Effect of Remifentanil on Narcotrend and Bispectral Index—Comparison with Propofol

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Abstract

BACKGROUND: Remifentanyl is a central acting μ -opioid receptor agonist used for balanced anesthesia and analgosedation. The effect of remifentanyl on the bispectral index (BIS) and the Narcotrend index (NT) during general anesthesia is controversial. In this study, we investigated the effect of remifentanyl on Electroencephalograph (EEG) under BIS and NT by administrating remifentanyl alone to patients, as compared with propofol.

METHODS: 30 patients were enrolled in this study randomized to receive target-controlled infusion of remifentanyl (2-6 ng/ml) or propofol (2-5 μ g/ml), respectively. The values of BIS, NT, vital signs and State of consciousness were recorded.

RESULTS: All patients remained consciousness throughout remifentanyl administration. However, a sharp decrease in NT was observed in each patient when CeREMI (remifentanyl effect site concentration) achieved 4/6 ng/ml. With the increasing of CePRO (propofol effect site concentration), the patient's consciousness gradually reached an anesthetic state ($P=0.000$). The linear correlation analysis showed that both BIS and NT had a high correlation in predicting CePRO, while a low correlation in predicting CeREMI. The effect of remifentanyl and propofol on EEG was different although NT/BIS index were at the same range. Remifentanyl induced a significant increase in δ power of the EEG. In contrast, propofol resulted in increases of δ and α power.

CONCLUSION: Our data demonstrated that when remifentanyl is used alone for analgesia, neither NT nor BIS can accurately reflect the patient awareness, especially for NT. A single numerical index of NT or BIS can correspond to different EEG wave form as well as consciousness state.

Trial registration: *Chinese Clinical Trial Registry, ChiCTR1900026874. 24/10/2019.*

<https://www.chictr.org.cn/listbycreator.aspx>

Highlights

1. Remifentanyl demonstrates dissociation of the NT/BIS index and the patients' real consciousness status
2. A single numerical index of NT or BIS can correspond to different EEG wave form as well as consciousness state.
3. Remifentanyl induces significant increase in δ power, while propofol resulted increases both δ and α power of the EEG waveform.

Introduction

Electroencephalograph (EEG) monitoring is an important method for detecting neurophysiological changes in the brain of patients during the perioperative period. Currently available depth-of-anesthesia

monitoring devices measure forehead EEG signals which then undergo complex mathematical models to give an exact numerical index, in order to measure patient's sedation level in an easy way. The most widely used bispectral index (BIS), which quantifies the relationship between component EEG frequencies.[1] Another variable, the Narcotrend index (NT), automatically classifies the spontaneous EEG into six stages from A to F. Both BIS and Narcotrend are multifactorial parameter derived from the EEG, which allow monitoring the degree of hyponosis.[2, 3]

BIS and Narcotrend appear to primarily monitor hypnosis and does not correlate with movement or autonomic responses to noxious stimuli under general anesthesia.[6] The effect of coadministered opioids on BIS and Narcotrend during general anesthesia is controversial. Several studies have shown that BIS and Narcotrend were insensitive to opioids. Guignard et al. found that changing the effect-site target remifentanyl concentration from 2 to 16 ng/ml had no effect on the baseline BIS during target-controlled propofol infusion before laryngoscope intubation.[4] Schmidt et al. found that 0.3 µg/kg/min remifentanyl infusion on the basis of target-controlled infusion had no statistical significance for all EEG variables (Including BIS and Narcotrend index) during the 10-minute observation period.[5] However, other studies demonstrated that the BIS decreased with increasing remifentanyl dose on the basis of constant target-controlled infusion.[6, 7] The effect of pure target-controlled infusion of remifentanyl on BIS and Narcotrend monitoring values remains unclear. So the purpose of this study was to investigate the effects of remifentanyl on BIS and Narcotrend compared to propofol infusion.

Methods

This randomized single-blinded study (blind to patient) was approved by *Medical Ethics Committee of Peking University Shenzhen Hospital* (Professor Tao Wang) on March 30, 2017 and written informed consent was obtained from all subjects who participated. The trial was registered before patient enrollment in the *Chinese Clinical Trial Registry* (registration number, ChiCTR1900026874; date of registration, 24/10/2019). The study included 30 patients who underwent elective surgery from October 2019 to June 2020. Selection criteria were patients aged between 18 and 65 yr, The American Society of Anesthesiologists (ASA) I-II, body mass index (BMI) 18.5-24 kg/m², and having general anesthesia. Exclusion criteria were as follows: history of an allergic reaction to any of the study medications, hypertension, diabetes, sleep apnea syndrome, advanced organ dysfunction, history of drug abuse, history of alcoholism, central system disease, and have taken medicines that affect the function of the central nervous system within 7 days before surgery.

All patients were fasted for 8 hours from solids and 2 hours from clear fluids before surgery. No patient received pre-anesthetic medication. Upon arrival in the operating room, standard monitoring was applied, including electrocardiogram, noninvasive blood pressure and pulse oximetry. An i.v. catheter was inserted into a large forearm vein and the lactated Ringer's solution was infused (10 ml./g).[4] The Observer's Assessment of Alertness/Sedation Scale (OAA/S) (Table 1) was recorded by another investigator who was blinded to the grouping. The EEG was recorded continuously using an Bispectral Index™ Monitor (*BIS VISTA™, USA*) and a Narcotrend™ monitor (*Narcotrend-Compact, Germany*). After skin preparation

with 75% alcohol, the BIS and the Narcotrend electrodes were placed according to the instructions of the manufacturers. *BIS Quatro sensor* needed to be monitored by SENSOR CHECK and NT electrodes impedances were kept below 8 k Ω to ensure optimal electrode contact.

Table 1
The Observer's Assessment of Alertness/Sedation Scale

Score	Responsiveness
1	Completely awake, responding normally to normal names
2	Slow response to normal call
3	No response to normal calls, and response to repeated calls
4	No response to repeated loud calls, only response to tapping the body
5	Does not respond to body shots, but does respond to noxious stimuli

Patients were randomly assigned to receive intravenous remifentanyl (remifentanyl group) or intravenous propofol (propofol group). Randomization was performed using computer-generated random number codes. The entire randomization sequence was generated before enrollment of the first participant. Group allocation codes were placed in sealed, opaque envelopes that were opened at the time of randomization. [4] In the remifentanyl group (remifentanyl group), experiment was begun with 2 ng/ml target-controlled infusion (*Fresenius Kabi, France*) of remifentanyl (*Remifentanyl Hydrochloride for injection, Yichang humanwell pharmaceutical, China*) followed by a stepwise increase (2 ng/ml) every 4 minutes until NT stage D was reached or the effect-site target remifentanyl concentration reached 6 ng/ml (Remifentanyl infusion using minto pharmacokinetics).[8, 9] In the propofol group (propofol group), experiment was begun with 2 μ g/ml target controlled infusion (*Fresenius Kabi, France*) of propofol (*Diprivan, Italy*) followed by a stepwise increase (1 μ g/ml) every 4 minutes until NT stage D was reached or the effect-site target propofol concentration reached 5 μ g/ml (propofol infusion using schnider pharmacokinetics).[9]

All patients maintained spontaneous ventilation with oxygen via facemask at 6L/min. BIS, Narcotrend indices and the Narcotrend stages were recorded continuously. BP, HR, and SPO₂ were recorded at 1-min intervals. Level of consciousness (using the modified OAA/S score shown in Table 1) was recorded at each targeted infusion rate. Upon completion of the final remifentanyl or propofol infusions, or if narcotrend index reached level D, the study was terminated and patients were prepared for general anesthesia induction. Hypotension and/or bradycardia were treated with fluid, or vasopressor administration as needed.

According to the results of the preliminary experiment, it was known that when the target concentration of remifentanyl reached 4ng/ml and the NT index reached D, the proportion of patients whose OAA/S score was still 1 was 100%. Set $\alpha = 0.1$, the error did not exceed 0.1, We used the PASS software to calculate the required sample size for a group of 14 cases, our research actually included 15 cases in each group and a total of 30 patients are included. Statistical analyses was performed by using SPSS statistics 20. Patient

characteristics were given as Mean $\pm$ SD. Linear regression analysis was used to analyze the correlation between NT and BIS during target-controlled infusion of remifentanil or propofol. Changes of SPO₂, MBP, HR and the four waveforms of EEG (% α , % β , % δ , % θ) extracted from the NT monitoring between different concentrations were analyzed by using one-way analysis of variance (ANOVA). Multiple comparison using SNK (with equal variance) or Tamhane's T2 (with unequal variance). Changes in the proportion of the four waveforms of the EEG (% α , % β , % δ , % θ) when NT stage D was reached were analyzed by using two-sample *t*-test. Change of OAA/S was analyzed by using Friedman M rand test. P <0.05 were considered statistically significant.

Results

Thirty consecutive subjects were analyzed for the study. There were no patient drop-outs due to protocol deviations. Patient demographics were described in Table 2.

Table 2
Patient characteristics. Data are Mean $\pm$ SD^d.

Characteristic	Remifentanil group (n = 15)	propofol group (n = 15)
Age (yr)	36 $\pm$ 13	37 $\pm$ 11
Weight (kg)	59 $\pm$ 9	60 $\pm$ 7
Height (cm)	166 $\pm$ 7	164 $\pm$ 7
Sex (F ^a /M ^b)	7/8	6/9
ASA ^c (I/II)	10/5	13/2
a: F = female,		
b: M = male		
c: ASA = American Society of Anesthesiologists		
d: SD = standard deviation.		

The OAA/S has been shown to correlate well with clinical reflection of the hypnotic component of anesthesia,[9] and in this study patients in the remifentanil group remained conscious throughout the experimental period. In the remifentanil group, there were no statistical differences in OAA/S at any effect site concentration. (Fig. 1a) However, a sharp decrease in the NT was observed when CeREMI achieve 4 or 6 ng/ml (Fig. 2a). BIS values showed a gradual decrease with increasing CeREMI (Fig. 2b), with eventually showing that most a few patients (4/15) reached BIS level consistent with general anesthesia (BIS=40-65).

With the increasing of effect-site concentration of propofol, the patient's consciousness gradually reached an anesthetic state (OAA/S = 5, $P = 0.000$; Fig. 1b). Consistent with the change in OAA/S, both NT and BIS gradually decreased to an anesthetic state (NT stage D, BIS = 40-65; Fig. 2c, 2d).

The linear correlation analysis between BIS and NT showed that both BIS and NT had a high correlation ($F=314.218$, $P = 0.000$, $r = 0.902$, $R^2 = 0.814$, $BIS = 7.297 + 0.847NT$) in predicting the concentration of propofol (Fig. 3), while a low correlation ($F = 30.033$, $P = 0.000$, $r = 0.591$, $R^2 = 0.349$, $BIS = -38.404 + 1.333NT$) in predicting the concentration of remifentanyl (Fig. 3).

When NT stage D was reached, the relative (%) power in α , β , θ , and δ in remifentanyl group were 4.47%, 2.35%, 19.17%, 74.00% respectively. While the relative (%) power in α , β , θ , and δ in propofol group were 19.04%, 9.33%, 10.92%, 60.71% respectively. The proportions of the four EEG waveforms (% α , % β , % δ , % θ) was statistically different between the remifentanyl and propofol group (% α : $P = 0.000$, % β : $P = 0.000$, % δ : $P = 0.009$, % θ : $P = 0.008$; Fig. 4 and Fig. 5). Notably, the EEG waveform showed a single peak of δ power in remifentanyl group when NT stage D was reached, while double peaks of δ and α power in propofol group. In the 2 groups, the changes of the four EEG waveforms (% α , % β , % δ , % θ) under different concentrations were shown in figure 4b and figure 5b (% α : $P = 0.000$, % β : $P = 0.001$, % δ : $P = 0.041$, % θ : $P = 0.000$ in Fig. 4b; % α : $P = 0.000$, % β : $P = 0.000$, % δ : $P = 0.000$, % θ : $P = 0.03$ in Fig. 5b).

The vital signs were shown in figure 6. With the exception of a small decrease in mean blood pressure (MBP) in the CePROP > 3 ng/ml group, MBP, HR and SpO₂ were comparable to their respective baseline levels. None of these patients had any episodes of apneic, hypotension or bradycardia. None of the patients required any airway interventions.

Discussion

Remifentanyl is a central acting μ -opioid receptor agonist used for balanced anesthesia and sedation.[10] The effect of remifentanyl administration on the bispectral index (BIS) and the Narcotrend index (NT) during anesthesia is controversial, raising the question as to whether the use of remifentanyl could confound EEG based measurements of depth of sedation or anesthesia. In this study, we investigated the effects of remifentanyl on BIS and NT monitoring and compared to the effect of propofol.

Infusion of both remifentanyl and propofol can reduce the NT index to stage D. However, the level of consciousness as measured by the OAA/S is significantly different between these groups with no patient in the remifentanyl group reaching a loss of consciousness. With increasing target concentration of remifentanyl, the decrease in BIS is not as significant as that of NT (11/15 with BIS = 65-85 and 4/15, BIS = 40-65). In the propofol group, both BIS and NT decreased in dose dependent manner. This observation suggests that these differing drugs have different effects on BIS, NT level of consciousness, and likely mechanism of action. When remifentanyl is used alone for sedation, BIS or NT were not consistent with the patient's level of consciousness.

The dissociation of the NT/BIS index and the patients' level of consciousness with remifentanyl infusion may be attributed to the distinct methodology of EEG processing by NT or BIS. We found that the effect of remifentanyl and propofol on EEG waveform is different although NT/BIS indexes were similar. Increasing effect site concentrations of remifentanyl caused a significant increase in δ power of the EEG waveform. In contrast, increasing effect site concentrations of propofol resulted in increases of both δ and α power of the EEG waveform.

The decreased level of consciousness observed with Propofol is thought to be mediated through the GABA_A receptors in the brain to induce loss of consciousness. The EEG pattern elicited by propofol anesthesia is characterised by increased alpha (8-12 Hz) oscillations that are coherent across the frontal cortex and increased delta (1-4 Hz) oscillations.[11] In an animal study, Fodale et al demonstrated that remifentanyl infusions resulted in a shift from low-amplitude, high-frequency activity during baseline to high-amplitude, low-frequency activity.[12] Carina Graversen et al. showed that remifentanyl (0.1 µg/kg/min dose infusion for 25 minutes) induced an increase in delta power.[13] By using standardized low-resolution brain electromagnetic tomography, the same group further demonstrated that alterations in brain oscillations during remifentanyl are mostly localized to frontal, fronto-temporal and fronto-central lobes.[14] In multichannel electroencephalography recording, remifentanyl disrupts the overall functional connectivity network properties of the EEG, with less long-range connections and less synchronized cortical activity primarily in the frontal and parietal brain areas.[15] These studies elucidate some of the mechanisms in altered EEG processing due to remifentanyl infusion.

In the current study, BIS and NT changes were determined with infusion of either remifentanyl or propofol. These findings may not be present with a combination of these two agents or in combination with other drugs as combinations of two or more drugs on processed EEG is not necessarily additive. In a previous study, Schmidt et al. found that 0.3 µg/kg/min remifentanyl infusion in addition to 3 µg/ml TCI of propofol had no statistical significant effect for all EEG variables (Including BIS and NT) during the 10-minute observation period.[5] However, Strachan et al. found that while on the 2 µg/ml TCI of propofol, BIS value was reduced by increasing infusion concentration of remifentanyl up to 0-0.1 µg/kg/min.[6] Consistent with this finding, Koitabashi et al. also reported that while on the 5 µg/ml TCI of propofol, the BIS decreased with the increase of remifentanyl dose (0.5-10 ng/ml).[7] Further investigations are still needed to understand how EEG changes according to different dosage combination of propofol and remifentanyl, with and without noxious stimuli.

In summary, our data show that when remifentanyl is used alone for analgesia, neither NT nor BIS are associated patient's level of consciousness, especially NT monitoring. In contrast, changes of propofol target concentrations and patients' consciousness state are consistently predicted with the BIS and NT levels. This finding suggested that the effect of NT and BIS are different with different type of anesthetic used. A single numerical index of NT or BIS can correspond to different EEG wave form as well as consciousness state. The effect of remifentanyl on EEG should be taken into consideration when NT/BIS is used to assess the depth of general anesthesia.

Declarations

Ethics approval: The study had been approved by the Medical Ethics Committee of Peking University Shenzhen Hospital. All methods were performed in according with the relevant guidelines.

Consent to participate: All selected patients had signed the informed consent form for this study.

Consent for publication: Not applicable.

Competing interests: The authors declare that they have no conflict of interest.

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Authors' contributions: The study was designed by Xirui Huang and Tao Luo. Material preparation and data collection were performed by Xirui Huang, Zhitao Li, Chenshu Liu and Rongfa Chen. The data analysis was performed by Tao Luo, Xirui Huang and Lingbin Sun. The draft of the manuscript was prepared by Xirui Huang, Yaqi Hu and Tao Luo.

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Availability of data and materials: All data are available in the presented tables and figures.

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Figures

Figure 1

Effects of remifentanyl/propofol on OAA/S

a: Relationship between OAA/S and effect-site concentration of remifentanyl. b: Relationship between OAA/S and effect-site concentration of propofol. Data are min to max in OAA/S. Significant changes from baseline (0 $\mu\text{g/ml}$) in OAA/S ($P = 0.000$). Abbreviation: OAA/S = the Observer's Assessment of Alertness/Sedation Scale, NT = the Narcotrend index, BIS = the bispectral index.

Figure 2

Effects of remifentanyl and propofol on the Narcotrend and BIS

a-b: Representative Narcotrend(a) and BIS(b) recording obtained during step-wise increasing remifentanyl effect site concentration from a same patient. c-d: Representative Narcotrend(c) and BIS(d) recording obtained during step-wise increasing propofol effect site concentration from a same patient. (a, b: remifentanyl 0, 2, 4, 6 ng/ml; c, d: propofol 0, 2, 3, 4, 5 µg/ml). Abbreviation: NT = the Narcotrend index, BIS = the bispectral index.

Figure 3

Effects of remifentaniil on BIS or NT

a: The linear correlation analysis between BIS and NT during target-controlled infusion of remifentaniil. b: The linear correlation analysis between BIS and NT during target-controlled infusion of propofol. Abbreviation: NT = the Narcotrend index, BIS = the bispectral index.

Figure 4

Effects of remifentanyl on the EEG waveform

a: the ratios of the four EEG waveforms (% α , % β , % δ , % θ) in the remifentanyl group when NT stage D was reached. b: Changes in the relative (%) power in α , β , δ , and θ under different concentrations of remifentanyl infusion (b1-4: % β : $P=0.001$, % α : $P=0.000$, % θ : $P=0.000$, % δ : $P=0.041$ respectively). c-f: Representative NT index (c1, d1, e1, f1), EEG waveforms (c2, d2, e2, f2) and raw EEG (c3, d3, e3, f3) changes during target-controlled infusion of remifentanyl (correspond to the concentration of remifentanyl 0, 2, 4, and 6 ng/ml respectively). Abbreviation: EEG = electroencephalograph, NT = the Narcotrend index.

Figure 5

Effects of propofol on the EEG waveform

a: the ratios of the four EEG waveforms (% α , % β , % δ , % θ) in the propofol group when NT stage D was reached. b: Changes in the relative (%) power in α , β , δ , and θ under different concentrations of propofol infusion (b1-4: % β : $P=0.000$, % α : $P=0.000$, % θ : $P=0.03$, % δ : $P=0.000$ respectively). c-f: Representative NT index (c1, d1, e1, f1), EEG waveforms (c2, d2, e2, f2) and raw EEG (c3, d3, e3, f3) changes during target-controlled infusion of propofol (correspond to the concentration of propofol 0, 2, 3, and 4 $\mu\text{g/ml}$ respectively). Abbreviation: EEG = electroencephalograph, NT = the Narcotrend index.

Figure 6

Changes in MBP, HR and SPO2 during remifentanyl (a, c, e) or propofol (b, d, f) infusion

Data are Mean $\pm$ SD for MBP, HR and SPO2 (propofol), and data are geometric mean (95%CI) in SPO2 (remifentanyl). *Significant changes from baseline (0 μ g/ml) in MBP ($P = 0.000$). Abbreviation: MBP = mean blood pressure, HR = heart rate, SPO2 = the saturation of haemoglobin with oxygenx.

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