERP characteristics confirmed that P300 was elicited by the target stimuli in the auditory oddball paradigm. Figure 3(b), 4(a), 4(b) shows the average time-domain graphs of ERPs measured within Fc2, C3, C4 electrodes, respectively. P300 detected with each electrode showed similar tendency as the P300 detected in the Fc1 electrode. The P300 amplitude detected within all selected electrodes showed statistically significant decrease in the sedation state compared to the awake state ($P<0.001$).

IV. Discussion

In this study, we showed that the amplitude of P300 decreased significantly in the deep sedation state induced by propofol compared to the awake state. Our finding suggests that depressed responses to auditory stimuli during propofol deep sedation may be caused by disturbances of auditory information processing.

It has been reported that the loss of hearing sense is the last during anesthesia induction and the first to be recovered during recovery from anesthesia(Jones and Konieczko 1986). Therefore, auditory evoked potential (AEP) is a research area of interest as a potential marker of anesthetic depth. Propofol have been widely used as general anesthetics in clinical practice. Also, since it is easy to titrate pharmacologic effects with various propofol pharmaco-pharmacodynamic models, researches are also underway to study AEPs related to anesthetic depth.

Several researches have shown that propofol affect auditory evoked potentials. Propofol abolishes N1 component as well as mismatch negativity (MMN) regarded as an automatic response to auditory input changes as the concentration increases(Heinke, Kenntner et al. 2004). Propofol substantially depress middle latency components(Chassard, Colson et al. 1989, Thornton, Konieczko et al. 1989) with little effect on brain stem components(Savoia, Esposito et al. 1988, Chassard, Colson et al. 1989). These suggest that propofol may have a significant effect on auditory information processing

The "oddball" stimulus paradigm, one of selective attention task, elicits long latency evoked potentials. We applied a standard tone (1000 Hz) and deviant auditory stimuli (1200Hz) in a random fashion using oddball paradigm. It is known that oddball paradigm give rise to P300 in the ERP(Picton 1992). According to context updating theory, if the incoming stimulus differs from the previous stimulus, the brain updates the context underlying the processing of sensory information with different features. P300 is thought to

represent information processing. Indeed, the positive relationship between P300 and attentional task such as recall of specific stimuli is observed(Fabiani, Karis et al. 1986). Therefore, the P300 can be disturbed in a variety of situations that affect consciousness level.

In agreement with our expectation, P300 is profoundly affected by sedative drugs. Also, propofol in sedative concentration predominantly affect P300 amplitude (Reinsel, Veselis et al. 1995). Therefore, previous studies suggest that P300 may be used as an indicator of impaired consciousness. In a study investigating the effect of propofol on P300, the infusion rate of propofol remained low to maintain conscious sedation state. Also, there was a large difference between the standard (1000 Hz) and the deviant tones (2500 Hz). Therefore, it was easy to distinguish them from the standard tone.

In this study, we investigated how P300 is affected under deep sedation rather than conscious sedation, unlike previous study. To the best our knowledge, this is the first study to investigate the effect of propofol on P300 utilizing oddball paradig in deep sedation, strictly titrated with target controlled infusion . We focused on deep sedation, since deep sedation, like general anesthesia, is unconscious and thus it is difficult to phenomenologically distinguish between the two states.. Also, we made it difficult to distinguish the standard and the deviant tone from each other. Thus, a significant reduction in the amplitude of P300 during propofol induced deep sedation means difficulty in distinguishing between similar auditory sounds, which are easily discriminable ther in the awake state.

During propofol administration, we maintained constant sedation level using target controlled infusion. Until now, target controlled infusion is the only drug delivery technique that keep pharmacologic effects stable (Schnider, Minto et al. 2016). If propofol is administered at a constant infusion rate, the effect of propofol increase or decrease with continued infusion. Therefore, when oddball paradigm was applied to the volunteers, it can be assumed that the degree of sedation was maintained within the stable range across the subjects.

Consistent with previous results, we have shown that P300 is also reduced under deep sedation by propofol. This suggests that propofol impairs auditory information processing as the depth of sedation level changes. The response impairment to verbal stimuli in deep sedation can be explained by the disturbance of auditory information processing, which is evidenced by a decrease of P300 amplitude.

It is interesting to note that changes in P300 during deep sedation generally predominate in the frontal and parietal area. Unlike previous studies, we observed ERP changes in the whole brain areas (the frontal, temporal, parietal, and occipital areas) with a 32 channel EEG. The P300 amplitude tended to decrease in frontal and parietal areas. Such decrease was not consistent in temporal and occipital areas,

When a rare stimulus comes to the brain, the frontal area is activated to gather attentional resources to distinguish these stimuli from standard stimuli. Then, the parietal area activates to facilitate access to memory storage and memory update(Naghavi, Nyberg et

al. 2005). In this regard, propofol at a concentration of inducing deep sedation could impair attentional engagement to new stimuli coming into the brain. Interestingly, we have shown that changes in fronto-parietal connectivity are an important component of propofol induced sedation(Kim, Kim et al. 2017) Given that propofol at a concentration of inducing sedation impair fronto-parietal communication, depressed fronto-parietal connections by propofol administration may also disturb auditory information processing, as seen in the present study.

However, we had some limitations in this study. This study focused to investigate changes in P300 in deep sedation. However, this change may be different as sedation level changes. Also, we did not measure the patient's responses to deviant stimuli such as pushing a button. Therefore, it is impossible to measure task-relevant ERPs in the present study. Further study is needed to clarify this issue.

In conclusion, we have shown that P300 amplitude was significantly decreased in propofol deep sedation. Our findings suggest that propofol at concentrations that cause deep sedation profoundly interfere with auditory information processing.

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Figure Index

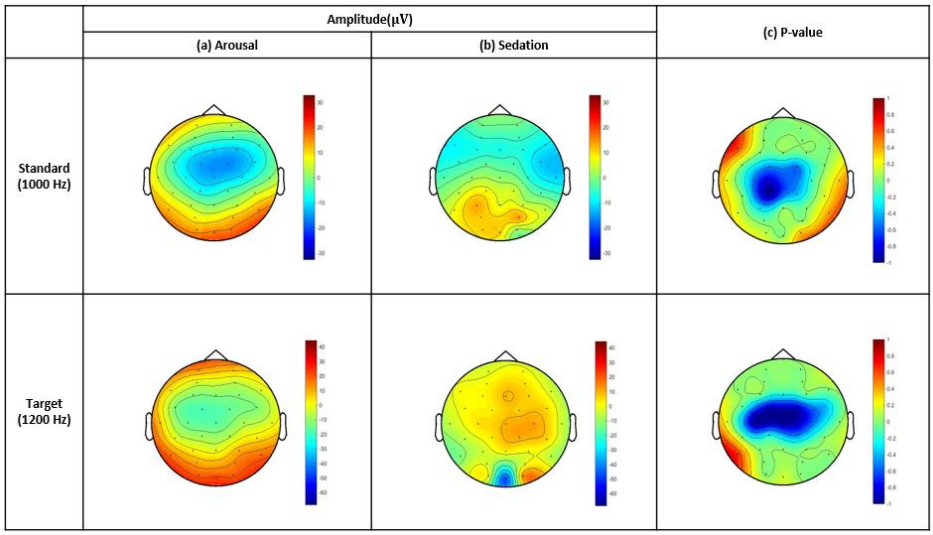

Figure 1. Topographic distributions of ERP amplitude in the 320-360 ms latency range. (a) Average ERP distributions in the arousal state. A cyanotic shift of the color indicates the areas with positive-going ERPs. Peak amplitude can be observed in the central region (b) Average ERP distribution in the sedation state. The ERP amplitude showed significant reduction compared to the arousal state. (c) ERP amplitude differences between arousal and sedative states are shown as p-value distribution of statistical differences. Peak difference can be observed in the central area

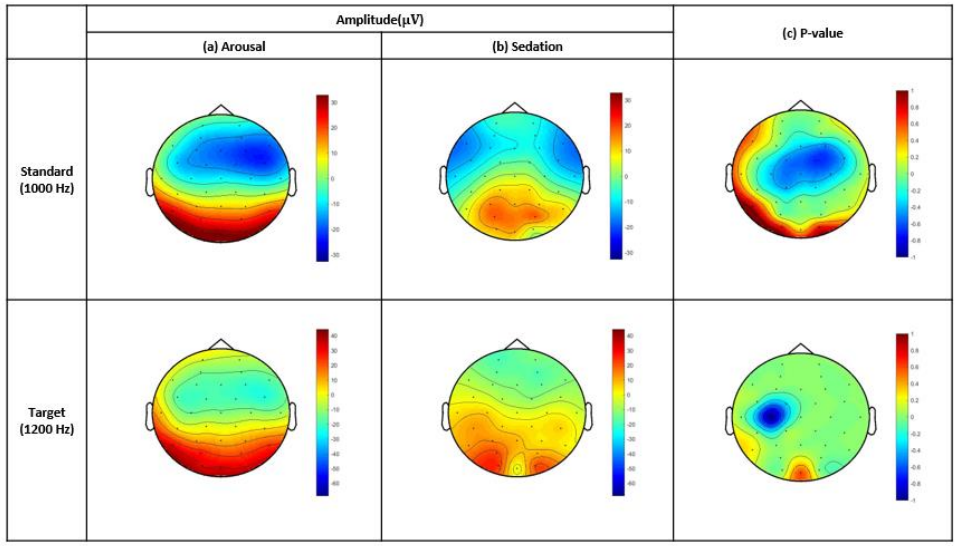

Figure 2. Topographic distributions of ERP amplitude in the 360–400–ms latency range. (a) Average ERP distributions in the arousal state. Peak amplitude can be observed in the parietal region (b) Average ERP distribution in the sedation state. The ERP amplitude showed significant reduction compared to the arousal state. (c) ERP amplitude differences between arousal and sedative states are shown as p–value distribution of statistical differences. Peak difference can be observed in the parietal area

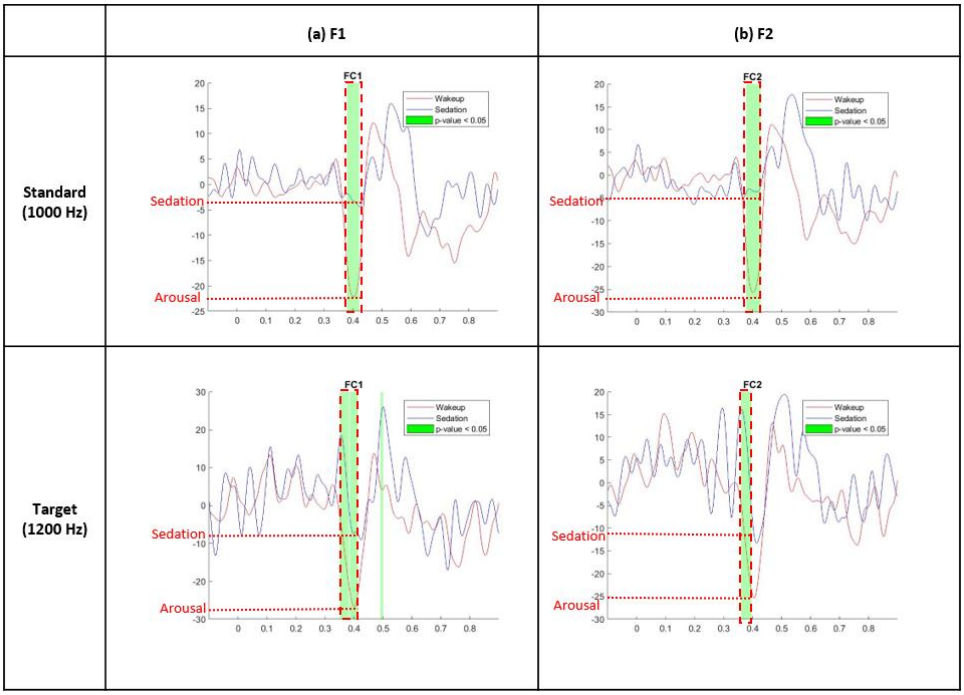

Figure 3. Average time-domain graphs of F1 and F2 electrodes in standard and target signal. Red lines in each graph represents EPR in the arousal state. Blue line represents ERP in sedative state. Statistically significant difference between each awake and sedative states($P<0.05$) are shown in green boxes. Red - dotted lines were used to enunciate P300 difference between arousal and sedative state.

(a) Average ERP graph obtained though F1 electrode. (b) Average ERP graph obtained though F2 electrode. In both the F1 and F2 electrodes, a significant P300 reduction was observed in sedative states.

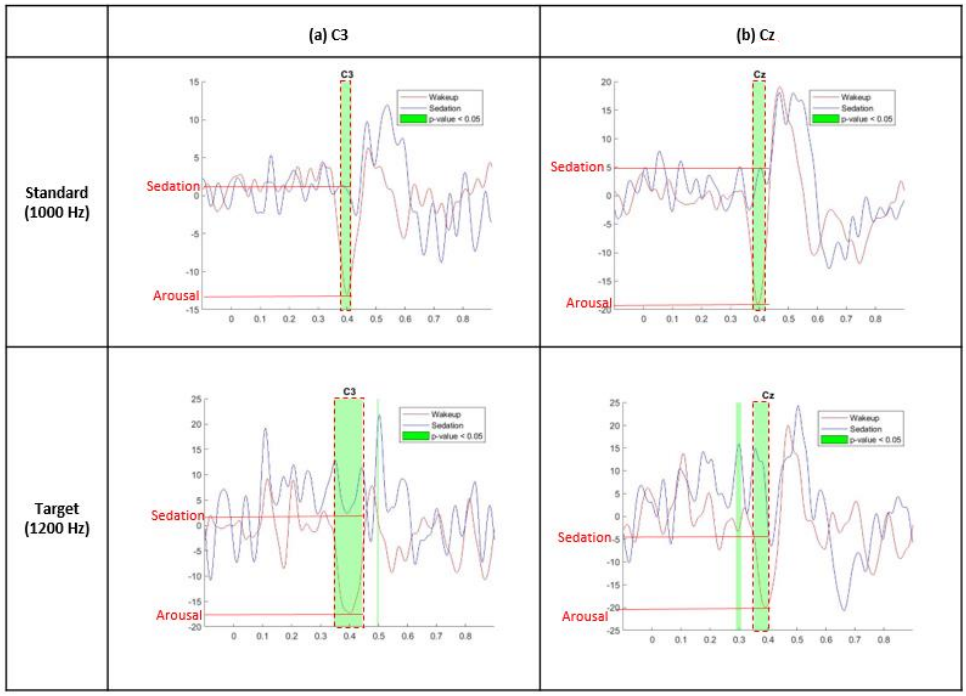

Figure 4. Average time-domain graphs of F1 and F2 electrodes in standard and target signal. Red lines in each graph represents EPR in the arousal state. Blue line represents ERP in sedative state. Statistically significant difference between each awake and sedative states($P<0.05$) are shown in green boxes. Red - dotted lines were used to enunciate P300 difference between arousal and sedative state.

(a) Average ERP graph obtained though F1 electrode. (b) Average ERP graph obtained though F2 electrode. In both the F1 and F2 electrodes, a significant P300 reduction was observed in sedative states.

초 록

1. 연 구 목 적

본 연구에서는 propofol으로 유도된 깊은 진정 상태에서 oddball paradigm으로 청각자극을 가하여 발생하는 event-related potential (ERP)을 유도하였다. 뇌의 집중과 인지과정과 밀접한 관계를 가진 P300이라는 ERP의 변화를 조사함으로써 propofol로 유도된 깊은 진정에서 나타나는 뇌의 정보처리 기전변화를 이해하고자 하였다.

2. 연 구 방 법

설문조사와 임상검사로 전신질환 및 정신장애가 없음이 확인된 20명의 자원자 (여성 10명, 남성 10명, 평균 연령 27.7세, 연령대 26-30세)가 본 연구에 참여하였다. 각 피험자의 뇌파는 국제 규격을 따르는 32 전극으로 구성된 EEG 기록 장비로 측정하였다. 뇌파 측정장치를 구동시킨 상태에서, 각성상태의 피험자에게 1000Hz의 표준자극 (p=0.8, n=400)과 1200Hz의 대상자극(p=0.2, n=100, 1200Hz)로 총 500개의 자극을 전달하였다. 이후, 깊은 진정상태에서 다시 한번 passive oddball task를 시행하여 뇌파를 측정하였다. 깊은 진정상태는 목표농도 조절주입법을 사용하여 마취과 의사의 관리하에 이뤄졌으며, Bispectral index (BIS)가 60 전후로 유지되게 하여 깊은 진정상태를 유지하였다. 뇌파 측정 완료와 동시에 propofol 투약이 중지되었으며, 피험자는 정상적인 활력 징후와 의식을 회복할 때까지 감시하였다. 측정된 뇌파에서 ERP를 추출하여 ERP의 지형적 분포를 확인하였으며 통계적으로 유의한 변화를 보이는 위치에 존재하는 전극들의 ERP에서 시간적 변화를 확인하였으며, 각성 상태와 깊은 진정상태에서 ERP

사이에 존재하는 통계적인 차이를 확인하였다.

3. 결과

P300는 320-360-ms와 360-400-ms의 잠복기 중에 관찰되었다. 지형적 분포를 확인한 결과, 320-360-ms 잠복기에서는 central area에 각성과 진정상태에서의 유의적인 변화가 확인되었으며, 360-400-ms 잠복기에서는 parietal area에서 유의적인 변화가 확인되었다. 깊은 진정상태에서 통계적으로 유의미하게 P300이 감소되었다.

4. 결론

Propofol을 이용한 깊은 진정에서 P300의 유의미한 감소가 발견되었다. 특히 Fronto-parietal region에서 그 변화가 발견되었다. Fronto-parietal region에서 발견되는 인지 후 기억 과정과 연관이 있어 보인다.

주요어 : Event-Related Potential, P300, Information Processing, Propofol, Sedation

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