치의학석사학위논문

Investigating the mechanism of sedation induced by dexmedetomidine with LORETA

뇌파분석을 통한 dexmedetomidine 의 작용기전에 관한 연구

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ABSTRACT

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PURPOSE: Dexmedetomidine (DEX) is a sedative, the use of which has been increasing in clinical practice. It acts as an agonist to pre-synaptic α2-adrenergic receptors with little effect on respiratory functions. Although consciousness impairment is closely related to disturbances of brain function at different frequency bands, time-varying DEX effects on cortical activity at specific frequency bands has not yet been studied.

METHODS: We analyzed the differences in activity of the cerebral cortex between awake and sedated status induced by DEX at specific frequency bands. Differences in standardized low resolution electromagnetic tomography

(sLORETA) obtained means were examined. sLORETA localizes multiple channel scalp recordings of cerebral electric activity to specific brain regions.

RESULTS: We have found an increased activity in the cuneus at delta band frequencies and the posterior cingulate cortex at theta frequencies, the cingulate gyrus at beta frequencies, the cuneus at gamma frequencies, and parts of the default mode network (DMN) and common midline core (CMC).

CONCLUSION: These results support the hypothesis that disinhibition of the DMN during sedation makes robust connections more prominent; from the perspective of information integration, the synchronized brain network impairs the efficiency of information processing.

Keywords : Consciousness; Dexmedetomidine; Electroencephalography; Sedation

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CONTENTS

ABBREVIATIONS

DEX	dexmedetomidine
GABA	gamma-aminobutyric acid
NREM	non-rapid eye movement
sLORETA	standardized low resolution electromagnetic tomography
EEG	eletroencephalography
BIS	bispectral index
BA	brodmann area
PCC	posterior cingulate cortex
DMN	default mode network
CMC	common midline core
ACC	anterior cingulate cortex
AC	auditory cortex

I. Introduction

Dexmedetomidine(DEX) is a sedative, the use of which has been increasing in clinical practice.[1] DEX has little effect on respiratory functions, therefore it may be useful in situations where procedures are performed within the airway, such as dental procedures. Unlike other sedatives, which act on GABA receptors, DEX acts as an agonist to pre-synaptic α2-adrenergic receptors. DEX inhibits the major arousal center, producing a sedative effect resembling NREM sleep II.[2] Considering the different action site of DEX compared to other sedatives, it can be speculated that DEX may have a different anesthetic mechanism relative to other sedatives. However, despite the fact that DEX has been widely used to sedate patients, few studies have been performed to elucidate the mechanisms of DEX-induced sedation from the perspective of cortical plasticity on a large scale.

Sedation can be considered the state between consciousness and loss of consciousness. Consciousness requires the integration of scattered information processed in different brain areas.[3,4] As such, anesthetic-induced impaired consciousness is likely to induce changes in cortical activity. Previous studies have shown that different levels of unconsciousness are associated with modulated activities within multiple brain regions. Understanding potential

cortical differences during sedation may be a prerequisite for understanding neural correlates of impaired consciousness. Functional neuroimaging studies have shown that DEX primarily disturbs long-range thalamocortical interactions.[2] However, time-varying DEX effects on cortical activity cannot be evaluated from neuroimaging studies providing the highest spatial resolution. In addition, the brain modulates its functions at specific frequency bands,[5] and consciousness impairment is closely related to disturbances in brain function at different frequency bands.[3] Even though long-range brain interactions are modulated at specific frequency bands, the cortical effects of DEX on whole brain areas in accordance with frequency bands has not yet been investigated.

This study analyzed the differences in cerebral cortex activity between awake and sedated status induced by DEX, by means of sLORETA (standardized low resolution electromagnetic tomography). sLORETA localizes cerebral electric activity obtained through EEG recordings from multiple channels to specific brain regions when used as a functional brain imaging method.[6,7] With the use of sLORETA, neurophysiological correlates of medical diseases have been investigated. However, few attempts have been made to investigate neural correlates of the sedative state using this technique.

Therefore, we aimed to investigate how cortical activity is altered during DEX sedation and to discover potential neural correlates of DEX-induced

impaired consciousness.

II. Materials and methods

1. Volunteer recruitment

With informed consent provided according to Institutional Review Board of Seoul National University, College of Dentistry approval, 20 healthy volunteers ranging from 20 to 40 years old were enrolled in this study. Each volunteer was instructed to fast for at least 8 hours prior to the experiment. Volunteers who had significant medical diseases and laboratory abnormalities were excluded from the study.

2. EEG recording and dexmedetomidine infusion

Volunteers were acclimated to a room shielded against sound and electric fields where electroencephalography was recorded. Thirty-two electrodes in the standard 10-20 international placement were attached after placing an appropriate EEG cap that best matched the head circumference of the volunteer. EEG was recorded referenced to an average EEG while keeping impedances at all electrodes below 5 kU. Data were stored to a PC at a sampling rate of 2048 Hz during the entire experiment. After obtaining EEGs for 5 min with eyes closed, DEX was administered as a 0.5 mcg/kg loading bolus over 10 min, followed by

a 0.5 mcg/kg/hr infusion until unconsciousness was reached. During the DEX infusion, cuff blood pressure, electrocardiogram, pulse-oximetry, and capnography were monitored. BIS was also monitored to evaluate sedation depth more objectively. We instructed volunteers to keep their eyes closed during the entire experiment, and defined loss of consciousness as loss of response to a verbal request to grasp the hand every 30 seconds. After reaching unconsciousness, we stopped DEX administration. Recovery of consciousness after discontinuing DEX infusion was evaluated as a positive response to grasp the hand upon verbal request or spontaneous eye opening. EEG was continuously recorded until the volunteer regained full consciousness evaluated by either the return to baseline BIS value or a positive response to the question "Are you feeling the same compared to before, when you were sitting in the dental chair?"

3. EEG preprocessing

Three minute-length epochs of EEG data were selected from all participants in two conditions, awake and sedated, and were analyzed. All episodic artifacts were removed from the EEG stream meticulously by manual inspection. The data were preprocessed by down-sampling to 256 Hz with a 0.5 Hz high-pass filter, a 70 Hz low-pass filter (fast Fourier transform filter applying a Hanning window) and a 60 Hz notch filter (sixty–fourth-order finite impulse

response (FIR) notch filters). EEG data pairs were baseline corrected to the average reference. In addition, ICA (independent component analysis) was performed to minimize artifacts from micro muscle movement, blinking, electrical noise and pulses from the carotid artery.

4. Source localization analysis

Standardized low-resolution brain electromagnetic tomography (sLORETA),[6] a functional imaging method using certain electrophysiological and neuroanatomical constraints, was conducted to estimate sources within the brain from electrical activity at the scalp in each of the following six frequency bands: delta (1.5~4 Hz), theta (4~8 Hz), alpha (8~12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz), and gamma (30-44 Hz).[8]

Effectively, sLORETA gives a single linear solution to the inverse problem of functional cortical localization based on extracranial measurements[8] and generates images of standardized current density with no localization bias.[6] The localization accuracy of sLORETA has been repeatedly validated by combining sLORETA with other localization methods, such as structural magnetic resonance imaging (MRI),[9] functional MRI[10,11] and positron emission tomography.[12,13]

5. Statistical analyses

To identify potential differences between awake and sedated states induced by the DEX infusion, voxel-by-voxel analysis using sLORETA was performed for the 6 frequency band between-condition comparisons of the current density distribution. Statistical nonparametric mapping (SPM) of sLORETA images was performed for each contrast using sLORETA's built-in voxelwise randomization tests (5000 permutations) and employing a log-F ratio statistic for independent groups with a threshold $P < 0.05$.

III. Results

Among 20 subjects, EEGs obtained from two subjects were contaminated with excessive artifacts, which could not be removed even by applying sophisticated preprocessing techniques; therefore, data from these participants were excluded from subsequent analyses.

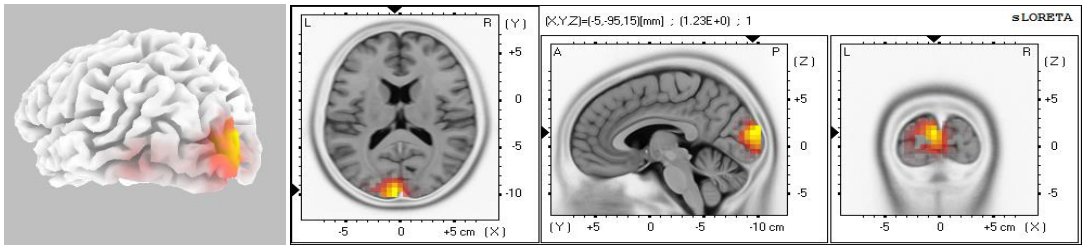
DEX-induced sedation was associated with cortical activity changes in different frequency bands. Compared to the baseline state, increased activity was seen in the cuneus (BA 18) in the delta frequency band, the posterior cingulate cortex (BA 23) in the theta frequency, the cingulate gyrus (BA 24) in the beta frequency band, and the cuneus (BA 18) in the gamma frequency bands and was most prominent during DEX-induced sedation (Figures 1-a, b, d, e). In contrast, relative to the awake state, decreased activity was seen in the fusiform gyrus (BA 20) in the alpha frequency bands that was most prominent during DEX-induced sedation (Figure 1-c). The cortical areas demonstrating significant changes during DEX-induced sedation for each frequency band are described in detail in Table 1.

Table 1. Cortical areas demonstrating significant changes during DEX-induced sedation for each frequency band

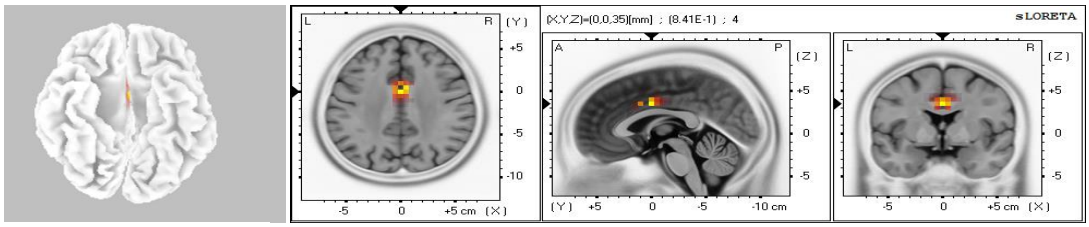
Frequency band	MNI Coordinates (x y z)			Voxel Value	Brodmann Area	Structure
Delta						
	-5	-95	15	1.23	18	Cuneus
	-5	-100	20	1.23	18	Cuneus
	-5	-100	15	1.23	18	Cuneus
	-5	-95	10	1.23	18	Cuneus
	-5	-100	10	1.23	18	Middle Occipital Gyrus
Theta						
	0	-50	25	1.06	23	Posterior Cingulate
	5	-50	25	1.06	23	Posterior Cingulate
	-10	-50	30	1.06	31	Precuneus
	-5	-50	30	1.05	31	Precuneus
	-10	-55	30	1.05	31	Precuneus
Alpha						
	-45	-25	-30	-1.31	20	Fusiform Gyrus
	-50	-25	-30	-1.31	20	Fusiform Gyrus
	-50	-25	-25	-1.31	20	Inferior Temporal Gyrus
	-40	-25	-20	-1.31	20	Fusiform Gyrus
	-40	-45	20	-1.31	13	Insula
Beta 1						
	0	0	35	0.84	24	Cingulate Gyrus
	5	5	35	0.84	24	Cingulate Gyrus
	5	0	35	0.83	24	Cingulate Gyrus
	0	0	40	0.83	24	Cingulate Gyrus
	0	10	35	0.83	24	Cingulate Gyrus
Gamma						
	-5	-100	10	0.83	18	Middle Occipital Gyrus
	-5	-100	5	0.83	18	Cuneus
	-5	-100	15	0.82	18	Cuneus
	-10	-100	15	0.82	18	Cuneus
	-5	-95	10	0.82	18	Cuneus

Figure 1. Statistical nonparametric mapping (SnPM) of sLORETA images for each band (a) delta (b) theta (c) alpha (d) beta 1 (e) gamma

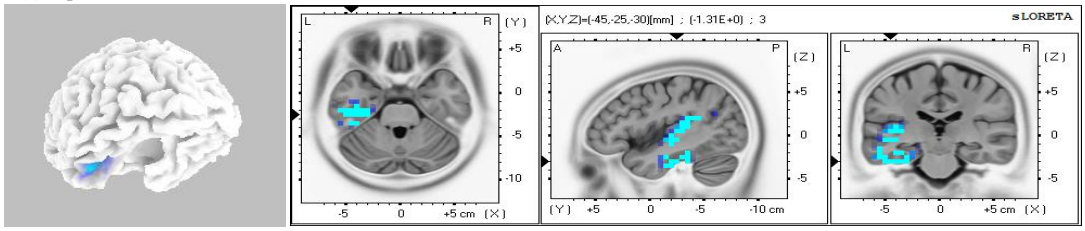
(a) delta



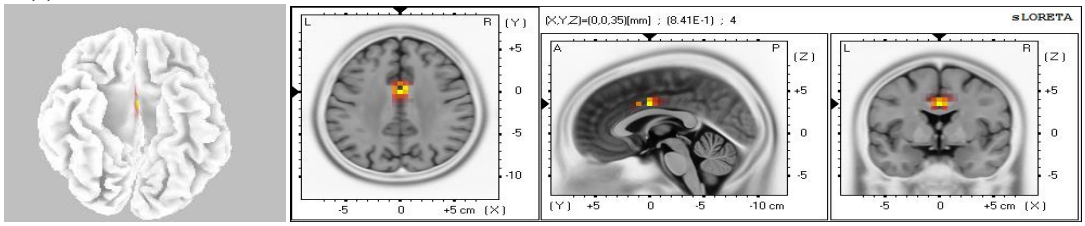
(b) theta



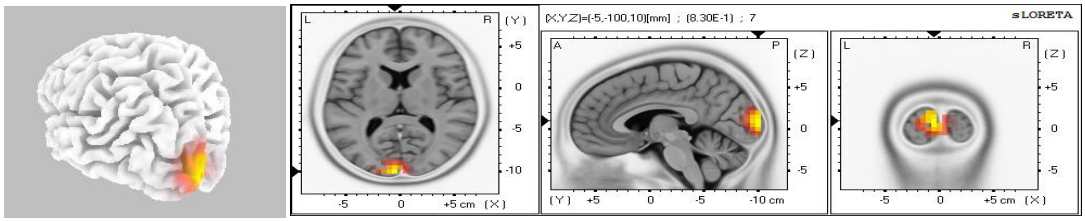
(c) alpha



(d) beta 1



(e) gamma



IV. Discussion

We found that DEX induced cortical activity changes during an impaired consciousness state. To the best our knowledge, this is the first study to investigate sedation-related cortical activity changes at each brain frequency band, with which the brain regulates its functions.[5]

We utilized an inverse modeling technique to determine which areas at specific brain frequency ranges were disturbed during DEX sedation. This inverse modelling method (sLORETA) is based on the fact that one neuron is synchronized with adjacent neurons, and this allows for electric source localization.[7,14] Through localizing the sources of electric activity, sLORETA statistically computes the difference in cerebral electrical activity between two states, and visualizes statistical results in a three dimensional distribution. This three dimensional distribution of statistical differences is shown as a current density distribution in the solution space, allowing for the detection of changes in brain activity more easily.[7,14] Until now, few studies have attempted to investigate the mechanism of impaired consciousness using the sLORETA technique, despite its advantages, such as its simplicity and graphical representation of brain activity difference between two conditions. This is the

first study to investigate the mechanism of DEX sedation using the sLORETA technique.

The default mode network (DMN) has been investigated as an anatomical and functional mechanism for maintaining attention and consciousness.[15] Also, the common midline core (CMC), including the midline precuneus/cuneus, prefrontal cortex, and other brain areas, is targeted by general anesthetics resulting in anesthesia.[16] The DMN is reported to be activated in situations where attention to external environments is not necessary. The DMN consists of multiple interacting subsystems within the brain. Even if the exact function of the DMN remains unclear, it is thought to play a critical role in internally-directed cognition. The DMN is activated during non-stressful resting states, such as autobiographical memory and planning for the future. DMN disturbance is also associated with the development of neuropsychiatric diseases, such as Alzheimer's, schizophrenia, autism, depression and attention deficit hyperactivity disorder.[17] In the DMN, the posterior cingulate cortex (PCC) acts as a hub, as it is functionally connected to other brain areas.[18] Considering the roles of the DMN and the CMC in regulating consciousness and mental states, it is likely that DEX may induce changes in both DMN and CMC activities, leading to impaired consciousness.

In agreement with this hypothesis, cortical activities were significantly

changed at the PCC, cuneus, and anterior cingulate cortex (ACC) among DMN and CMC structures during DEX-induced sedation. However, cortical activities in these areas were augmented, contrary to our expectation. Our results appear to contradict those of previous studies demonstrating impaired activity in these brain areas during general anesthesia.[16,19] It remains unclear why DEX activated cortical functions in these areas during sedation. However, a recent study may provide an explanation for increased brain-specific activity appearing somewhat contradictory in a DEX-induced sedative state.

In agreement with our results, functional connectivity of the PCC, known as the hub among DMN structures, to other brain area increases during propofol sedation.[20] In an awake state, the arousal center in the brainstem inhibits PCC function.[20] During sedation, as the connection from the arousal center to the PCC weakens, the PCC paradoxically increases functional connectivity to other brain areas. The PCC acts as a hub within the DFM brain network[18] and connects to other brain areas, such as the cuneus and anterior cingulate cortex, in which increased activation during sedation was observed in this study. Taken together, it can be hypothesized that these observed increased activities may be the result of disinhibition during sedation, making the robust connections more prominent. Also, from the perspective of information integration, the synchronized brain network impairs the efficiency of information processing.[21] In clinical practice,

we frequently observe that responses to external stimuli, such as verbal, auditory, and visual stimuli, are impaired under sedation. Increased activation during sedation may be the explanation for impaired and delayed responses to stimuli during sedation.

At the alpha frequency bands, we observed decreased cortical activity at the auditory cortex (AC) and the fusiform gyrus, where significant cortical activity alterations were observed during sedation. The fusiform gyrus is involved in processing word recognition and visual information.[22] Auditory stimulation is associated with AC activation. The PCC plays an important role in auditory perception.[23] Perceived auditory stimulation is the prerequisite for word recognition.[24] Event-related potentials during auditory stimulation are significantly affected in the alpha frequency range.[25] The present study demonstrated deactivation in temporal brain areas in the alpha frequency bands which may explain the delayed response to verbal stimuli. In this study, all subjects showed a delayed response to verbal stimuli for the purpose of evaluating the level of consciousness before unconsciousness was achieved. Considering the importance of the fusiform gyrus in regulating visual perception, DEX may also impair the efficiency of visual stimulus processing, leading to blurred or double vision [26] during sedation, even though the subjects were instructed to close their eyes in our experimental design.

Although we demonstrated several neural correlates that may be associated with DEX-induced sedation, we note several limitations that should be addressed in future studies. First, we focused on changes in cortical activity during DEX sedation. However, a change in brain activity does not guarantee alterations in brain network properties. Without changes in brain activity, functional connectivity between different brain areas may be changing.[20] Second, changes in cortical activity, as shown in this study, may represent different patterns during different levels of sedation. Investigating cortical activity during DEX infusion at a constant level of effect-site concentration may be needed to elucidate the mechanism that underlies different levels of impaired consciousness. Furthermore, EEG changes between different levels of sedation should also be compared to better understand transitional changes from consciousness to unconsciousness.

In summary, we have found that cortical activity changes in different brain frequency ranges during DEX sedation. These alterations may explain the mechanism of DEX sedation, thus allowing for the possibility to track changes in levels of consciousness as an objective marker during DEX administration.

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국문초록

뇌파분석을 통한 dexmedetomidine의 작용기전에 관한 연구

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목적

덱스메데토미딘은 임상에서 사용이 증가되고 있는 진정제이다. 시냅스 전 알파2 아드레날린성수용체에 작용하며, 호흡기능에 미치는 영향은 미미하다는 장점이 있다. 현재 의식의 변화는 뇌파의 주파수 대역별 변화와 연관이 있다고 알려져 있으나, 아직 덱스메데토미딘에 의해 유도된 진정 상태에서, 시간 흐름에 따른 주파수 대역별 대뇌피질 활성도에 관한 연구는 이루어져있지 않다.

연구재료 및 방법

각성상태와 덱스메데토미딘에 의해 유도된 진정상태 간의, 대뇌 피질 활성도의 주파수 대역별 차이를 분석하였다. sLORETA (standardized low resolution electromagnetic tomography)를 사용하여 얻은 평균값의 차이를 분석하였다. sLORETA는 대뇌피질 활성

도의 각 채널 기록 값을 뇌 특정 부위로 국소화 하는 방법이다.

결과

각성상태와 비교하였을 때 진정상태에서, 각각 델타와 감마 주파수 대역에서는 설상엽, 세타 주파수 대역에서는 뒤의 대상피질, 베타 주파수 대역에서는 대상회에서 증가된 활성도를 관찰할 수 있었는데, 이 부위들은 Default mode network (DMN)와 common midline core (CMC)이다.

결론

덱스메데토미딘에 의해 유도된 진정상태에서의 DMN 탈억제가 DMN 내의 강한 연결을 더욱 두드러지도록 유도하며, 동시 통합화된 대뇌 네트워크가 정보처리의 효율성을 감소시킨다.

주요어 : 의식(Consciousness), Dexmedetomidine, Electroencephalography, 진정(Sedation)

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