의학석사 학위논문

The efficacy of intraoperative EEG to predict the occurrence of emergence agitation after sevoflurane anesthesia in children

세보플루레인 마취 후 각성 발작의 예측 인자로서의 수술 중 뇌파 검사의 유용성

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The efficacy of intraoperative EEG to predict the occurrence of emergence agitation after sevoflurane anesthesia in children

by
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A thesis submitted to the Department of Anesthesiology and Pain Medicine in partial fulfillment of the requirements for the Degree of Master of Science in Medicine (Anesthesiology and Pain Medicine) at Seoul National University College of Medicine

June 2013

Approved by Thesis Committee:

Professor _____Chairman
Professor _____Vice chairman
Professor _____

Abstract

Introduction: Emergence agitation (EA) is common after sevoflurane anesthesia in children, but its appearance cannot be predicted. We investigated whether the intraoperative EEG during sevoflurane anesthesia can indicate the occurrence or degree of EA in children.

Methods: EEG-derived parameters (SEF_{95}, beta, alpha, theta, and delta power) were measured at 2.0 vol% (during the maintenance of anesthesia) and 0.7 vol% (during emergence) end-tidal sevoflurane (EtSEVO) anesthesia in 29 pediatric patients (aged from 1 to 6 years). EA was evaluated using the emergence agitation score (EAS; 1-5) at the post-anesthetic care unit (PACU) on arrival (EAS 0) and at 15 and 30 minutes after the arrival (EAS 15 and EAS 30). The correlation between EEG-derived parameters and EA score was analyzed using Spearman correlation, and receiver operating characteristic (ROC) curve analysis was used to measure the predictability.

Results: EA occurred in 11 patients. The alpha power at 0.7 vol% of EtSEVO was positively correlated with EAS 15 and EAS 30 (Spearman correlation coefficient; 0.392 and 0.566, p = 0.035 and 0.001, respectively). The theta/alpha ratio at 0.7 vol% of EtSEVO was negatively correlated with EAS 30 (Spearman correlation coefficient; -0.478, p = 0.009). There were no significant differences in SEF_{95} at 2.0 vol% and 0.7 vol% of EtSEVO between patients with EA and those who without EA. The area under the ROC curve of the percentage of alpha bands at 0.7 vol% of EtSEVO and the occurrence of EA was

0.672.

Conclusions: We conclude that children showing high alpha powers and low theta powers (= low theta/alpha ratio) during emergence from sevoflurane anesthesia are at high risk of EA in PACU. (cris.nih.go.kr number, KCT0000652)

Keywords: Children, Emergence agitation, Intraoperative EEG, Sevoflurane

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Introduction

Sevoflurane is the most commonly used anesthetic agent. Its low blood/gas coefficient, non-pungency, and non-airway irritating properties made it as the anesthetic agent of choice for rapid induction and emergence in infants and children. However, emergence agitation (EA) after sevoflurane anesthesia is a concern for pediatric patient and caregivers. EA or emergence delirium (ED) is defined as an 'acute and transient confusional state',[1] and one of the most common side effects after general anesthesia with sevoflurane in children. The incidence reporting of EA is various from 10% to 50%, even up to 80%.[2-5]

EA itself is self-limited and does not show the severe sequelae, but it might cause difficulties in managing patients during post-anesthetic care unit (PACU) stay. Therefore, there were many literatures to prevent EA.[6-11] Also several risk factors of EA such as pre-school age[12], preoperative temperament and anxiety degree[13,14], sevoflurane[15,16], or surgical procedures[4] were suggested. However, there was no definite intraoperative predictive factor for EA.

There were several literatures reporting the abnormal findings of electroencephalography (EEG) in children during delirious status.[1,17,18] These findings suggested that the patients with EA showed the different EEG during general anesthesia. There was also one study that reported postoperative EA was associated with an increase in the portion of slow EEG rhythm at the lowest BIS value during the induction of anesthesia in children.[19] Therefore, EEG findings might have a correlation to the occurrence of EA in children.

We investigated whether the intraoperative changes of EEG during sevoflurane anesthesia are related with the occurrence or degree of

EA in children.

Methods

Patients and study design

This prospective double-blinded study was approved by the Institutional Review Board of Seoul National University Hospital (H-1202-094-399; Apr 12, 2012, Seoul, Korea) and registered at cris.nih.go.kr (KCT0000652). After obtaining of informed consent from parents or guardians whose children were planned to get strabismus surgery, we recruited 31 patients aged from 1 to 6 years. They were classified as American Society of Anesthesiologists physical status I or II. Patients with an abnormal airway, reactive airway disease such as asthma, or a history of upper respiratory tract infection in the preceding 4 weeks, mental retardation, attention deficit hyperactivity disorder, or cerebral palsy were excluded.

The patients did not receive premedication. Upon arrival at the operating room, the patients were monitored with electrocardiography (ECG), pulse oximetry (SpO_2), noninvasive arterial blood pressure, end-tidal CO_2 ($ETCO_2$), end-tidal sevoflurane concentration (EtSEVO), and single channel electroencephalographic monitor (EEG) (Solar 8000, GE, Milwaukee, WI, USA). All data from the patient monitor was recorded and stored in a personal computer.

Anesthesia was induced with 6 mg/kg of sodium thiopental and 0.02 mg/kg of atropine. After loss of consciousness, the patients were ventilated with 8.0 vol% of sevoflurane in 6 L/min of oxygen via a pediatric circle system. The patients were fully relaxed with 0.6 mg/kg of rocuronium and appropriate size of laryngeal mask airway (LMA) was inserted. The anesthesia was maintained around 2.0 vol% of sevoflurane (1 minimum alveolar concentration; 1MAC) in

approximately 50% oxygen in air with a total inflow of 2.5 L/min. The patients were ventilated with appropriate respiratory rate and tidal volume to keep 35-40 mmHg of $ETCO_2$. The concentration of sevoflurane was maintained 2.0 vol% during surgery and adjusted by blood pressure or heart rate. At the end of surgery, the concentration of sevoflurane reduced and maintained 0.7 vol% (MAC-awake) for 5 minutes before turning the vaporizer off. If the patient could response the verbal comment, LMA was removed and the patient was transferred to the post-anesthetic care unit (PACU) when he/she was fully awakened. In the PACU, ECG, NIBP, SpO_2, and the respiratory rate were checked.

EA was evaluated, using the emergence agitation score (EAS) (Table 1),[20] when the patient was first arrived at the PACU (EAS 0), 15 minutes after arrival (EAS 15), and 30 minutes after arrival (EAS 30) by one anesthesiologist at the 3 points. EA was defined when the children showed an EAS of 4 or 5 at least once, and 0.1 μg/kg of nalbuphine was administered intravenously to treat EA.

Analysis of EEG data

EEG was recorded continuously during anesthesia. Single monopolar channel was recorded from Ag-AgCl electrodes placed on the forehead. The electrode impedance was checked automatically and maintained at less than 5 kΩ. The EEG was analyzed in the frequency domain automatically. Spectral edge frequency 95 (SEF_{95} = the frequency below which 95% of the EEG power is located), spectral bands of beta (13-30 Hz) , alpha (8-13 Hz), theta (4-8 Hz) and delta (0-4 Hz) were analyzed, calculated and expressed as a percentage of total spectral power. These EEG-derived parameters at 2.0 vol% (during the

maintenance of anesthesia) and 0.7 vol% (during emergence) of sevoflurane anesthesia were analyzed. For quality control of EEG data, EMG signal greater than 50Hz were excluded.

Statistical analysis

Patients' characteristics were compared between patients with EA and patients without EA using Mann-Whitney U-test. The correlation of EEG-derived parameters and EAS was analyzed using Spearman correlation. If there was meaningful correlation, simple regression analysis was performed. ROC curve of EEG parameters and overall EA (EAS ≥ 4) were analyzed to evaluate the predictability of them. Statistical analysis was performed using SPSS 19.0 (IBM, Somers, NY, USA). *P* value < 0.05 was considered significant.

Table 1. Emergence agitation score.

Score	Behavior
1	Sleeping
2	Awake, calm
3	Irritable, crying
4	Inconsolable crying
5	Severe restlessness, disorientation

Results

Thirty one patients were enrolled this study and completed the EEG recording. However, two patients were discarded because of the data artifacts of EEG.

Patients' characteristics, surgery, anesthetic, and PACU stay time, and depth of anesthesia as SEF_{95} were shown in table 2. The incidence of EA was 11 out of 29 patients (37.9%). Six patients experienced EA on the arrival at PACU. Four who developed EA at 15 minutes after the arrival had an EAS of 2 or 3 at the arrival. After these 10 patients had been given 0.1 mg/kg of nalbuphine, only three still showed EA at 30 minutes after the arrival. One patient suffered EA through the PACU stay (39 minutes). The use of nalbuphine was effective in 63.4% (7/11). However, subgroup analysis showed no difference between responders and non-responders to nalbuphine. There was no significant adverse effect at PACU in any child.

Spearman correlation of EEG-derived parameters during sevoflurane anesthesia (2.0 and 0.7 vol% of EtSEVO) and EAS are shown in Table 3. The alpha power at 0.7 vol% of EtSEVO was positively correlated with EAS 15 and EAS 30 (Spearman correlation coefficient; 0.392 and 0.566, p = 0.035 and 0.001, respectively). The theta/alpha ratio at 0.7 vol% of EtSEVO was negatively correlated with EAS 30 (Spearman correlation coefficient; -0.478, p = 0.009). There were no significant differences in SEF_{95} at 2.0 vol% and 0.7 vol% of EtSEVO between patients with EA and patients without EA (Table 2.). An example of the different courses of theta and alpha powers during sevoflurane anesthesia in patients with and without EA is shown in Figure 1.

The area under the ROC curve of EEG-derived parameters for EA is

shown in Table 4. The area under the ROC curve of the percentage of alpha bands at 0.7 vol% of EtSEVO and the occurrence of EA was 0.672 (Figure 2.), and 29.3% of alpha bands at 0.7 vol% of EtSEVO showed a 72.7% sensitivity and 55.6% specificity. The positive predictive value (PPV) and negative predictive value (NPV) were 0.58 and 0.43.

Table 2. Patients' characteristics.

	All (n=29)	EA(+) (n=11)	EA(-) (n=18)	*p* value
Age (year)	3.7 ± 1.5	3.7 ± 1.3	3.7 ± 1.6	0.95
Sex (M/F)	14/15	6/5	8/10	N/A
Weight (kg)	102.1 ± 12.3	104.2 ± 11.1	100.9 ± 13.2	0.64
Height (cm)	16.3 ± 4.3	16.7 ± 3.9	16.1 ± 4.6	0.55
Surgery time (min)	26.2 ± 12.2	29.8 ± 15.6	24.1 ± 9.4	0.34
Anesthetic time (min)	47.2 ± 13.8	50.9 ± 16.4	45.0 ± 11.9	0.41
PACU stay (min)	36.0 ± 9.1	35.1 ± 8.6	36.5 ± 9.7	0.71
SEF_{95} at 2.0 vol% (Hz)	12.1 ± 2.7	11.6 ± 2.4	12.4 ± 3.0	0.44
SEF_{95} at 0.7 vol% (Hz)	18.7 ± 3.8	18.2 ± 3.3	19.0 ± 4.1	0.78

Values are presented as mean ± SD.

Statistically significant, *P < 0.05

EA; Emergence agitation, EA(+); Patients with emergence agitation, EA(-); Patients without emergence agitation, PACU: Post-anesthetic care unit.

Table 3. Correlation analysis of EEG-derived parameters and EA score.

EtSEVO	EEG (Mean ± SD)		Spearman correlation coefficient (*p* value)		
			EAS 0	EAS 15	EAS 30
2.0 vol%	SEF_{95}(Hz)	12.1 ± 2.7	-0.213 (0.267)	-0.012 (0.951)	-0.195 (0.311)
	Beta(%)	19.5 ± 4.8	-0.241 (0.208)	-0.136 (0.481)	-0.185 (0.338)
	Alpha(%)	22.2 ± 4.7	-0.117 (0.547)	0.216 (0.261)	0.046 (0.813)
	Theta(%)	25.7 ± 4.8	0.173 (0.369)	-0.269 (0.158)	-0.243 (0.203)
	Delta(%)	32.3 ± 7.1	0.049 (0.800)	0.066 (0.732)	0.235 (0.220)
	Theta/Alpha	1.2 ± 0.3	0.200 (0.297)	-0.243 (0.204)	-0.181 (0.346)
0.7 vol%	SEF_{95}(Hz)	18.7 ± 3.8	0.075 (0.697)	0.018 (0.927)	-0.160 (0.408)
	Beta(%)	32.6 ± 8.3	0.033 (0.863)	-0.005 (0.979)	-0.169 (0.381)
	Alpha(%)	31.3 ± 7.0	0.144 (0.456)	0.392 (0.035)*	0.566 (0.001)*
	Theta(%)	16.8 ± 4.7	0.006 (0.977)	-0.164 (0.395)	-0.248 (0.194)
	Delta(%)	19.1 ± 6.3	-0.022 (0.090)	-0.306 (0.107)	-0.146 (0.449)
	Theta/Alpha	0.6 ± 0.2	-0.134 (0.489)	-0.282 (0.139)	-0.478 (0.009)*

Statistically significant, *P < 0.05

EA; Emergence agitation, EtSEVO; End-tidal sevoflurane concentration, EAS 0; EA score at the arrival on post-anesthetic care

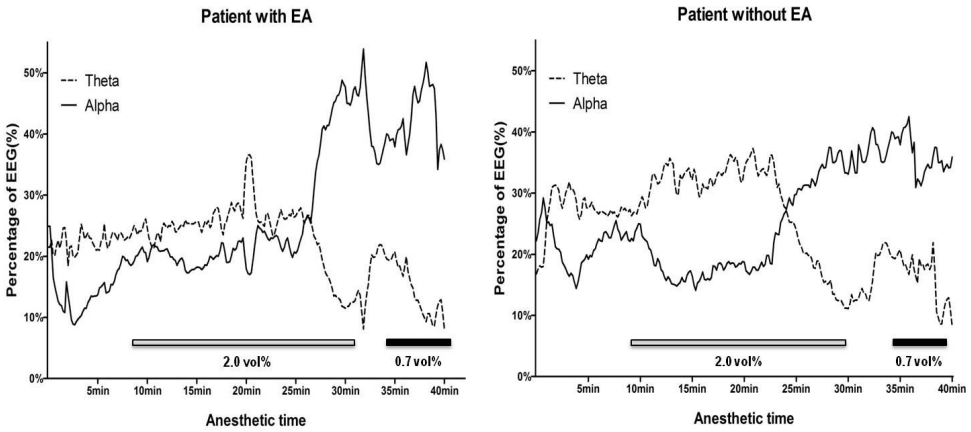
unit, EAS 15; EA score 15 minutes after arrival, EAS 30; EA score 30 minutes after arrival, SEF_{95}; Spectral edge frequency 95.

Table 4. AUC of ROC curve of EEG-derived parameters for EA.

EEG-parameters	EtSEVO	AUC of ROC curve
Alpha	0.7 vol%	0.672
Theta/Alpha ratio	0.7 vol%	0.374

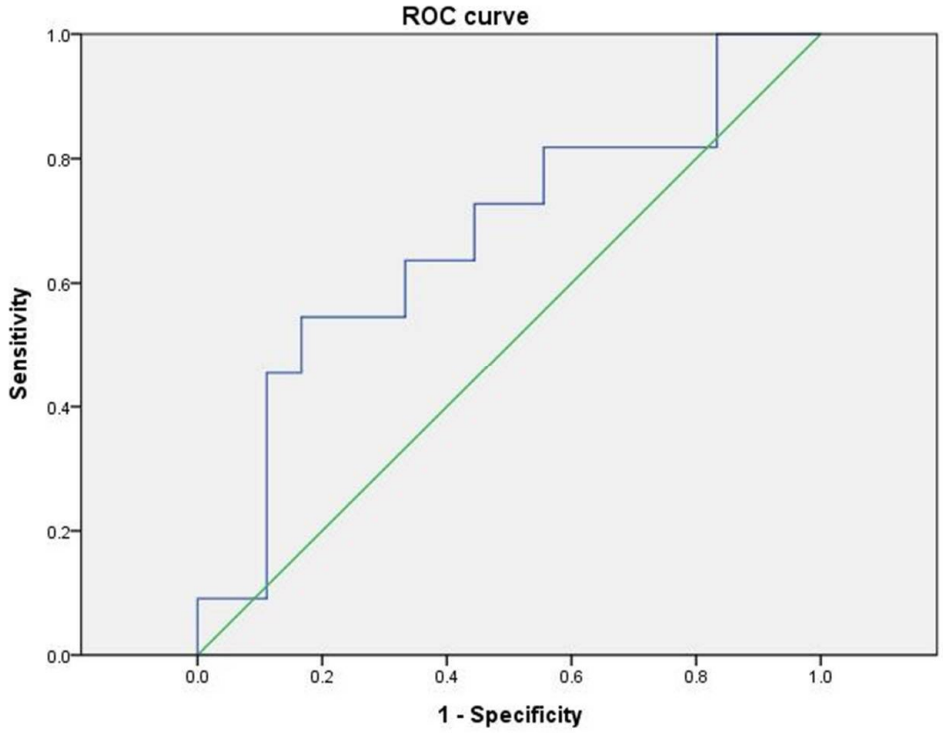
EA; Emergence agitation, AUC; Area under curve.

Figure 1. An example of time courses of percentages of theta and alpha bands of EEG during sevoflurane anesthesia.



3-year-old child with emergency agitation (EA) (left) showed high alpha power and low theta power during the maintenance of anesthesia (theta; 22.7, alpha; 23.5, theta/alpha ratio; 0.96, and SEF_{95}; 16.6) and emergency (theta; 12.8, alpha; 46.2, theta/alpha ratio 0.28, and SEF_{95}; 11.1), whereas 3-year-old child without EA (right) showed low alpha power and high theta power during the maintenance of anesthesia (theta; 34.0, alpha; 19.8, theta/alpha ratio; 1.71, and SEF_{95}; 11.3) and emergency (theta; 17.1, alpha; 36.1, theta/alpha ratio; 0.47, and SEF_{95}; 17.2). EAS of these children at 0, 15, and 30 minutes after post-anesthetic care unit arrival were '3 / 5 / 4' (left), and '2 / 1 / 2' (right), respectively. End-tidal sevoflurane concentrations are shown with bars.

Figure 2. ROC analysis of alpha power at 0.7 vol% of EtSEVO and the occurrence of EA. The area under ROC curve is 0.672.



EA; Emergency agitation, EtSEVO; End-tidal sevoflurane concentration

Discussion

Our data showed significant relationship between the percentage of EEG bands (high alpha powers) during emergence from sevoflurane anesthesia and the EAS in PACU.

The rhythmic activity in EEG is divided into several specific frequency bands; in the present study, the relative portion of beta, alpha, theta, and delta waves were monitored. Beta waves (13-30 Hz) are thought to be the result of sensory stimuli activating reticular activating system which desynchronizes the thalamic pacemaker cells. Alpha waves (8-13 Hz) are usually seen in relaxed, awake patients with their eyes closed, and thought be related to the decrease of inhibitory activity of reticular nucleus on thalamic pacemaker cells. During alpha wave-predominant meditation or light sedation, thalamic pacemaker cells regulate and synchronize the thalamocortical activity. Theta waves (4-8 Hz) are normally seen during sleep and thought to be related to the inhibition of thalamic pacemaker cells by gamma-aminobutyric acid (GABA)-ergic action of reticular nucleus. During deep sleep, delta (0-3 Hz) waves are prominent and reflect extreme depression of thalamus.[21]

According to the thalamic theory, halogenated inhalation anesthetics cause unconsciousness by decreasing the neuronal activity of thalamocortical neurons (thalamic shunt).[22] Previous studies revealed this influence of inhalation anesthetics on EEG-derived parameters (SEF_{95} and the four frequency bands)[23,24]; incremental concentration of inhalation anesthetics changes the EEG from fast (beta- and alpha-) waves during spontaneous arousal to slow (theta- and delta-) waves during anesthesia. SEF_{95} has been used to estimate the depth of

anesthesia and previous studies suggested SEF_{95} values for adequate anesthesia (10-14 Hz) and awaken state (15-20 Hz).[23,24] The values of SEF_{95} data in the present study during the maintenance of anesthesia (2.0 vol% of EtSEVO) and emergence (0.7 vol% of EtSEVO) were within these ranges, respectively (Table 2.). However, SEF_{95} value does not reflect the relative percentage of each spectral band (beta, alpha, theta, and delta-waves); it only reflects the sum of them. Therefore, it might be possible that there was a difference in alpha and theta bands without the difference in SEF_{95} values between patients with EA and without EA (Table 2.).

The previous study presented that children those who demonstrated agitation during induction showed slower EEG frequency during the second minute of induction compared with those who did not demonstrate agitation regardless of the kinds of premedication.[19] In the present study, induction of anesthesia was performed with high concentration of sevoflurane (8.0 vol%) with high fresh gas flow rate (6 L/min). Therefore, changes of EEG-derived parameters during induction were so rapid to observe. Instead, we obtained EEG-derived parameters at 0.7 vol% of EtSEVO (MAC-awake) for 5 minutes during emergence.

Higher alpha power and lower theta/alpha ratio during emergence from sevoflurane anesthesia were positively correlated to EAS in PACU. This trend means less GABA-ergic inhibition of thalamic pacemaker cells, and more thalamocortical activity during emergence from sevoflurane anesthesia.[22] Taken together, rapid recovery from EEG suppression of sevoflurane anesthesia was correlated with high EAS at PACU. There are two possible explanations for this phenomenon; patients with EA have high baseline EEG activity and/or

are more resistant to EEG suppression of sevoflurane. However, the PPV and NPV of alpha power at 0.7 EtSEVO were low and failed to show good predictablity of the occurrence of EA.

Smit DJ *et al.* [25] showed that individual differences in EEG spectral power reflect their genetic variance in brain development. Factors such as neuronal myelination, synaptic density, and dendritic outgrowth affect the volumes of gray and white matter and eventually results in different baseline theta and alpha spectral powers. Pediatric patients have large individual differences in the development of their central nervous system[26], and these differences can affect not only their baseline EEG activity and their EEG response to sevoflurane anesthesia, but also postoperative EA. However, no evidence exists regarding these issues.

We could not monitor postoperative EEG during PACU stay due to motion artifacts. There is no previous study about EEG monitoring in PACU. Previous studies conducted in intensive care unit or ward presented that the delirious patients showed significant lower alpha power and higher theta power, resulting in high theta/alpha ratio.[27-30] However, only one study was conducted in pediatric patients,[27] and only one study was conducted after general anesthesia. [30] Therefore, pediatric EEG data during EA after sevoflurane anesthesia could be hardly obtained.

There are several limitations in the present study. At first, it was a non-controlled, observational study of small score. Second, as mentioned before, we could not measure EEG at PACU, because of patients' discomfort and involuntary movement. Monitoring EEG at PACU, especially during EA, would have given more information about EA. Third, sevoflurane that remain in the body may played a role in

sedation, pain control, and EA at PACU. Forth, the present study was conducted under sevoflurane anesthesia for strabismus surgery. Although adequate muscle relaxation was achieved and EMG was monitored simultaneously to exclude the effect of electric activity muscle, passive movement of extra-ocular muscle and eyelid would affect the EEG signal. Also, along with otolaryngeal surgery, strabismus surgery showed high incidence of EA than other pediatric surgery.[4]

In the present study, the authors found that the relative percentage of EEG bands during sevoflurane anesthesia showed significant relationship with postoperative EAS. Children showing high alpha powers and low theta/alpha ratio during emergence from sevoflurane anesthesia are at high risk of EA at 15 and 30 minutes after the arrival on PACU and need more careful attention.

Larger clinical trial with EEG monitoring at PACU and during EA should be needed in the future for an accurate assessment. Also, investigating the effect of alpha power-lowering at the emergence from sevoflurane anesthesia to prevent EA may clarify the relationship between intraoperative EEG and EA.

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국문 초록

서론: 마취 후 각성발작 (Emergence agitation; EA)은 소아 환자의 세보플루레인 마취 후 흔히 나타나는 부작용이지만, 그 발생을 예측하는 것은 어렵다. 본 연구는 수술 중 뇌파 (Electroencephalograpy; EEG) 측정을 통하여 수술 후 각성발작을 예측할 수 있는지 밝히기 위하여 진행되었다.

방법: 뇌파 측정은 29명의 소아 환자에서, 호기말 세보플루레인 농도(EtSEVO) 2.0 vol% (마취 유지 중)과 0.7 vol% (마취 회복 중)일 때 이루어졌으며, SEF95, beta, alpha, theta, 및 delta power를 측정하였다. 각성 발작은 1점부터 5점으로 이루어진 각성발작점수 (Emergence agitation score; EAS)를 사용하여, 마취 회복실 도착 직후(EAS 0), 도착 15분 뒤(EAS 15), 도착 30분 뒤(EAS 30)에 측정하였다. 뇌파 측정값들과 각정 발작 점수와의 관계는 Spearman correlation과 단순 회귀 분석을 사용하여 분석하였으며, 유의한 변수의 진단적인 유용성을 알아보기 위해 receiver operating characteristic (ROC) 곡선을 그려보았다.

결과: 마취 회복 중(0.7 vol% EtSEVO)에서의 alpha power는 EAS 15와 EAS 30과 양의 상관관계를 보였다 (순서대로, Pearson 상관계수; 0.392 및 0.566, P=0.035 및 0.001). 마취 회복 중(0.7 vol% EtSEVO)의 theta/alpha 비율 또한 EAS 30과 음의 상관관계를 보였다 (Pearson 상관계수; -0.478, P = 0.009). 마취 회복 중(0.7 vol% EtSEVO)의 alpha power와 각성발작의 발생여부로 작성한 ROC 곡선의 곡선하면적은 0.672이었다.

결론: 세보플루레인 마취를 받는 소아 환자에서 마취 회복 중에 높은 alpha power와 낮은 theta/alpha 비율을 보인 환자에서는 마취 후 각성발작의 위험이 높다. (cris.nih.go.kr number, KCT0000652)

주요어: 각성 발작, 소아, 수술 중 뇌파, 세보플루레인

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