## Cerebral Electricalactivity as a Tool in Evaluating Anesthetic Effect during Balanced Anesthesia with Sevoflurane

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**Objectives:** The present study was undertaken to provide basic information about bilateral frontal cerebral electrical activity after induction, before and after skin incision, and at a steady state during sevoflurane anesthesia at the end tidal concentration 1, 1.2, 1.4 and 1.6 MAC and determine the association between the electrical cerebral activity with other clinical end points, i.e. motor responses and post-operative recall.

*Material and Method:* the Dual Channel Brain Activity, ABM2 ( $DATEX^R$ ) was used to continuously monitor frontal EMG and electrical cerebral activities (i.e. frequency and amplitude) of both hemispheres in 20 adult female patients undergoing balanced anesthesia in Maharaj Chiang Mai Hospital. The eligible patients were randomly assigned to receive 1.0 MAC, 1.2MAC, 1.4MAC or 1.6MAC of a mixture of sevoflurane and 66.67% nitrous oxide in oxygen during anesthesia. The anesthesia was induced with 5 mg/kg thiopental and supplemented with 1-1.5 microgram per kilogram of fentanyl. The standard dose of pancuronium or atracurium was given during maintenance.

**Results:** After induction with 5 mg/kg thiopental, the mean (95% confidence interval) of frontal EMG significantly decreased from 2.66 (1.63,4.29) to 1.41 (0.2,1.61). When eyelash reflex was absent, the mean (95%CI) frequency and amplitude of the right frontal EEG was 3.89 (3.29, 4.497) Hz, 39.58 (32.11, 47.05) microvolt and left frontal EEG was 3.84 (3.43, 4.25) Hz, 33.55 (28.59, 38.61) microvolt. The findings were consistent with the raw EEG shown on the monitor, i.e. a progressive decrease in the frequency and an increase in the amplitude. During maintenance with the inhaled anesthetics, there was a statistically significant decrease in frequency of right frontal in those who had received the inhaled anesthetic concentration to reach 1.4 and 1.65 MAC (p < 0.05)(repeated measure ANOVA). At the steady state of end tidal concentration of the sevoflurane there was consistency in decreasing frequencies and increasing amplitudes of both hemispheres of the groups with higher MAC values (p < 0.05) (Table 3). However, the authors failed to demonstrate the relationships between EEG changes and other clinical responses.

**Conclusion:** The present study has provided basic information about cerebral electrical activity during the balanced anesthesia with sevoflurane. As anesthesia deepened by increased MAC, the frequency decreased and the amplitude increased.

Keywords: EEG, Balanced anesthesia, Hypnosis, Sevoflurane

J Med Assoc Thai 2005; 88 (11): 1574-81 Full text. e-Journal: http://www.medassocthai.org/journal

Evaluation of the depth of anesthesia is fundamental to anesthetic practice. Depth of anesthesia depends on the interaction of two factors: the anesthetic-hypnotic component creating a state of unconsciousness and the surgical stimulus, which may activate the nervous system and increase the patient's level of consciousness, somatic and autonomic reactivity<sup>(1)</sup>. Prior to the use of muscle relaxants, maintaining the appropriate depth of anesthesia was a balance between abolishing movement to pain while maintaining adequate respiration. With the absence of move-

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ment on incision it was safe to assume that the patient was not aware. Controversy exists on the use of these measures to monitor loss of consciousness. These investigators used hemodynamic or somatic (movement) response to surgical stimuli as the clinical end-point to assess the accuracy of the different indicators of anesthetic depth<sup>(2-5)</sup>, but it is known that these clinical endpoints are inaccurate for this purpose<sup>(6,7)</sup>. However with the use of muscle relaxants, it became necessary to be certain that the administered concentration of anesthetic agent was adequate to prevent awareness<sup>(8)</sup>. The use of neuromuscular blocking agents can lead to unintentional awareness when the hypnotic component of anesthesia is not strong enough. If the receptor concentration of the anesthetic-hypnotic drug is too low, the drug may cause variable levels of awareness<sup>(9)</sup>. On the other hand, unnecessary high doses of anesthetics can lead to undesirable effects, i.e. cardiovascular depression, respiratory depression and longer postoperative recovery times<sup>(10,11)</sup>. Therefore, the optimization of anesthetic medication is necessary to provide all components of adequate anesthesia (i.e. hypnosis, analgesia and muscular relaxant). Electroencephalogram patterns are known to change with the depth of sedation<sup>(12,13)</sup> and general anesthesia level<sup>(14,15)</sup>. Changes of cerebral electrical activity may reflect changes of the hypnotic component of anesthesia. The present study was conducted to evaluate the hypnotic component of anesthesia by using EEG, and to provide the baseline information about the values of cerebral electrical activity at various clinical concentrations of inhaled anesthetics (as determined by the end tidal concentrations to achieve the desirable MAC values). The objectives of the present study were: 1) To provide basic information about the bilateral frontal cerebral electrical activity after induction with 5 mg/kg IV Thiopental, before and after skin incision during anesthesia with a mixture 2:1 nitrous oxide in oxygen and sevoflurane at the end tidal concentration to achieve 1, 1.2, 1.4 and 1.6 MAC of the inhaled anesthetics. 2) To determine the bilateral frontal cerebral electrical activities during the surgical procedure at the steady state of end tidal concentration of the inhaled anesthetics to achieve 1, 1.2, 1.4 and 1.65 MAC of the inhaled agents. 3) To determine the relationship between the frontal cerebral electrical activity and the alveolar concentration of the inhaled anesthetics. 4) To determine the association between the electrical cerebral activity and other clinical end points, i.e. motor responses and post-operative recall of intraoperative events.

## Material and Method *Patients*

The studied subjects consisted of 20 ASA class I-II adult patients. All were female undergoing elective non-cardiac surgery under endotracheal general anesthesia. Patients with any neurological or psychiatric disorders, cranial surgery, medication acting on the central nervous system and a history of cardiac, pulmonary, hepatic or renal diseases were excluded.

### Interventions

All eligible patients were visited by the attending anesthesiologist and received 0.2 mg./kg of diazepam for oral premedication. The anesthesia was induced with thiopentone 5 mg/kg and fentanyl 1-1.5 microgram/kg. After loss of consciousness (as determined by loss of the eyelash reflex), succinylcholine 1 mg/kg was given for neuromuscular block and the tracheal was intubated. After intubation, each patient was ventilated with 66.67% nitrous oxide in oxygen. Then, each patient was randomly allocated to receive either about 0.8%, 1.2%, 1.6% or 2% of end tidal sevoflurane concentrations to achieve 1.0 MAC, 1.2 MAC, 1.4 MAC or 1.6 MAC of a mixture of sevoflurane and nitrous oxide in oxygen (The desired MAC values were shown on the gas monitor, Capnomac Ultima<sup>TM</sup>). The initial skin incision standardized at 2 cm was performed by the surgeon after a period of more than 10 min to allow for adequate preparation of the surgical area and to establish the full return of the train-of-four peripheral nerve response to stimulation. After the patient's response to skin incision was assessed (within 15 seconds after incision), standard doses of pancuronium or atracurium were given. Extension and deepening of the incision for surgical purposes was commenced afterwards. The anesthesia was maintained until the end of surgery.

### Monitoring and Data Acquisition

Standard monitoring during anesthesia included ECG, pulse oximetry, NIBP, ETCO<sub>2</sub> and peripheral nerve stimulator (TOP GUARD<sup>R</sup>). The concentrations of anesthetic gases i.e. CO<sub>2</sub>, N<sub>2</sub>O and sevo-flurane were measured by Capnomac Ultima<sup>TM</sup>, Datex. The gas monitor was calibrated before the anesthesia started.

The EMG of the frontal scalp muscle and the EEG of both frontal hemispheres were continuously monitored by the Dual Channel Brain Activity, ABM2 (DATEX<sup>R</sup>). Silver chloride electrodes were positioned at FP1 and FP2 with the reference electrode at the

nasion and the ground electrode at the mastoid. The real time raw EEG of each hemisphere was shown in the real time mode +/-100 microvolt. The EEG information was updated every second and shown as mean frequencies and mean amplitude of each hemisphere. Only valid values of the EEG and EMG parameters were obtained every 5 minutes. On the following postoperative day, each patient was interviewed by the other investigators who were blinded to the assigned group for recalling the questions and answers verbally given during operation.

### Data Analysis

The valid values of the EMG and EEG parameters were obtained every 5 minutes. The means and its 95% confidence intervals of these values of individual patients after receiving 5 mg/kg thiopental (until loss of eyelash reflex), after intubation, before and after skin incision and at the steady state end tidal concentrations of the inhaled anesthetics during the operation were calculated. The paired T Test was used to compare the EEG values before and after skin incision. The analysis of variance was used to compare the EEG values at the steady state of end tidal concentrations among the four groups. The repeated measure ANOVA was used for multiple comparison of the repeated measuring values in individual patients. A p value of 0.05 was considered statistically significant.

### Results

All of the studied patients were female with the mean (95% CI) age of 41.05(37.52,44.58) years and mean (95% CI) body weight of 54.35 (50.3,58.4) kg (Table 1). The mean (95% confidence interval) of the frontal EMG before induction of anesthesia was 2.66 (1.63,4.29). Because the high EMG levels and eye movement could interfere with the EEG signal in conscious or active patients, the summary statistics of the EEG

values of the awaken patient were not calculated.

#### EMG AND EEG during induction

After induction with 5 mg./kg thiopentone and fentanyl 1-1.5 microgram/kg, the mean (95% confidence interval) of the frontal scalp EMG significantly decreased from 2.66 (1.63,4.29) to 1.41 (0.2,1.61). When eyelash reflex was absent, the mean (95% CI) frequency and amplitude of the right and left frontal EEG values were 3.89 (3.29, 4.497) Hz, 39.58 (32.11, 47.05) microvolt and 3.84 (3.43, 4.25) Hz, 33.55 (28.59, 38.61) microvolt respectively. The findings were consistent with the change of raw EEG shown on the monitor, i.e a progressive decrease in the frequency and an increase in the amplitude.

### EEG changes during intubation and maintenance before skin incision

Table 1 shows the characteristics of patients in the four groups based on the doses as determined by the end tidal concentration of nitrous oxide in oxygen and sevoflurane to achieve 1, 1.2, 1.4 and 1.6 MAC. There was no statistical difference among the four groups based on age and weight (p > 0.05).

From Table 2, controlled data couldnot be recorded because of high EMG level interference, after induction with 5 mg/kg thiopental the raw EEG was consistently shown on the monitor in decreasing frequencies and increasing amplitudes of both hemispheres. There were no statistically significant differences in EEG activities among the four groups (p > 0.05). After intubation, there was a consistent increase in frequencies and decrease in amplitudes. There were no differences in EEG activities among the four groups (p > 0.05). During maintenance with the inhaled anesthetics before the skin incision, there was a statistically significant decrease in frequency of the right frontal area in those who had received the inhaled anesthetic concentration to reach 1.4 and 1.65 MAC (p < 0.05).

Group	1 MAC	1.2 MAC	1.4 MAC	

Table 1. Characteristics of patients in groups based on the inhaled anesthetics dose

Group	1 MAC	1.2 MAC	1.4 MAC	1.6 MAC
sex, female (n) age (yr)	5	5	5	5
mean	38.22	39.50	40.00	46.5
95%CI	(31.16, 45.29)	(35.97, 43.03)	(34.35, 45.66)	(38.90, 54.10)
weight (kg)				
mean	47.96	57.83	55.06	56.5
95%CI	(39.87, 56.05)	(46.83, 68.83)	(47.92, 62.20)	(48.93, 64.10)

# The mortor responses and EEG changes before and after skin incision

From Table 3, there were no significant changes in the frequency before and after skin incision within the group. The frequencies in both hemispheres of group 1.4 and 1.65 MAC were significantly lower than in the 1 MAC group (p = 0.037). Only three out of 20 patients moved during the initial skin incision and the authors failed to demonstrate the association between the motor responses during the skin incision and EEG

### activities.

### The EEG at the stabilization of anesthesia

At the steady state of end tidal concentration of sevoflurane there was a consistent decrease in frequencies and increase in amplitudes of both hemispheres of groups with higher MAC values (p < 0.05). However, we failed to demonstrate the relationships between EEG changes and other clinical responses. All the studied patients did not show any evidence of

 Table 2. Mean values (95%CI) of the frontal EEG after induction, and after intubation in each group before giving a mixture of 1:2 nitrous oxide in oxygen and sevoflurane

Group	1 MAC	1.2 MAC	1.4 MAC	1.65 MAC	р
After induction					
Right frequency(Hz)	4.00 (2.4, 5.6)	4.00 (2.5, 5.5)	3.40 (2.6, 4.1)	4.25 (3.3, 5.2)	0.67
Left frequency(Hz)	3.70 (2.6, 4.8)	3.60 (3.1, 4.1)	3.80 (3.1, 4.5)	4.40 (3.3, 5.5)	0.53
Right amplitude(microvolt)	32.70 (29, 35)	39.40 (16, 13)	36.20 (28, 45)	44.00 (34, 54)	0.13
Left amplitude(microvolt)	33.10 (20, 27)	31.40 (21, 24)	31.60 (27, 36)	39.00 (29, 49)	0.37
After intubation					
Right frequency(Hz)	7.10 (5.4, 8.8)	5.90 (4.3, 7.4)	6.60 (4.7, 8.5)	7.50 (0.2, 14.8)	0.87
Left frequency(Hz)	6.60 (4.2, 9)	5.80 (4.3, 7.2)	7.60 (5.4, 9.8)	8.25 (2.5, 18.9)	0.75
Right amplitude(microvolt)	14.50 (11, 19)	24.21 (15, 33)	29.00 (7.1, 51)	23.00 (16, 29)	0.14
Left amplitude(microvolt)	15.80 (6.3, 25)	23.60 (18, 30)	22.80 (9.8, 36)	28.50 (26, 31)	0.27
During maintenance before skin incision					
Right frequency(Hz)	7.50 (5.9, 8.1)	5.00 (3.5, 6.5)	4.80 (4.1, 5.5)	4.25 (3.8, 4.7)	0.04
Left frequency(Hz)	7.10 (5.0, 9.2)	5.30 (3.8, 6.9)	4.80 (4.1, 5.5)	4.25 (3.8, 4.7)	0.17
Right amplitude(microvolt)	19.00 (8.1, 29)	24.00 (15, 32)	24.00 (18, 30)	27.00 (22, 32)	0.27
Left amplitude(microvolt)	14.20 (8.9, 20)	20.80 (13, 28)	22.00 (17, 28)	25.60 (20, 31)	0.12

Table 3. Mean values (95% CI) of the frontal EEG after before skin incision, after skin incision and at the steadystate of end tidal concentration of sevoflurane & nitrous oxide in oxygen to achieve 1 MAC, 1.2 MAC,1.4 MAC and 1.65 MAC during the operation

Group	1 MAC	1.2 MAC	1.4 MAC	1.65 MAC	р	
Before incision						
Right frequency(Hz)	7.00 (5.9,8.1)	5.00 (3.5, 6.5)	4.80 (4.1,5.5)	4.25 (3.8,4.7)	0.037	
Left frequency(Hz)	7.10 (5.0,9.2)	5.30 (3.8, 6.9)	4.80 (4.1,5.5)	4.25 (3.8,4.7)	0.17	
Right amplitude(microvolt)	19.00 (8.1,29)	24.00 (15, 32)	24.00 (18,30)	27.00 (22,32)	0.27	
Left amplitude(microvolt)	14.20 (8.9,20)	20.80 (13, 28)	22.00 (17,28)	25.60 (20,31)	0.1	
After incision						
Right frequency(Hz)	7.25 (5.6,8.9)	5.00 (3.5, 6.5)	4.60 (4.1,5.1)	3.75 (3.2,4.3)	0.025	
Left frequency(Hz)	8.25 (5.3,11)	5.70 (4.0, 7.3)	4.80 (4.1,5.5)	3.50 (2.9,4.1)	0.05	
Right amplitude(microvolt)	18.80 (4.0,34)	26.39 (13, 39)	24.40 (19,29)	35.00 (19,51	0.24	
Left amplitude(microvolt)	11.80 (5.0,19)	22.30 (12, 32)	21.10 (5.3,26)	35.00 (19,51)		
At stead state of end tidal concentration during operation						
Right frequency(Hz)	8.40 (7.4,9.4)	6.30 (4.6, 8.0)	5.00 (4.3,5.6)	4.00 (3.2,4.8)	0.01	
Left frequency(Hz)	8.80 (7.8,9.8)	6.50 (4.6, 8.3)	5.00 (4.4,5.6)	4.10 (3.1,5.1)	0.01	
Right amplitude(microvolt)	9.30 (8.4,10.1)	15.80 (11, 20)	23.80 (20,28)	30.00 (23,37)	0.004	
Left amplitude(microvolt)	9.40 (7.9,10.9)	14.80 (10, 20)	19.00 (17,21)	30.00 (20,40)	0.005	

J Med Assoc Thai Vol. 88 No. 11 2005

the recall during anesthesia and operation.

### Discussion

Electroencephalography is a medical imaging technique that reads scalp electrical activity generated by brain structures. EEG is used in clinical practice for detecting cerebral ischemia, monitoring for barbiturate suppression of oxygen cerebral metabolic rate and studying the CNS effects of drugs<sup>(16,17)</sup>. Interpreting the EEG during anesthesia attempts to monitor the effects of anesthetic agents in suppressing cerebral electrical activity<sup>(18,19)</sup>. The EEG can be obtained with the standard 19-electrode method however this is timeconsuming and impractical and requires expert interpretation. For the present study the authors used bilateral frontal electrodes where both frontal and nasion are convenient locations for electrode placement<sup>(20)</sup>. However, the use of EEG for monitoring depth of anesthesia is limited due to lack of "gold standard" in detecting the anesthetic depth.

Attempts to correlate EEG with clinical end points in previous studies have not been uniformly reported positive. In the present study the authors couldnot demonstrate the association between the electrical cerebral activity and other clinical end points, i.e. motor responses and post-operative recall of intraoperative events. Electroencephalographic measures, which reflect cortical activity, also failed to predict movement perfectly during thiopental anesthesia in humans<sup>(21)</sup> and isoflurane anesthesia in rats<sup>(22)</sup>. As the origin of movement in response to painful stimulation during anesthesia apparently is below the cortex<sup>(23)</sup>, measures of brain stem or spinal cord function might perform better. In a more recent study, Dwyer et al found that these measures do not predict depth of isoflurane anesthesia as defined by the response to surgical incision, the response to verbal command or the development of memory(24). This was also demonstrated by others<sup>(25)</sup>.

Many studies used end-tidal concentration to predict movement in patients given volatile anesthetics<sup>(26)</sup>. Concentration is both a measurable and reliable indicator because of the ease with which alveolar concentrations are established, maintained, and monitored, the reliability of the relationship between alveolar and brain concentrations<sup>(27)</sup>, and the steepness of the population dose-response curves for these agents <sup>(28)</sup>. In the present study at the steady state of end tidal concentration of the inhaled anesthetic, there is a consistent decrease in frequencies and increase in amplitudes of both hemispheres of groups with higher MAC values, the anesthetic effects on EEG was shown that the increasing depth of anesthesia (increase MAC from 1.0-1.65 MAC) decreased the frequency and increased the amplitude in EEG, as shown in other studies<sup>(29-31)</sup>.

The artifact in the recorded EEG may be either technical or patient-related. Technical artifacts, such as AC power line noise, can be decreased by decreasing electrode impedance and by shorter electrode wires. Between electrode and neuronal layers current penetrates through skin, skull and several other layers. Weak electrical signals detected by the scalp electrodes are massively amplified, and then displayed on paper or stored to computer memory<sup>(32)</sup>. The authors used commonly used scalp electrode consists of Ag-AgCl disks, 3 mm in diameter, with long flexible leads that can be plugged into an amplifier<sup>(33)</sup>. AgCl electrodes can accurately record also very slow changes in potential<sup>(34)</sup>. Patient-related artifacts are unwanted physiological signals that may significantly disturb the EEG, such as any minor body movement, sweating, EMG, and eye movements.

In the present study, although frequencies and amplitude of EEG also appeared during the period prior to induction, the authors could not record the controlled data. Because the high EMG levels and eye movement could interfere with the EEG signal in conscious or active patients, the summary statistics of the EEG values of the awake patient were not calculated. Comparison between EEG values before induction and after induction also could not be calculated, and also cannot compare with after intubation or maintenance. In patients who are not completely paralyzed by neuromuscular blocking agents, an EMG can be recorded from various muscle groups. Especially facial and neck muscles are used<sup>(35-37)</sup>. It has been shown that increasing EMG activity of facial and neck muscles reflects both recovery from the effect of neuromuscular blocking agents and a reduced depth of anesthesia, induced either by increased intensity of surgical stimulation or reduced anesthetic concentrations<sup>(35-38)</sup>. For the EEG, the interpretation of subtle changes in the raw EEG requires a trained electroencephalographer. Therefore, processing these EEG signals is required.

Most traditional processed EEG parameters are derived form power spectrum analysis. Recently, bispectral index has been introduced to clinical practice. Its use together with other modalities such as somato-sensory evoked potentials can help to learn more about pharmacodynamic of anesthetics.

In conclusion, the present study has provided basic information about cerebral electrical activity

during the balanced anesthesia with sevoflurane. As the anesthesia deepened by increasing MAC, the frequency decreased and the amplitude increased.

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### การใช้คลื่นไฟฟ้าสมองเพื่อศึกษาผลของยาสลบระหว่างการสลบแบบ Balanced Anesthesia ด้วย Sevoflurane

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**วัตถุประสงค**์: เพื่อศึกษาข้อมูลเบื้องต<sup>้</sup>นของการเปลี่ยนแปลงคลื่นไฟฟ้าสมองส่วน frontal หลังจากการนำสลบก่อน และหลังการลงมีดผ<sup>่</sup>าตัด และขณะที่ระดับยาดมสลบsevofluraneในทางเดินหายใจคงที่ที่ 1, 1.2, 1.4 และ 1.6 MAC และศึกษาความสัมพันธ์ระหว่างการเปลี่ยนแปลงของ EEG และการตอบสนองทางคลินิกอื่น ๆ เช่นการขยับตัว หรือ การระลึกเหตุการณ์ที่เกิดขึ้นระหว่างการผ่าตัดได้

**วัสดุและวิธีการ**: ตรวจคลื่นไฟฟ้าสมองในผู้ป่วยเพศหญิง 20คน ที่ได้รับยาสลบแบบ balanced anesthesia ที่โรงพยาบาลมหาราชนครเชียงใหม่ ด้วยเครื่อง ABM2 (DATEX) แสดง frontal EMG, frequency และ amplitude ของสมองทั้งสองซีก โดยสุ่มแยกเพื่อใช้ sevoflurane 1.0, 1.2, 1.4, และ 1.6 MAC ร่วมกับ nitrous oxide 66.67% นำ สลบด้วย thiopental 5 มิลลิกรัม/กก. และ fentanyl 1.5 ไมโครกรัม/กก. จากนั้นให้ pancuronium หรือ atracurium ในขนาดมาตรฐานระหว่าง maintenance

**ผลการศึกษา**: หลังการนำสลบด้วยthiopental ค่าเฉลี่ย frontal EMG (95%CI) ลดลงจาก 2.66 (1.63, 4.29) เป็น 1.41 (0.2, 1.61) และเมื่อ eyelash reflex หายไป ค่าเฉลี่ย frequency และ amplitude ของ frontal EEG ด้านขวาเท่ากับ 3.89 (3.29, 4.497) Hz, 39.58 (32.11, 47.05) MV และด้านซ้ายเท่ากับ 3.84 (3.43, 4.25) Hz, 33.55 (28.59, 38.61) MV คลื่นไฟฟ้าสมองแสดงข้อมูลดิบ พบการลดลงของ frequency และการเพิ่มขึ้นของ amplitude อย่างต่อเนื่อง ระหว่าง maintenance wบ frequency ด้านขวาลดลงอย่างมีนัยสำคัญทางสถิติที่ sevoflurane 1.4 และ 1.6 MAC (p < 0.05) (ANOVA) และเมื่อระดับsevofluraneในทางเดินหายใจคงที่ ที่ 1, 1.2, 1.4 และ 1.6 MAC พบ frequency ลดลง amplitude เพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ (p < 0.05) เมื่อได้รับMACสูงขึ้น (ตารางที่ 3) แต่จากการศึกษาครั้งนี้ ผู้วิจัยไม่สามารถแสดงให้เห็นความสัมพันธ์ระหว่างการเปลี่ยนแปลงของ EEG และการตอบสนองทางคลินิกอย่างอื่น **สรุป**: การศึกษาครั้งนี้ได้ข้อมูลเบื้องต้นของการเปลี่ยนแปลงคลื่นไฟฟ้าสมองส่วน frontal ระหว่างการสลบแบบ balanced anesthesia ด้วย sevoflurane และพบ frequency ลดลง amplitude เพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ (p < 0.05) เมื่อได้รับ MAC สูงขึ้น