The optimal effect-site concentration of remifentanil and propofol for keeping proper anesthesia and promoting early recovery during patient state index-guided anesthesia.

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Abstract

Backgroud: To determine the most suitable effect-site concentration of remifentanil and propofol for keeping proper anesthesia depth and early recover quickly under guidance of patient state index (PSI). Methods: Elective gynecological laparoscopic surgery patients received concentration of propofol in high concentration (3 ug/mL, N = 25), middle concentration (2.5 ug/mL, N = 24), low concentration (2 ug/mL, N = 28) during maintenance. After finished intubation, propofol was adjusted to the target concentration by grouping, the concentration of remifentanil relied on the reaction of the formerly tested patient using 0.4 ng/mL as a step size began with 3.5ng/mL under PSI monitored. The primary measurements were the concentration of remifentanil, the change of intra-procedural data, and post-operation data including times to handle the change of the depth of anesthesia, blood pressure (BP) and heart rate (HR), extubation time, duration in PACU, hospital day, VAS score in the first day after sugery. Secondary measurements were density spectral array, intra-operative awareness, postoperative delirium. Results: The group of middle concentration required the minimum time for extubation and staying in PACU, kept steady process of anesthesia ($P<0.05$), the EC50 of remifentanil to suppression irritation from incision were 2.96 ng/mL (95% CI 2.75 to 3.14 ng/mL) in this group. Besides, low doses of remifentanil were more obvious than high doses in alpha wave of Density spectral array. Conclusions: With PSI guided anesthesia, the effect-site concentration of propofol was 2.5 ug/mL, keep stable anesthesia process and effective early postoperative recovery, meanwhile, EC50 of remifentanil was 2.96 ng/mL.

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Running head: The optimal concentration of remifentanil and propofol under guidance of patient state index.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT -

The effects of propofol and REM combination are better than the more effective ones, and REM metabolizes quickly and is more conducive to early recovery of patient.

PSI has been shown to conform to the trend of BIS under general anesthesia.

WHAT THIS STUDY ADDS -

1. It's not true that the higher concentration of the REM, the lower concentration of propofol is more beneficial to the patient. The optimal effect-site concentration of remifentanil and propofol can be recieved.
2. DSA can assist in the evaluation of the situation of analgesic drug compared with PSI reflects anesthesia depth.
3. PSI performs better than BIS in detecting consciousness.

Abstract

Backgroud : To determine the most suitable effect-site concentration of remifentanil and propofol for keeping proper anesthesia depth and early recover quickly under guidance of patient state index (PSI). **Methods** : Elective gynecological laparoscopic surgery patients received concentration of propofol in high concentration (3 ug/mL, N = 25), middle concentration (2.5 ug/mL, N = 24), low concentration (2 ug/mL, N = 28) during maintenance. After finished intubation, propofol was adjusted to the target concentration by grouping, the concentration of remifentanil relied on the reaction of the formerly tested patient using 0.4 ng/mL as a step size began with 3.5ng/mL under PSI monitored. The primary measurements were the concentration of remifentanil, the change of intra-procedural data, and post-operation data including times to handle the change of the depth of anesthesia, blood pressure (BP) and heart rate (HR), extubation time, duration in PACU, hospital day, VAS score in the first day after sugery. Secondary measurements were density spectral array, intra-operative awareness, postoperative delirium. **Results:** The group of middle concentration required the minimum time for extubation and staying in PACU, kept steady process of anesthesia ($P<0.05$), the EC50 of remifentanil to suppression irritation from incision were 2.96 ng/mL (95% CI 2.75 to 3.14 ng/mL) in this group. Besides, low doses of remifentanil were more obvious than high doses in alpha wave of Density spectral array. **Conclusions:** With PSI guided anesthesia, the effect-site concentration of propofol was 2.5 ug/mL, keep stable anesthesia process and effective early postoperative recovery, meanwhile, EC50 of remifentanil was 2.96 ng/mL.

Key words: Remifentanil; Propofol; Electroencephalography; Conscious Sedation; Anesthetics, Intravenous

Introduction

To achieve the ideal state of anesthesia, three common and important goals are needed, namely unconsciousness, inactivity and control of the autonomic nervous response to surgical stimuli[1, 2]. Clinically, propofol[3] and remifentanil (REM)[4, 5] are two intravenous maintenance drugs commonly used in balanced anesthesia. Not only can satisfactory hypnotic and analgesic effect achieved, but also smaller concentration needed when the two drugs combined[6]. In the field of anesthesia, it is important to quantification of drug interactions for better drug administration[7]. Studies have reported different concentrations during the combination of propofol and REM under various conditions[8-10]. The concentration of propofol and REM in combination that can achieve the goal of early postoperative recovery is still being explored.

Electroencephalography (EEG) is considered to be an important part of monitoring organs in anesthesia management[11]. The patient state index (PSI, SedLine® Root, Masimo Inc., Irvine, CA, USA)[12] is a reference index provided by the SedLine Brain Monitor, with a reference range of 0-100 and an ideal anesthetic depth of 25-50 (compared to 40-60 recommended by other monitors). It has been shown to be similar to the change of the bispectral index (BIS, Medtronic, Minneapolis, Minnesota, USA) during induction, maintenance and wake-up[13, 14]. Unlike BIS, PSI would test asymmetries of electrical activity in patients' brains, morever, it improved algorithm[15]. Many studies reported the effect-site concentration of drugs controlling autonomic responses to stimulation under BIS-guided anesthesia[16-18], there is little research on the effects of coadministration of propofol and REM on PSI. Besides, the impact of opioid administration on the BIS during general anesthesia is debatable[19]. In fact, several investigators have pointed out that BIS to be insusceptible to opioid addition, whereas others have reported a hypnotic activity[20]. Therefore, density spectral array (DSA) was introduced to observe the analgesic effect.

Therefore, we designed a study to find a suitable combination concentration of propofol and REM which can not only maintain the appropriate depth with stimulus but also promote early recovery of patients under the guidance of PSI. Besides, to explore whether the use of opioid agents (i.e., remifentanil) could confound function of depth of sedation or anesthesia.

Methods

The study was approved by the Ethics Committee for Clinical Trials of the First Hospital affiliated of China University of Science and Technology, Hefei, China [approval no. : 2021-ky095]. The research was signed in the Chinese Clinical Trial Registry before patients enrollment (ChiCTR 2000040130). All participants completed written informed consent.

Patients scheduling gynecological laparoscopic operation with American Society of Anesthesiologists (ASA) physical status I or II were enrolled in this research. All patients aged range is between 30 and 65, body mass index (BMI) in between 18.5 and 29.5 kg/m^2. They were eliminated if anyone met any of the following standards: poor compliance or non-cooperate; presence of serious disease (cardiovascular disease, bronchial asthma, uncontrolled severe hypertension, fearful blood system dysfunction, liver or kidney dysfunction, obvious electrolyte abnormalities); second degree atrioventricular block, bradycardia (HR$<$ 50 bpm), low blood pressure (SBP$<$ 90 mmHg); history of neurological disease, chronic pain, drug addiction and alcoholism, long-term opioid use; history of allergy to opioids; slow intestinal peristalsis or intestinal obstruction; participant in clinical trials involving other drugs within four weeks; the presence of other conditions. Patients were split into 3 groups according to the effect-site concentration of propofol at in high concentration (3 ug/mL), middle concentration (2.5 ug/mL), low concentration (2 ug/mL) respectively during maintenance.

All participants fasted for 8 h, intravenous access was established after reaching the operating room, and received lactated Ringer's or colloid solution maintained to expand blood volume. All patients avoided receiving any sedative or analgesic drugs before induction of anesthesia, and measured vital parameters, including invasive arterial blood pressure, cardiac rate, electrocardiography, pulse oxygen saturation, nasopharyngeal temperature and end-tidal carbon dioxide partial pressure. For BIS and PSI monitoring, set different single-use, disposable sensors at the forehead after the skin was cleaned with alcohol swabs. The two sets of EEG recording electrodes were closed to where they were used, in line with the manufacturer's recommendations, and there was no significant interference between the two monitoring systems. (*Fig. 1*).

Preoxygenated with 100% oxygen before induction. General anesthesia was induced with TCI propofol 4 µg/mL and REM 4 ng/mL[21], after PSI dropped below 50, or the eyelash reflex disappearance, muscle relaxation was performed with rocuronium 0.5mg/kg. Controlled breathing for 5 min, inserted tracheal tube, meanwhile, set mechanical ventilation as target a PETCO2 in the 35 - 45 mmHg and SpO2 > 95%. Kept the patient's body temperature between 36.0 °C and 37.0 °C. Anesthesia was maintained with propofol and REM, which were adjusted to the target concentration according to the patient's group.

Sufentanil was administered with 0.15 - 0.7 µg/kg half an hour after the operation began to achieve the long-term analgesia. Propofol and REM were quit by the end of surgery. Patients were organized in a post-anesthesia care unit (PACU), set back to the inpatient ward with a Steward resuscitation score of above 4[22] after surgery. All patients used patient-controlled analgesia for 48 h. The ingredient consisted of 2.5 µg/kg sufentanil and 2 mg granisetron (total volume of 100 ml, including 0.9% normal saline).

The first patient of respective group administrated an effect-site concentration of REM at 3.5 ng/mL, then determined by using a modified up-and-down sequential method[23, 24]. In other words, the reaction of each patient decided the concentration of REM set to the succeeding patient. If the reaction of the previous patient was positive (the PSI value increased by >10 during 2 min after skin incision), the concentration given to the next patient was increased by 0.4 ng/mL. Otherwise, the concentration was decreased by 0.4 ng/mL. Adjusted the concentration of REM according to the group to hold PSI between 25 and 50, if excceed 25% of initial concentration, the patient was eliminated during the period of anesthesia. Infused additional fluids and an intermittent bolus of ephedrine when observed hypotension. Equally, cardiac rate was modulated with atropine of 0.05 mg if lower than 50 beats/min, and esmolol of 20 mg on condition that exceeding 100 beats/min.

Recorded the PSI, BIS, HR and MAP at the following moments: before the induction (T_0), induction of anesthesia (T_1), 1 min after intubation (T_2), pre-incision (T_3), 2 min after incision (T_4), discontinuation of drugs (T_5) and extubation (T_6). Additionally, , Incidence of adverse events (including PSI exceed the recommended range, hypertension, hypotension, bradycardia), duration of operation, extubation time, residence time in PACU, hospital day, VAS score in the first day after operation, the occurrence of intraoperative awareness, postoperative delirium were registered. Density spectral array (DSA) was saved at SedLine® Root during the surgery.

According to the sequence method, when each group reached at least seven positive points, the experiment was completed.

SPSS version 27.0 (SPSS Inc., Chicago, IL, USA) was employed for statistical analyses. The modified up-and-down sequential method and probit analysis were used for the EC50 of REM with different concentration of propofol. All data were tested for normality by Shapiro test. The PSI, BIS, HR and MAP at each time were analyzed by using repeated measures ANOVA. Characteristics data of the patients, surgery, anesthesia and postoperative data among groups using one-way analysis of variance (ANOVA) for continuous variables. When a difference in proportions was found among the groups, and a Least Significance Difference or Tamhane T2 was made for multiple comparisons. ROC curve was used to compare the sensitive of PSI and BIS. $P < 0.05$ was regarded as a statistical difference. Quantitative data were perfomed as the mean (standard deviation) (SD), median [Min, Max], or number (n).

Results:

The Flow diagram is shown in *Fig. 2* . Three patients refused to intervention management after entering the operating room, four patients were excluded for surgery method changed, and two were lost to follow-up. Finally, enrolled 78 patients in the study: 25 patients in high concentration group, 24 patients in middle concentration group, 28 patients in low concentration group.

No differences in age, BMI, HR and MAP among the three groups (*Table 1*).

3.1 Primary endpoint

Concentration-change data for each patient received by the up-and-down treatment were performed in Fig. 3 (A, B, C). According to up-and-down method and probit analysis, REM EC50 1.82 ng/mL (95% CI 0.94 to 2.27 ng/mL) in high group, 2.96 ng/mL (95% CI 2.75 to 3.14 ng/mL0) in middle group, 5.14 ng/mL (95% CI 4.86 to 5.47 ng/mL) in low group (*Fig. 3* D).

There was also no significant difference in MAP, HR, PSI and BIS related to surgery among the three groups (*Fig. 4*), but compared with middle and low group, the change of MAP and HR of high group were more obvious at T_4.

Operation duration, hospital day, VAS score in the first day after sugery did not make imparity among three groups, however, the dose of REM made statistical significance ($P<0.05$). Compared with other two group,the incidence of adverse events, the extubation and lengths of PACU stay in middle group was shortest (*Table. 2*). All three groups denied intraoperative awareness and hyperpathia, no postoperative delirium occurred.

3.2 Secondary endpoints

The analgesic response of REM can be obtained by DSA (*Figure. 5*), EEG changes caused by different concentrations of REM were analyzed. It can be seen that the slow delta wave (0.5-4HZ) and alpha wave (8-12HZ) in a is more obvious than b in every part of the figure.

The area under the ROC curve (*Fig. 6*) for the PSI and BIS after incision were 0.953 ± 0.02 and 0.888 ± 0.04, respectively, it was confirmed that the two indexes could predict the consciousness state of patients, and PSI was more sensitive than BIS.

Discussion

In this Prospective study of the optimal effect-site concentration of REM and propofol to keeping proper depth of anesthesia and promote early postoperation recover under PSI guided anesthesia. We found EC50 of REM at 2.96ng/mL When co-adminstration with 2.5 ug/mL propofol, the PSI, BIS, MAP and HR remained stable during anesthesia, and minimum time of extubation and staying in PACU needed.

Previous research[1, 6, 25] described in detail the importance of multimodal drugs and argued that coadministration of narcotic drugs with different mechanisms usually produces a synergies effect with theoretical advantages, multimodal medications, which can help patients recover more quickly. Compared with propofol, REM has no opioid accumulation effect, mainly used as an analgesic, had the advantage of rapid action, short maintenance time, metabolism by a specific esterase. In this study, we found that when propofol was 2.5ug/mL, the anesthesia process of patients was more stable, that is, the depth of anesthesia, blood pressure and heart rate were less needed to deal with measures. In this group, EC50 of REM could be calculated as 2.96 ng/mL by sequential method. Therefore, this can provide reference for drug concentration collocation in clinical process.

Theoretically, according to the advantages of REM, TCI 2 ug/mL propofol, the extubation time should be the shortest. However, our study showed, compared with other two groups, the patients in middle concentration group experienced the shortest extubation and PACU stay time. According to the preceding report, awakening time from anesthesia relies on various elements, involving age, sex, BMI, operation time, drugs administration[26, 27] and metabolism of muscle relaxants[28, 29]. In this study, these factors make little difference. Another research demonstrates that the increase in plasma propofol concentration was increased by coadministration of REM due to a decreased cardiac and hepatic blood flow[30], and there was a significant increase in REM in the third group, which may account for the results of this study.

Although PSI appeared later than BIS, PSI has many advantages over BIS. In this study, we found that PSI was more sensitive than BIS for the change of anesthesia depth after skin incision, which was in keeping with previous studies, PSI performs better than BIS in detecting consciousness, and less impact of the shock device on the PSI value during surgery[15]. There are several reasons account for this advantage. Firstly, unlike BIS only equipped with 4 electrodes, the SEDLine EEG sensor consists of 6 electrodes: 4 channels (R2, R1, L1, L2), 1 reference channel (CT) and 1 ground channel (CB). It can collect information from both sides of the brain to detect asymmetry in the patient's electrical activity. Next, this algorithm is improved by considering individual background differences and brain responses of different patients to different anesthetics[12, 31]. Finally, less impact of the shock device on the PSI value during surgery.

Another advantage is that the Sedline® monitored bilateral brain function and symmetry by DSA display. DSA converts complex EEG waveforms into color-comparable EEG. Further, it can show how oscillations in EEG change over time as well as changes in anesthetic drug doses or the intensity of stimulation that could be harmful[32, 33]. A review described three types of EEG changes caused by nociceptive stimulation about general anesthesia: (1) beta arousal, (2) (paradoxical) delta arousal, and (3) alpha dropout[32]. Studies have suggested that in patients with low opioid analgesia, α activity increases, and in patients with satisfactory analgesia, α disappears[34]. In our study, under PSI guide, the concentration of propofol reduced with the required concentration of REM increased in a certain range. This phenomenon showed that sedative synergistic effect of REM was reflected from PSI values which was similar to previous studies[1, 6]. We compared the same group to rule out the effects of different doses of sedative hypnotics, the change in DSA result from REM was observed in different groups of patients. From the comparison of several groups of patients in this study, it can be seen the minimum concentration of REM group α activity increases; however δ wave did not change obviously. The result performed that DSA could help anesthesiologists evaluate sedation and analgesia level dynamically togerther with PSI value compared to BIS applied lonely.

There are some limits to the study. The selected criterias for this study were patients who scheduled for laparoscopic surgery with general anesthesia, which would entail limited stimulation and a relatively smooth operation. Most of the patients were middle-aged healthy women, and demographics and surgery itself had little impact on the results of the study. During the experiment, we made a more detailed choice of patients who needed full uterus (or attachment) removal via laparoscopy, excluding ovarian cyst removal or simple attachment removal of patients. All patients underwent laparoscopic surgeries, but differences in internal pain were observed. Two types of surgeries were relatively short in duration, which could easily cause errors in the results of data analysis. However, only patients who underwent laparoscopic surgery were selected and patients with open abdominal disease were not selected was the first limit of this study. Second, considering the influence of hepatic propofol clearance in our study, the inadequacy was that no detection of plasma concentration at the time of extubation. Besides, the brain waves of propofol were dominated by slow δ wave and α wave oscillations. In our study, REM and propofol were given simultaneously, which may affect the final conclusion. Therefore, to accurately draw the effect of REM on the EEG, further research is needed after excluding influencing factors.

Conclusions

As our study disclosed, under the PSI guided, patients experience steady anesthesia process and effective early postoperative recovery when TCI 2.5 ug/mL propofol and remifentanil EC50 was 2.96 ng/mL. These results can facilitate the implementation of ERAS and provide reference for anesthesiologists in clinical drug management and monitoring device selection.

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Authors' contributions

Sheng Wang have given substantial contributions to the conception or the design of the manuscript, Wenjing Han and Tingting Li to acquisition, analysis and interpretation of the data. All authors have participated to drafting the manuscript, Sheng Wang revised it critically. All authors read and approved the final version of the manuscript. All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

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TABLES

Table 1. Patient demographics Values are expressed as the means (SD). *BMI,* body mass index; *HR,* heart rate; *MAP,* mean arterial pressure.	**Table** 1. Patient demographics Values are expressed as the means (SD). *BMI,* body mass index; *HR,* heart rate; *MAP,* mean arterial pressure.	**Table** 1. Patient demographics Values are expressed as the means (SD). *BMI,* body mass index; *HR,* heart rate; *MAP,* mean arterial pressure.	**Table** 1. Patient demographics Values are expressed as the means (SD). *BMI,* body mass index; *HR,* heart rate; *MAP,* mean arterial pressure.

	High (N=25)	Middle (N=24)	Low (N=28)
Age(yr)	48 (7)	44 (7)	46 (6)
BMI (kg.m^{-2}) m¡2)	24 (4)	24 (2)	24 (2)
HR (bpm)	80 (5)	77 (6)	78 (6)
MAP (mmHg)	139 (19)	134 (15)	140 (18)

Table 2. post-operation data. Data are expressed as means (SD) or median [Min, Max]. **P<0.05* indicates significant diffe

Operation duration (min)
Dose of remifentanil (ug)
Incidence of adverse events,n (%)
Extubation time (min)
Duration in PACU (min)
VAS
Hospital day (d)

FIGURE LEGEND

Figure 1.? Placement of BIS and PSI patches on the patient's forehead.

Figure 2.? Flow diagram of the study

Figure 3.? Consecutive target REM concentrations during PSI guide anesthesia for EC50 determination among groups. The red triangle represents "positive"; and the blue dot represents "negative". (A) The variation of concentration of REM according to the change of PSI in high group; (B) The variation of concentration of REM according to the change of PSI in middle group; (C) The variation of concentration of REM according to the change of PSI in low group. (D) REM EC50 and its 95% confidence interval of groups.

Figure 4. ? The time of change in MAP, HR, PSI and BIS. (A) The change of MAP. (B) The change of HR. (C) The change of PSI. (D) The change of BIS.

Figure 5. ? Density spectral arrays showing EEG spectral activity of six patients from different groups. a represent the minimum concentration while b represent maximum. (A, B, C) Change of DSA among high, middle and Low group. (D) dispaly brain wave shape and its power value.

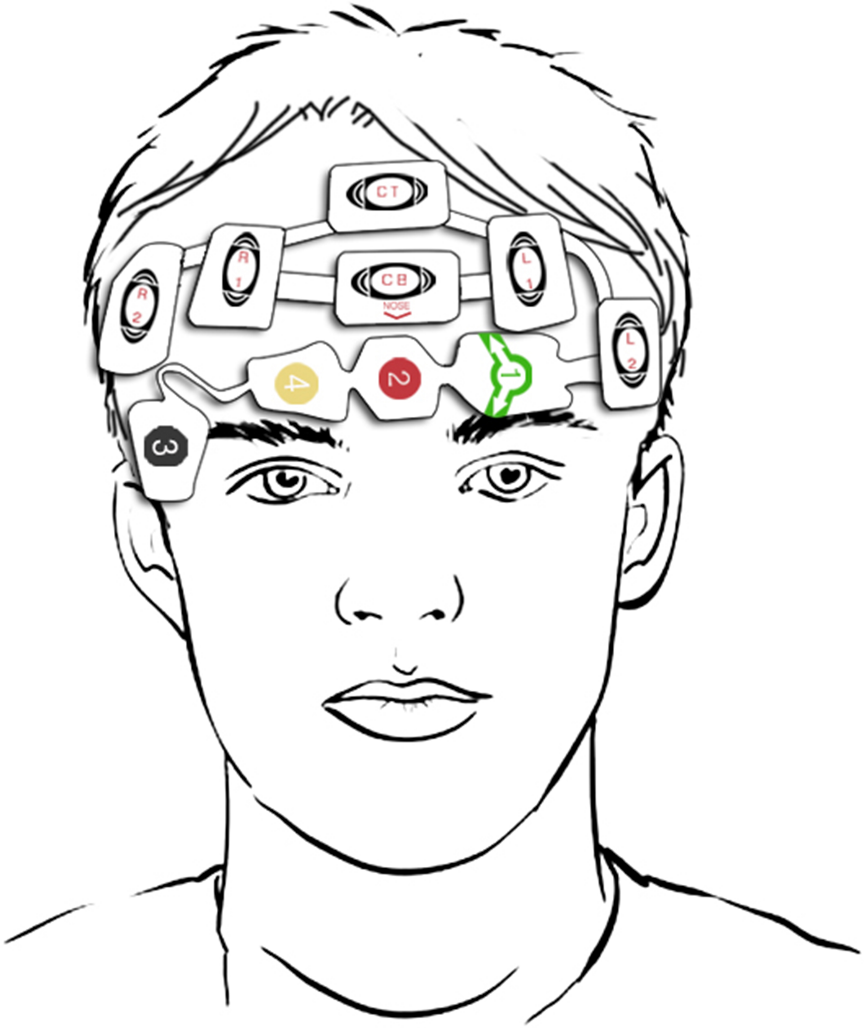
Figure 6.?The ROC curve of PSI and BIS. The area under the PSI curve was greater than the area under the BIS curve (0.95 ± 0.02 versus 0.89 ± 0.04, respectively).

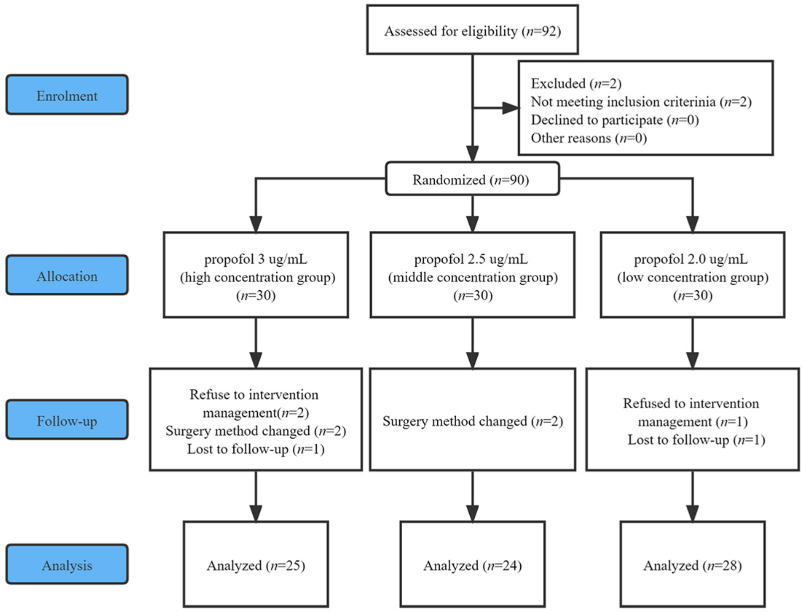
Table 1. Patient demographics Values are expressed as the means (SD). *BMI*, body mass index; *HR*, heart rate; *MAP*, mean arterial pressure.

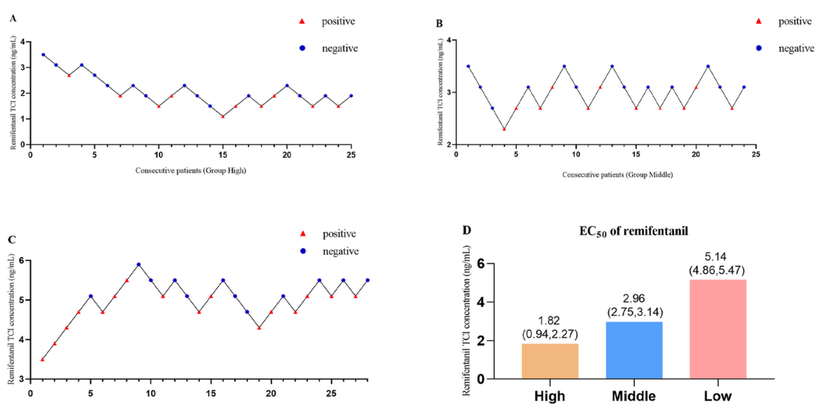
	High (N=25)	**Middle (N=24)**	**Low (N=28)**
Age(yr)	48 (7)	44 (7)	46 (6)
BMI (kg. m^{-2})	24 (4)	24 (2)	24 (2)
HR (bpm)	80 (5)	77 (6)	78 (6)
MAP (mmHg)	139 (19)	134 (15)	140 (18)

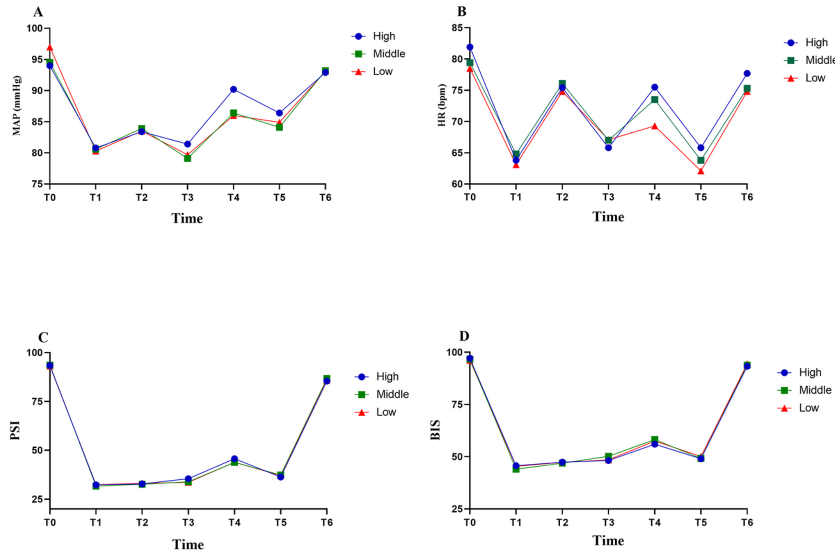
Table 2. Post-operation data. Data are expressed as means (SD) or median [Min, Max]. *$P<0.05$ indicates significant difference compare with group Middle; #$P<0.05$ indicates significant difference compare with group Low.

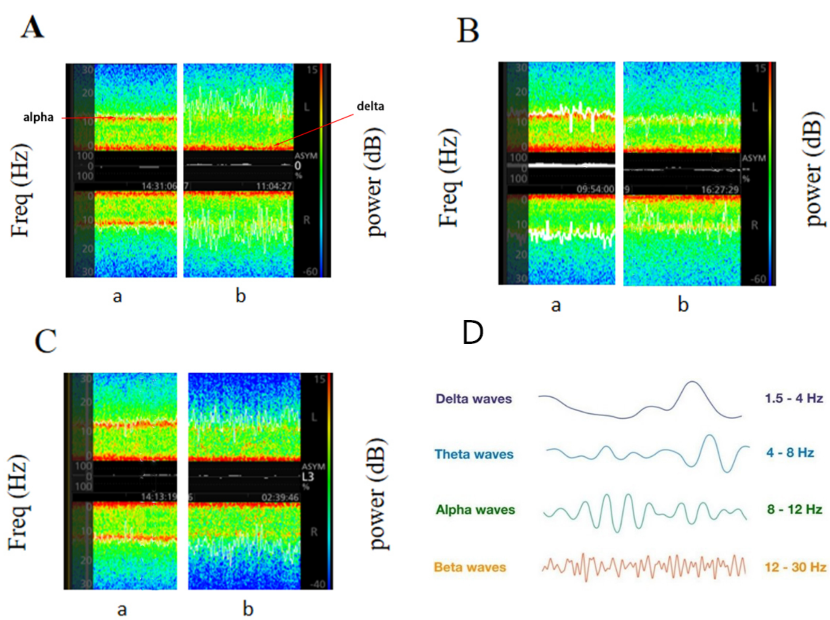
	High (N=25)	Middle (N=24)	Low (N=28)
Operation duration (min)	155 [105, 210]	145 [100,220]	135 [90,310]
Dose of remifentanil (ug)	78 [44,112)*#	86 [64,138]#	120 [72,178]
Incidence of adverse events,n (%)	7 [4,11]*	6 [1,9]	7 [3,10]*
Extubation time (min)	13.0 [6,20]*#	6.5 [3,12]#	10.0 [5,15]
Duration in PACU (min)	49.0 [35,60]*#	39.0 [35,48]	40.5 [35,55]
VAS	3 [1,6]	3 [1,5]	2 [1,5]
Hospital day (d)	8 [5,18]	7[5,20]	7 [5,10]

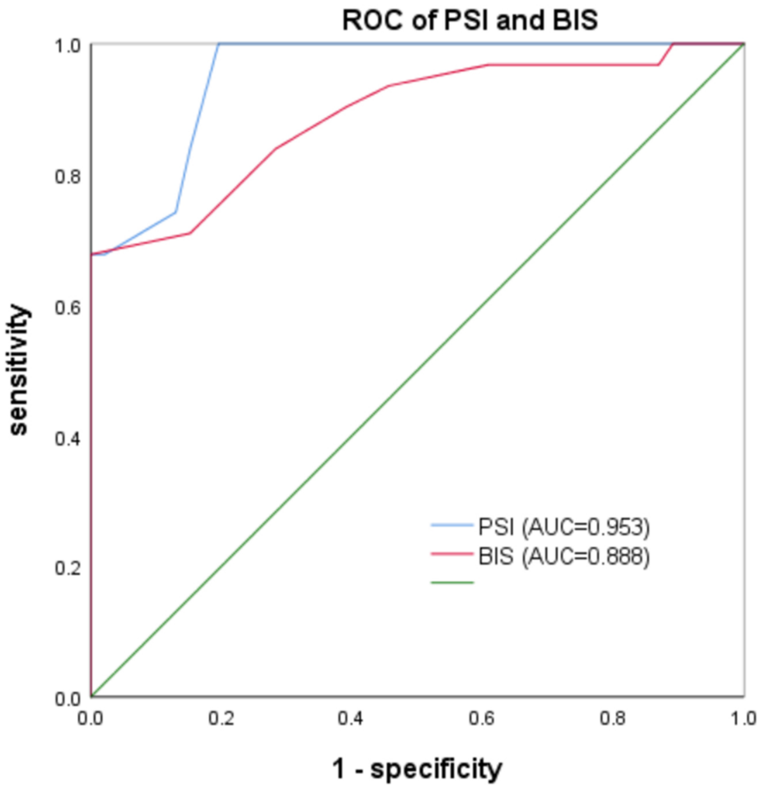

CT
CB
NOSE
R 1
R 2
L 1
L 2
4
2
1
3


Assessed for eligibility (n=92)
Enrolment
Excluded (n=2)
Not meeting inclusion criterinia (n=2)
Declined to participate (n=0)
Other reasons (n=0)
Randomized (n=90)
Allocation
propofol 3 ug/mL
(high concentration group)
(n=30)
propofol 2.5 ug/mL
(middle concentration group)
(n=30)
propofol 2.0 ug/mL
(low concentration group)
(n=30)
Follow-up
Refuse to intervention management(n=2)
Surgery method changed (n=2)
Lost to follow-up (n=1)
Surgery method changed (n=2)
Refused to intervention management (n=1)
Lost to follow-up (n=1)
Analysis
Analyzed (n=25)
Analyzed (n=24)
Analyzed (n=28)


A
positive
negative
Consecutive patients (Group High)
B
positive
negative
Consecutive patients (Group Middle)
C
positive
negative
Remifentanil TCI concentration (ng/mL)
Consecutive patients (Group Low)
D
EC50 of remifentanil
Remifentanil TCI concentration (ng/mL)
1.82
(0.94,2.27)
2.96
(2.75,3.14)
5.14
(4.86,5.47)
High
Middle
Low


A
MAP (mmHg)
100
95
90
85
80
75
T0 T1 T2 T3 T4 T5 T6
Time
High
Middle
Low
B
HR (bpm)
85
80
75
70
65
60
T0 T1 T2 T3 T4 T5 T6
Time
High
Middle
Low
C
PSI
100
75
50
25
T0 T1 T2 T3 T4 T5 T6
Time
High
Middle
Low
D
BIS
100
75
50
25
T0 T1 T2 T3 T4 T5 T6
Time
High
Middle
Low


A
alpha
delta
Freq (Hz)
power (dB)
a
b
B
Freq (Hz)
power (dB)
a
b
C
Freq (Hz)
power (dB)
a
b
D
Delta waves
1.5 - 4 Hz
Theta waves
4 - 8 Hz
Alpha waves
8 - 12 Hz
Beta waves
12 - 30 Hz


ROC of PSI and BIS
sensitivity
1 - specificity
0.0
0.2
0.4
0.6
0.8
1.0
PSI (AUC=0.953)
BIS (AUC=0.888)