An Alternative Method for Determination of Anesthesia Depth

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KEY WORDS: remifentanil, depth of anesthesia, electroencephalography (EEG), quantitative EEG analysis, spectral analysis

ABSTRACT
In this study we investigated quantitative electroencephalography (QEEG) changes in subjects with two doses of remifentanil, and the relation between anesthesia level and basic EEG waveforms, topographically.

Twenty healthy subjects, undergoing varicose vein surgery, received total intravenous (IV) technique of anesthesia with propofol (4mg/kg/h) and different remifentanil infusions (0.4 µg/kg/min for Group I and 0.2 µg/kg/min for Group II). All subjects were evaluated by QEEG changes before anesthesia and monitored throughout the anesthesia procedure. Effects of surgical procedure and awareness responses on these parameters also were evaluated.

All 20 subjects showed similar changes with 2 different doses of remifentanil. Before anesthesia, visual analysis of EEG and QEEG analysis had no significant changes between the groups. In the first group, absolute frequency of delta significantly increased throughout the procedure, compared with the second group. After surgical incision posterior beta power predominance significantly increased as a determinant of light anesthesia level in the second group, represented an arousal responses. The higher dose (0.4 µg/kg/min) remifentanil infusion had lower mean frequency of QEEG than the 0.2 µg/kg/min infusion rate.

When both low- and high-dose infusions are used, visual and quantitative analysis of EEG have a significant role in evaluating anesthesia level.

INTRODUCTION
The aim of anesthesia is preventing the sensation of pain and ensuring a state of
unconsciousness and sedation so that
the patient cannot recall the surgical
procedure. Total intravenous anesthe-
 sia (TIVA) has been put forward as a natu-
 ral extension of balanced anesthesia.
TIVA has gained increasing importance
with the advent of new drugs such as
propofol and opioid derivatives. Remifen-
tanil hydrochloride (G187084B), one of
the opioid agents used in TIVA applica-
tion, is a phenylpiperidine derivative with ν-opi-
oid agonist effects and unique pharma-
cokinetic properties. Estimation of “depth of anesthesia” is
an ongoing problem. The use of clinical
signs for assessing depth of anes-
thetia, though universally applied, is
notoriously unreliable. Heart rate,
blood pressure, indirect hemodynamic
measurements are commonly used in
anesthesia practices to determine anes-
thesia level. Nevertheless, hemodynamic
responses are inadequate for following a
patient’s state of consciousness.

For this ongoing problem, character-
istic electroencephalography (EEG)
waveforms and computerized analyses
are regarded as more sensitive methods
to assess patient consciousness during
general anesthesia. Today, nonparamet-
ric methods (eg, interval analysis, power
spectrum analysis, bispectral analysis),
parametric methods, mimetic analysis,
matched filters, and topographic analysis
are being used for various purposes to
analyze EEG. The most commonly used
method is Fast Fourier Transform (FFT)
which was a statistical method for the
transformation of EEG wave using a
special analysis.

While halogenated inhalation anes-
thetics lead to dose-related amplitude
and frequency reduction in EEG, intra-
 venous analgesics cause less evident
changes, such as the fluctuation of wave
amplitude in EEG. Furthermore, when
compared with inhalation anesthetics,
intravenous sedative-hypnotic drugs
(droperidol, barbiturates, benzodi-
 azepins, etomidate, propofol), after ini-
tial activation, result in loss of alpha,
increased frontal beta in low doses, and
diffuse theta activity in high doses. Also,
opiates caused a loss of beta activity
and, in higher doses, increased general-
ized delta activity.

Although several attempts have
been made to describe anesthesi-
induced topographic changes in the
EEG, dose-related changes of
remifentanil and the relationship
between the anesthesia level and basic
EEG power had not been explored.
Therefore, the aims of this study are to
compare the quantitative EEG (QEEG)
changes in subjects with two doses of
remifentanil and to investigate the rela-
tionship between anesthesia and basic
EEG waveforms, topographically.

MATERIAL AND METHODS
Subject Population
This cross-sectional case control study
was conducted at the Mersin University
Hospital. After obtaining approval from
the Ethics Committee and written
informed consent, 20 right-handed
patients (graded as ASA I, II) undergo-
ing elective varicose vein surgery were
selected for the study. We chose only
right-handed subjects because of the
physiological hemisphere asymmetry of
the EEG analysis.

Anesthesia Protocol
After the computerized EEG data for
normality were collected, anesthesia
induction was performed with propofol
(2 mg/kg) and remifentanil (0.5 μg/kg). After
achieving neuromuscular block
with cis-atracurium (0.15 mg/kg), the
trachea was intubated. Each patient was
given 5 mL/kg lactated Ringer’s solu-
tion during the operation. The patients
were randomly divided into two groups.
Group I was administered propofol 4 mg/
kg/h, remifentanil 0.4 μg/kg/min.
Figure 1. The comparison of the effect of 2 doses of remifentanil on mean frequencies of (A) delta, (B) theta, (C) alpha, and (D) beta waves. It is shown that absolute delta power is more prominent in the first group throughout anesthesia.
Group II was administered remifentanil 0.2 µg/kg/min and the same infusion rate of propofol as was used in Group I. Electrocardiography (ECG), pulse oximetry, systolic blood pressure (SBP), diastolic blood pressure (DBP), and
heart rate (HR) measurements by non-invasive methods (Drager Cicero M, Germany) were recorded at 3 minute intervals throughout the surgical procedure.

**EEG Protocol**

Computerized EEG data were collected from the 14 monopolar electrode sites of the International 10/20 system, referred to Cz. The following 12 channel and Ag-AgCl disk electrodes (Medelec, Oxford, England) were used for the data collection: O1-P3, P3-T5, T5-T3, T3-F7, F7-F3, F3-Fz, Fz-F4, F4-F8, F8-T4, T4-T6, T6-P4, and P4-O2 (transverse montage). Electrodes were applied with collodion, and impedances were kept below 5 KΩ-W. EEG recordings were made with Medelec Profile Equipment and software (Oxford, England). The EEG amplifiers had band passes from 0.3 Hz to 70 Hz (3 dB points), with a 60 Hz notch filter. The frequency and amplitude of the device were adjusted to 15 mm/sec and 100 μV, respectively. The same neurology and biophysics specialists, who are unaware of the patient subgroups, analyzed the EEG data of patient groups visually and quantitatively.

The QEEG measurements were made before and after anesthesia induction (Step I and Step II), after surgical incision (Step III), and during the operation (Step IV) at transverse montage (Figure 1). Data were subsequently segmented into consecutive 1.28-second periods. Periods contaminated by blinks, eye movements, and technical artifacts were excluded from analysis using a rejection criterion of ±100 μV on any channel. These criteria produced artifact-free data, as verified by direct visual inspection of the raw data. The artifact-free EEG was converted from the time to the frequency domain using an FFT. Distributions of basic EEG waves by frequency (ie, delta [0.5 Hz to 3 Hz], theta [3.5 Hz to 8 Hz], alpha [8.5 Hz to 12 Hz], and beta [12.5 Hz to 30 Hz]) and the mean frequency of each step were determined by power spectra using an FFT. General distribution patterns of each waveform in each step of the procedure were averaged irrespective of the channels, for all subjects.

**Statistical Analysis**

The data obtained from each step were compared using multivariate analysis of variance for repeated measures and Mann-Whitney U, Wilcoxon W tests were used for statistical analysis of hemodynamic data. For the analysis of the quantitative data, a variance analysis model using a total of 4 factors was used. These factors and their levels were in the following order: transverse montage (12 channels), anesthesia procedure (4 steps), EEG waveforms (alpha, beta, theta, delta, and mean frequency), and subject groups (Groups I and II). Pearson correlation analysis was performed by the Enter method for the correlate between the hemispheres and topographic regions. Mean values were expressed as ± SD. All tests were 2-tailed and only P values ≤0.05 level were considered significant.

**RESULTS**

The median age of subjects was 25.3 years (±7 years) and ranged from 17 to 38 years.

Visual analysis of EEG recordings showed increased amplitude and slow wave activity during the anesthesia induction and throughout the procedure, accompanied by sparse sleep spindle and K complexes. During the surgical incision, increased beta activity was observed. The comparison of 4 major waveforms and mean frequency according to each step of anesthesia and 2 doses of remifentanil are summarized in Table 1 and Figure 1.

According to changes by QEEG, both remifentanil doses maintained
effective anesthesia levels after induction. There was no significant difference of the EEG recordings after anesthesia induction of both groups and absolute frequency of delta significantly increased in Group I during surgical incision ($P=0.02$, 95% CI: 0.72-10.06) and throughout the anesthesia ($P=0.004$, 95% CI: 3.01-13.80). After surgical incision, an increase in beta activity in posterior regions of hemispheres in Group II was more dominant than in Group I (19.98±4.82% vs. 31.24±3.81%, $P=0.000$, 95% CI: 15.35-71.6). These results suggest increased arousal response in Group II, and according to the mean frequency of QEEG, there was a more steady-state depth of anesthesia in Group I compared with Group II ($P=0.03$, 95% CI: 0.13-4.19).

When all the EEG data collected from both of the groups was averaged, there was an important increase of delta activity ($P=0.014$, CC=0.777) and decrease of alpha activity ($P=0.021$, CC=0.746) in frontal regions. There was an important hemisphere asymmetry in favor of the right hemisphere (nondominant hemisphere). In addition, increased beta activity ($P=0.05$, CC=0.651) was determined in the left frontal regions. The analysis of hemisphere asymmetry showed increased frontal delta power ($P=0.03$, CC=0.701) and decreased alpha power ($P=0.04$, CC=0.696) in the right frontal regions, compared with the left. Also, increased temporal delta power ($P=0.04$, CC=0.689) and decreased beta power predominance ($P=0.003$, CC=0.860) were assessed in the right frontal regions, compared with the left. There was no significant hemisphere asymmetry in the parietal and occipital regions.

As an important parameter, mean frequency (BF) showed significant difference only in Step IV between the groups, in favor of high remifentanil doses (Group I). Lower value of BF represented a high percentage of slow waves as an indicator of anesthesia depth (Table 1).

<table>
<thead>
<tr>
<th>Wave forms</th>
<th>Step I</th>
<th>Step II</th>
<th>Step III</th>
<th>Step IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta Group I</td>
<td>35.08±5.25</td>
<td>62.40±6.68</td>
<td>47.63±4.90*</td>
<td>44.42±5.94*</td>
</tr>
<tr>
<td>Group II</td>
<td>30.27±5.27</td>
<td>63.62±5.82</td>
<td>42.23±5.03</td>
<td>36.01±5.54</td>
</tr>
<tr>
<td>Theta Group I</td>
<td>13.48±6.17</td>
<td>12.27±4.48</td>
<td>13.63±3.50</td>
<td>15.33±3.47</td>
</tr>
<tr>
<td>Group II</td>
<td>17.59±3.97</td>
<td>12.08±3.67</td>
<td>12.05±4.46</td>
<td>14.87±5.69</td>
</tr>
<tr>
<td>Alpha Group I</td>
<td>18.43±4.35</td>
<td>14.63±3.44</td>
<td>18.02±3.41</td>
<td>19.00±3.39*</td>
</tr>
<tr>
<td>Group II</td>
<td>20.98±6.35</td>
<td>14.34±4.27</td>
<td>18.50±3.20</td>
<td>16.64±1.52</td>
</tr>
<tr>
<td>Beta Group I</td>
<td>33.64±4.30</td>
<td>12.84±2.84</td>
<td>19.98±4.82</td>
<td>21.93±5.99</td>
</tr>
<tr>
<td>Group II</td>
<td>31.36±4.84</td>
<td>12.55±4.25</td>
<td>31.24±3.81**</td>
<td>21.92±5.92</td>
</tr>
<tr>
<td>BF Group I</td>
<td>7.53±1.92</td>
<td>2.63±0.85</td>
<td>3.20±0.76</td>
<td>3.57±1.50</td>
</tr>
<tr>
<td>Group II</td>
<td>7.37±2.04</td>
<td>2.63±0.83</td>
<td>3.20±1.63</td>
<td>5.73±2.65*</td>
</tr>
</tbody>
</table>

Step I: before anesthesia
Step II: after anesthesia induction
Step III: after surgical incision
Step IV: during surgery
BF: mean frequency
* $P<0.05$
** $P<0.001$
DISCUSSION

The results recorded in this study showed important differences between the two remifentanil doses using hemodynamic and EEG data, especially with the higher doses (0.4 µg/kg·min⁻¹) in nondominant frontotemporal regions of the records.

Although several attempts have been made to describe anesthesia-induced topographic changes in the EEG and to explore the role of EEG during anesthesia monitoring, none of these reports provided direct comparisons across different doses of anesthetics.

Other studies have suggested that EEG is a valuable method for determining anesthesia depth. A correlation between anesthesia and various EEG parameters (e.g., EEG power spectrum, Bispectral index [BIS]) has been reported in these studies. BIS, a statistical and empiric parameter, has been supported by several studies for determining anesthesia depth. Although the acceptance of QEEG waves using spectral index methods for determining anesthesia is growing, manually (visually) evaluated EEG wave analysis methods also can be used.

In this study modifications were made to the filter and recording settings of that routine EEG used in the EEG laboratory of Neurology Department.

Bischoff and colleagues used a 16-channel recording system accompanied with ECG for artifact control and electrocuglography monitoring to assess electrophysiological arousal response to surgical stimulation. Investigators reported a decrease in delta intensity, and alpha dominance in the central regions of the brain as a response to intubation and surgical incision. In our study, transcortical montage was preferred because of its 12-channel recording system and representation of a wide cortical region. Additionally, this method serves as an analysis of regional differences and hemisphere asymmetry during the deepest stage of anesthesia. To achieve artifact control, the filter gap was increased and accompanying ECG monitoring and EEG recordings were divided into 5-second sections; the average of 30 sections was evaluated for each step. Eye movements were evaluated visually. In this study, EEG wave changes were evaluated and no significant difference was found between the Groups in Step II. EEG wave changes, thought to be related to a decrease of anesthesia depth (Step III), occurred after incision.

McGregor and colleagues compared the combinations of remifentanil-isoflurane and remifentanil-propofol among patients undergoing varicose vein surgery and found that in the measurements of auditory evoked response, remifentanil 0.5 µg/kg·min⁻¹ + propofol depressed the response produced by surgical incision. According to 2 studies reported by Strachan and colleagues and Hogue and colleagues, infusion of remifentanil at 0.1 µg/kg·min⁻¹ reduced BIS scores and greater reduction in BIS scores were detected with incremental infusion of remifentanil. In addition, intraoperative response could be controlled effectively in applications of remifentanil infusion at 0.25 µg/kg to 4.0 µg/kg·min⁻¹.

Our results, as reported in Table 1 and Figure 1, demonstrate that an adequate anesthesia level was reached in both groups. On the other hand, the level of anesthesia was maintained at a more steady state with remifentanil infusion at 0.4 µg/kg·min⁻¹ as indicated by an increase in delta activity and a decrease in mean frequency. The superiority of the method used in this study over BIS is that it enables us to obtain a wider cortical recording. However, a lack of simultaneous interpretation is a great disadvantage. The authors believe that the data in the current study can
become more practical with a software cooperation study. Therefore, the method used in this study can be presented as a more effective method.

As reported by Kisimoto and colleagues, the current study showed an important hemispheric and regional asymmetry, predominance right hemisphere, and frontal an temporal regions in patients anaesthetized with propofol and remifentanil. These findings are in contrast to those studies of Gugino and colleagues which were made by sevoflurane and propofol. It is possible that hemispheric and topographical differences not observed in this study represent different study protocols. On the other hand, regional differences between the propofol and sevoflurane groups were generally similar to this study’s results. As recommended by Gugino and colleagues, our results suggest that QEEG can be used to monitor anesthetic delivery with the changes of the right hemisphere and anterior regions of the brain predominantly. These findings had two important implications. QEEG could first be used to explore the neuro-anatomical basis of the depth of anesthesia and then to indicate depth of anesthesia simply and reliably. In the authors’ opinion, correlated with depth of anesthesia level, high doses of remifentanil created more prominent slow wave (delta and theta) activity and a simultaneous decrease in alpha and beta activity. These changes might be shown by decreased mean frequency and represent a decrease in cortical/cortical generator activity with a shift toward control by the thalamocortical and hippocampal/septal generators of slow wave activity. Arousal, triggered by surgical incision, might be associated with reversal of these effects.

CONCLUSION

It was concluded that visual and quantitative analysis of EEG have significant roles in the evaluation of the patient’s consciousness and level of anesthesia.

REFERENCES


