Changes in topographic electroencephalogram during deepening levels of propofol sedation based on alertness/sedation scale under bispectral index guidance

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Abstract

Background: Sedation has been associated with numerous changes on electroencephalogram (EEG) but there is a need to clarify specific alterations in relation to deepening levels of sedation with different agents. We aimed to evaluate the effect of deepening levels of sedation induced by propofol and how they compare to natural sleep.

Methods: Fifty consecutive neurologically normal patients who underwent upper gastrointestinal endoscopy while sedated with propofol were included. Topographic EEG spectral maps and the bispectral index (BIS) values were obtained at four time points: wakefulness, mild sedation, deep sedation and recovery. Observer's Assessment of Alertness and Sedation (OAA/S) score was used to assess sedation levels.

Results: Propofol induced increased delta (0.5–3.5 Hz) and gamma (25–40 Hz) power throughout sedation. In addition, there was decreased alpha power (9–11.5 Hz) in the occipital area and increased global beta (12–25 Hz)/gamma (25–40 Hz) power during mild sedation. Deep sedation was associated with increased theta (4–7 Hz)/alpha (9–11.5 Hz)/beta (12–25 Hz) power, which was maximal frontally.

Conclusion: There are distinct changes associated with deepening levels of propofol induced sedation that distinguish it from natural sleep. This suggests that different mechanisms are involved in them and warrants further investigations to clarify the nature of these changes.

Key words: sedation, sedatives, propofol, EEG, topographic, Observer's Assessment of Alertness/Sedation Scale, bispectral index, endoscopy, upper gastrointestinal.

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Propofol is a short acting intravenous anesthetic agent that is widely used to induce and maintain conscious sedation that allows patients to tolerate unpleasant procedures when they are awake as well as deeper levels of sedation that are similar to slow wave sleep, and absence of response to painful stimulation [1–3]. The graded fashion of disruption in consciousness induced by propofol might reflect involvement of specific circuits within the brain with deepening levels of sedation but the exact mechanisms by which this occurs are poorly understood. There is evidence suggesting a role for γ-aminobutyric acid (GABA) receptors present on neurons throughout the brain [4–6]. These circuits are also heavily involved during natural sleep but it is not clear whether the circuits involved during natural and sedated sleep are different. Sleep studies have suggested that consciousness can be disrupted when the electroencephalogram (EEG) changes from low-voltage fast beta (12–25 Hz) or gamma (> 25 Hz) activity to large delta (0.5–4 Hz) waves [7]. There is also some suggestion that conscious awareness and perception are maintained, in part, by the synchronization of gamma (> 25 Hz) and/or theta (4–8 Hz) waves across large areas of the cortex [8–10]. These changes have not been confirmed in sedated sleep as the previous EEG studies with anesthesia have produced conflicting results [11–13]. Furthermore, most EEG studies have focused on the transition from wakefulness to sleep, and the different levels of sedation are not well described [14, 15]. Delineation of the changes that occur with different levels of sedation may help clarify the mechanisms underlying disturbed consciousness by different anesthetic agents.

In the current study we used topographic EEG mapping and bispectral index score (BIS) analysis to delineate the effect of deepening levels of propofol

induced sedation. In order to ensure that the effect was due to propofol use only, we included neurologically normal patients who underwent upper gastrointestinal endoscopy. We chose these EEG based modalities because they offer better temporal and spatial resolution compared to conventional EEG.

METHODS

Study design and participants

This was a prospective observational study carried out on 50 consecutive neurologically and cognitively normal patients undergoing upper gastrointestinal endoscopy between 2015 and 2018. All patients were recruited by the same operator. They were examined by the same medical doctor prior to recruitment to determine that they did not suffer from any disorder that may alter brain function and affect the EEG or other measures.

Inclusion criteria were age 20–50 years and American Society of Anesthesiologists (ASA) physical status I–III [16]. Exclusion criteria were as follows: lack of patient consent, patients with contraindication to regional techniques (e.g. allergy, anxiety or orthopnea), pregnancy, mentally disabled patients or those with cognitive limitations, history of chronic use of sedatives, narcotics, alcohol or illicit drugs, patients with impairment of cardiac, respiratory, hepatic, or renal function and patients not suitable for processed EEG monitoring as determined by the researcher, surgeon or attending anesthesiologist.

The patients were instructed to refrain from using alcohol or any medication 48 hours before the procedure, and all were fasting for at least 8 hours prior to the endoscopy. The procedures were all carried out in the morning (9.00 a.m. to 12.00 p.m.) to avoid any potential effect of circadian rhythm on sedation.

In compliance with the Helsinki Declaration, ethical approval for this study was provided by the Ethical Committee of Tamayoz Clinic in June 2014 and informed written consent was obtained from each patient.

Sedation protocol

Oxygen was administered to patients at a rate of 2–3 L min^{-1} using a nasal catheter before induction. Each patient then received an initial propofol 1% dose according to their body weight (40 mg in patients weighted < 70 kg, and 60 mg in patients ≥ 70 kg, followed by repetitive doses of 10–20 mg). Maintenance of anesthesia was achieved with incremental boluses of 10 to 30 mg of propofol. The quantity and timing of the bolus were decided by the anesthesiologist based on development of inadequate anesthesia.

The 5-point Observer's Assessment of Alertness/ Sedation (OAA/S) Scale was used every 3 min to determine the sedation level in each case and to help titrate the infusion rate. *Wakefulness* was defined as the baseline state without any drug administration and with the patient obeying verbal commands, *mild sedation* was defined as OAA/S = 3 (responds only after name is spoken loudly and/or repeatedly), *deep sedation* was defined as OAA/S = 1 (does not respond to mild prodding or shaking), and *recovery* was defined as OAA/S = 5 (responds readily to name spoken in a normal tone). The target was deep sedation (OAA/S = 1). At this point the endoscope was inserted. If the patients had a body response upon endoscope insertion, the propofol bolus was added.

Continuous monitoring of vital signs was carried out throughout the procedure. The time to deep sedation was the time period from first drug bolus dose to procedure initiation and the recovery time was the period from endoscopy end to full orientation (the patient was able to provide his/her correct date of birth). Any adverse reactions that occurred were also recorded. These included hypoxemia (defined as SpO$_2$ falling below 90%), hypotension (systolic or diastolic blood pressure values decreasing by 20% or more) and bradycardia (heart rate less than 50 beats/minute). In the case of occurrence of any of these complications a standard management was introduced.

EEG monitoring

Continuous digital EEG monitoring was performed using the standard 10–20 electrode system. Twelve channels were recorded on an E-series EEG amplifier using Profusion EEG4 software (Compumedics Ltd. Melbourne, Australia). The electrodes were placed on the scalp in the preoperative holding room. EEG was recorded by using a low frequency filter of 0.53 Hz and a high frequency filter of 70 Hz. Paper speed was 3 cm s^{-1} and the sensitivity was 5 µV mm^{-1}. After data collection, the EEG data were filtered offline with a 0.5–100 Hz bandpass filter for analysis. Epochs with artifacts (DC bias, blinks, slow eye movement, etc.) were excluded. Data from the electrodes with artifacts were substituted with the extrapolated virtue values from the neighboring channels. After artifact rejection, each set of EEG data was subjected to a 2-s epoch, and each epoch was processed using fast Fourier transformation (FFT) analysis to obtain the absolute power at each electrode in the following six bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), spindle (12–15 Hz), beta (15–25 Hz) and gamma (25–40 Hz). In each 2-min period, EEG was analyzed in 2-s epochs, resulting in 60 epochs.

Bispectral index monitoring

A BIS VISTA (Covidien, Mansfield, MA USA) processed EEG bilateral monitor was used. This gen-

TABLE 1. Patient characteristics, mean ± SD or *n*

Variable		Values
Age (years)		43.6 ± 15.7
Gender (male)		26
Height (cm)		172.1 ± 21.4
Body mass (kg)		81.4 ± 37.2
ASA status	I	36
	II	11
	III	3

ASA – American Society of Anesthesiologists

TABLE 2. Range of central hemodynamics measured throughout the procedure

Variable	Values
Heart rate/min	87.7–98.4
Blood pressure (mm Hg)	119.4–131.3
O$_2$ saturation (%)	98.4–99.8
Respiratory rate/min	12.3–16.7

TABLE 3. Sedation details, mean ± SD

Variable	Result
Procedure time (min)	16.2 ± 9.1
Sedation time (min)	25.5 ± 8.5
Total propofol dose (induction + maintenance; mg)	147.6 ± 53.6
Time to deep sedation (s)	94.3 ± 41.7
Recovery time (min)	12.9 ± 9.3

erates a unitless index – the bispectral index (BIS index) – that ranges from 0 to 100, with 100 indicating full consciousness. The BIS electrodes were attached to the forehead and temple of the patient on each side using two sets of bilateral BIS sensor electrodes. BIS ≥ 85 indicated wakefulness, 66–84 indicated mild sedation and ≤ 65 indicated deep sedation. EEG and BIS data were recorded simultaneously and continuously beginning just prior to induction of sedation to the time the patient was ready for transport from the operating room following the procedure. Analyses included data recorded at four time points: wakefulness (baseline), mild sedation, deep sedation (loss of consciousness; OAA/S 1) and recovery.

Statistical analysis

The data are presented as average (mean ± SD) or frequency (%). For EEG data, low power spectral density, 10*log10 (µV2/Hz), was used to describe the absolute spectral power. For each participant, the power spectrum density and statistical analyses were conducted with the MATLAB-based EEGLab toolbox. To explore the long-range coordination

of neural activity, all 20 electrodes were included in the topographic analysis. The χ^2 test or Fisher's exact test was used for correlation of EEG and BIS with the sedation level (wakefulness, moderate sedation, deep sedation and recovery). $P < 0.05$ was adopted as significant.

RESULTS

Clinical and demographic characteristics are shown in Table 1. Tables 2 and 3 summarize the vital signs recorded throughout the procedure and sedation details. All the patients tolerated the endoscopy well. There were no reports of any significant side effects related to the procedure including any sedation related adverse events. In addition, although administration of propofol may lead to clinically observed seizures as reported by Stasiowski *et al.* [17], no epileptiform discharges were recorded, nor was there any seizure activity experienced by any of the patients. All patients left the center the same day and no hospitalization was required for any.

Figure 1 summarizes the changes observed on EEG spectral power analysis with deepening sedation. Overall, the main change was increased global delta power (0.5–3.5 Hz) with increasing doses of propofol. There was also an increase in the gamma range (25–40 Hz) which lasted throughout the sedation period.

As shown in Table 4, compared to wakefulness, there was a significant decrease in BIS with mild sedation ($P < 0.05$). A marked drop occurred with deep sedation and loss of consciousness ($P < 0.01$).

Compared to wakefulness the following changes were observed on EEG spectral analysis:
- Mild sedation: Frontally there was increased spectral power in the delta (0.5–3.5 Hz) and beta (12–25 Hz) ranges and decreased power in the alpha range (9–11.5 Hz). There was also a decrease in occipital alpha power and a global increase in delta, beta and gamma power.
- Deep sedation: There was a sustained increase in global delta power (0.5–3.5 Hz). All other frequency bands were also increased but the maximum increase was in the theta (4–7.5 Hz) and beta (12–25 Hz) ranges. This was mainly observed frontally.
- Recovery: There was decreased power in the alpha range (9–11.5 Hz), mainly observed at the frontal and occipital regions.

DISCUSSION

In the current study we studied a cohort of neurologically normal patients with no evidence of any cognitive disorder likely to affect brain dynamics while undergoing propofol induced sedation for upper gastrointestinal endoscopy. We observed gradual discrete changes in EEG and BIS dynamics
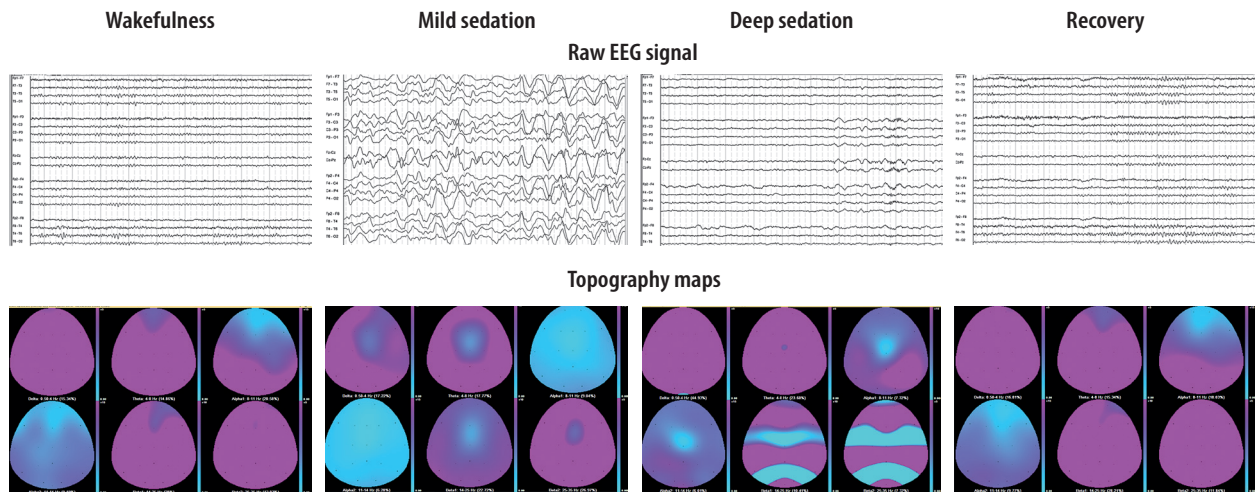
| Wakefulness | Mild sedation | Deep sedation | Recovery |

Raw EEG signal

Topography maps

FIGURE 1. Changes observed on electroencephalogram (EEG) spectral analysis with deepening of sedation with propofol. Top rows show representative EEG traces during wakefulness, mild sedation, deep sedation and recovery. Bottom rows illustrate the frequency band specific changes in EEG topography that occur during these transitions

from wakefulness passing through mild to sedation and then recovery.

In addition to a sustained increase in slow delta (0.5–3.5 Hz) waves and fast beta and gamma frequencies (12–40 Hz) predominantly in frontal electrodes throughout sedation, there were also distinctive changes with deepening of sedation. During mild sedation, alpha power (9–11.5 Hz) decreased in the occipital area with increased global beta/gamma power (12–40 Hz). Deep sedation showed an increase in theta (4–7.5 Hz), alpha (9–11.5 Hz) and beta (12–25 Hz) power, which was maximal in the frontal region. The increase in fast frequencies persisted after deep sedation and until recovery. BIS collects and processes EEG waveforms recorded from electrodes placed frontally. The value is calculated from three components: spectral analysis, bispectral analysis and temporal analysis [18]. This explains why the BIS values drop significantly with deep sedation as it reflects the increased delta activity in the frontal leads. It appears that the influence of the synchronous increase in frontal beta and gamma powers played a minor role in total BIS value analysis.

Like natural sleep, sedation is a state of decreased arousal. The clinical manifestation ranges from drowsiness to unconsciousness. There are many behavioral similarities between sleep and anesthesia, suggesting there is some sort of connection between these states [19]. Moreover, propofol acts on many brain areas that have been implicated in the initiation and maintenance of natural sleep [20]. Further support for this comes from several EEG reports of increased delta power in fronto-medial areas during both natural and sedated sleep [21, 22] and animal studies that propose that there are similarities in the homeostatic processes that modulate and are modulated by both

TABLE 4. Bispectral index (BIS) values recorded with deepening of sedation, mean $\pm$ SD

Conscious level	Dose of propofol (mg)	BIS value
Baseline (wakefulness; OAA/S = 5)	–	92.3 $\pm$ 4.9
Mild sedation (OAA/S = 3)	133.4 $\pm$ 46.1	76.3 $\pm$ 11.9
Deep sedation (OAA/S = 1)	156.8 $\pm$ 31.5	61.9 $\pm$ 5.7
Recovery (OAA/S = 5)	–	88.6 $\pm$ 3.9

OAA/S — Observer's Assessment of Alertness/Sedation Scale

propofol and normal sleep [23–25]. We also found a global increase in slow waves that was maximal in the frontocentral region, but the increase in alpha rhythms as well as the faster beta and gamma frequencies we observed has not been described during natural sleep [11, 26, 27]. Furthermore, there was a notable distortion of spindles and other normal sleep phenomena with propofol and there was involvement of posterior brain regions, which is not a pattern seen in natural sleep. The most likely explanation for this is that propofol acts on GABA receptors present on neurons throughout the brain [8–10], while sleep is generated by specific thalamocortical circuits [28]. It is therefore not expected that propofol will induce changes that are identical to the heterogeneous circuits of neuromodulation that occur during normal sleep [20]. Alpha rhythms (8–12 Hz) are recorded over the occipito-parietal cortex of awake humans when they are in a relaxed state with their eyes closed. They disappear with increased arousal and performance of cognitive activities. Spindle waves occur at a similar frequency to alpha rhythms (12–15 Hz) but are recorded during early slow wave (stage 2) sleep, being much less frequent or even disappearing during deeper slow-wave sleep. Both the alpha power and the spindle power change in all parts of

the cortex from wakefulness to different stages of sleep [29–32]. They share similar mechanisms, with the main pacemaker lying in the GABAergic reticular nucleus in the thalamus [33–36]. Propofol resulted in decreased posterior alpha and increased anterior alpha with deepening of sedation. It appears that it potentiates the GABAergic input within thalamo-cortical circuits, resulting in alterations within them that result in patterns different to those seen in both arousal and natural sleep [37, 38].

During slow wave sleep, cortical and thalamic neurons oscillate between a hyperpolarized down-state with little spiking and a depolarized up-state when firing rates can exceed wakefulness [39]. This is reflected by slow waves on EEG and is thought to result in a decrease in effective connectivity [40, 41] which leads to reduced ability of the brain to integrate information and consequently a decrease in the level of consciousness [39–42]. This is probably the mechanism through which anesthesia induces loss of consciousness, and thus studying the effect of anesthetic agents is a unique tool to examine the relationship between slow waves and effective connectivity. In our study we found an increase in beta and gamma power with deepening sedation. Gamma power, gamma synchrony, and theta synchrony have all been proposed to contribute to conscious awareness [8–10, 43] and there are also some reports of decreased gamma power during sleep and anesthesia [44, 45]. This is contrary to our findings and to reports of increased gamma power in animals during anesthesia [12]. In fact, there was an increase in gamma power in anterior head regions. Beta and gamma rhythms are associated with cortical activities and higher levels of cognitive functions, including sensory gating, attention, perception and motor control [4–6]. While it is possible that the interpretation of the results of faster frequencies was confounded by muscle and ocular-related EEG [45, 46], we do not think this was a major factor in our study because we underwent extensive measures to only include clean artifact-free epochs in the analysis. The results thus suggest that gamma activity responds differently to propofol and, more importantly, that gamma activity is not sufficient to maintain consciousness when slow waves are present.

We did not use functional electromyography (fEMG) to monitor for myoclonic activity which could have affected BIS scores. We do not feel this had an influential effect on our results, especially since we were very careful to only include neurologically normal participants with no history of seizures. Furthermore, there were no epileptiform discharges recorded in any of the patients either during the resting EEG or provoked by propofol [47]. Nevertheless, it is a potential limitation of our study.

In this study we demonstrated the existence of a distinct pattern of EEG changes associated with deepening of sedation induced by propofol. While it shares some similarities with natural sleep, there are distinguishing features suggesting different mechanisms and cortical circuits involved in induced versus natural sleep. Further studies are warranted to delineate the underlying mechanisms leading to this.

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