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ORIGINAL ARTICLE

Decrease of the peak heights of EEG bicoherence indicated insufficiency of analgesia during surgery under general anesthesia

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Abstract

Background Studies show that the two peak heights of electroencephalographic bicoherence (pBIC-high, pBIC-low) decrease after incision and are restored by fentanyl administration. We investigated whether pBICs are good indicators for adequacy of analgesia during surgery.

Methods After local ethical committee approval, we enrolled 50 patients (27–65 years, ASA-PS I or II) who were scheduled elective surgery. Besides standard anesthesia monitors, to assess pBICs, we used a BIS monitor and freeware Bispectrum Analyzer for A2000. Fentanyl 5 μg/kg was completely administered before incision, and anesthesia was maintained with sevoflurane. After skin incision, when the peak of pBIC-high or pBIC-low decreased by 10% in absolute value (named LT10-high and LT10-low groups in order) or when either peak decreased to below 20% (BL20-high and BL20-low groups), an additional 1 g/kg of fentanyl was administered to examine its effect on the peak that showed a decrease.

Results The mean values and standard deviation for pBIC-high 5 min before fentanyl administration, at the time of fentanyl administration, and 5 min after fentanyl administration for LT10-high group were 39.8% (10.9%), 26.9% (10.5%), and 35.7% (12.5%). And those for pBIC-low for LT10-low group were 39.5% (6.0%), 26.8% (6.4%) and 35.0% (7.0%). Those for pBIC-high for BL20-high group were 26.3% (5.6%), 16.5% (2.6%), and 25.7% (7.0%). And those for pBIC-low for BL20-low group were 26.7% (4.8%), 17.4% (1.8%) and 26.9% (5.7%), respectively. Meanwhile, at these trigger points, hemodynamic parameters didn't show significant changes.

Conclusion Superior to standard anesthesia monitoring, pBICs are better indicators of analgesia during surgery.

Trial registry Clinical trial Number and registry URL: UMIN ID: UMIN000042843 https://center6.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000048907

Keywords Electroencephalogram · Nociception · EEG bicoherence · General anesthesia · Fentanyl · Intraoperative monitoring · Opioids

Introduction

During general anesthesia, since pain is a phenomenon of consciousness, autonomic responses to nociceptive stimuli may occur without pain perception or indication. There is no established objective method, however, for monitoring nociceptive inputs to the unconscious brain. Anesthesiologists usually judge insufficiency of analgesia by watching for body movement in response to surgical stimuli or for hemodynamic changes. Monitoring of autonomic responses has been provided by some commercial devices, but it is known that they are influenced by cardiac pacemakers and by several drugs that affect autonomic responses. Laferrière-Langlois et al. [1] wrote in their recent issue that nociception monitors remain by comparison underdevelopment and

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underutilized. Thus, monitor for nociception is still under development.

When nociceptive inputs reach the brain, they may elicit hormonal and neuronal stress responses. To protect the patients from such stress, it is important to know if nociceptive input is reaching the brain. It is known that electroencephalogram (EEG) data can reveal both the occurrence of noxious stimuli and concentration changes of anesthetic [2]. Meanwhile, EEG derived indices, such as the Bispectral index (BIS), Entropy (SE, RE) or Patient state index (PSI), may be used to assess level of hypnosis during anesthesia. They give no indication, however, of noxious inputs or adequacy of analgesia.

EEG bicoherence, quantified quadratic phase-coupling (QPC), is a derived-frequency component of EEG data [3]. Previous study showed that, at surgical levels of anesthesia, two peaks of EEG bicoherence emerge in the bi-frequency space around the diagonal line: one peak arises at around 4 Hz (pBIC-low), and the other at around 10 Hz (pBIC-high) [4]. Another study showed that pBICs (pBIC-low and pBIC-high) decreased after incision and can be restored by administering 3 g/kg of fentanyl [5]. This study investigated whether pBICs (pBIC-high and pBIC-low) could become indicators for adequacy of analgesia only at incision.

In the present study, we extended investigation into whether pBICs indicate analgesia during surgery. Figure 1 shows the changes of pBIC-high, BIS and estimated effect-site concentration (Ce) of propofol and fentanyl during laparoscopy assisted trans-vaginal hysterectomy for 49 year-old female patient in our preliminary study. In this case, we administered fentanyl when pBIC-high was considerably decreased without strict criteria (indicated by thick arrows), while Ce of propofol was kept constant at 3.2 mg/mL during surgery. Neuromuscular blocker was administered in requirement. Propofol was infused with Diprifuzor™. Ce of fentanyl was calculated using pharmacokinetics/pharmacodynamics parameters by Shafer et al. [6] pBIC-high values were increased after fentanyl administration while BIS values were stable between 40 and 50. However, in two points (indicated by thin arrows) when pBIC-high decreased, BIS values increased due to electromyogram (EMG) contamination, which suggested the delay of fentanyl administration and the insufficiency of analgesia. At theses points, we administered neuromuscular blocker as well as fentanyl, after that BIS values were rapidly returned, while increases of pBIC-high were delayed by 1–2 min. This indicated that body movement could occur when fentanyl administration was delayed. This preliminary case indicated that decrease of pBIC-high during surgery also might suggest insufficiency of analgesia, and administration of fentanyl could restore them. Here, we aimed to clarify whether pBICs could become good indicators for appropriate analgesia.

Methods

This study was conducted with approval from the hospital's ethics committee (Kansai Medical University Center for Ethical Review; IRB# 2,021,187) and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at University Hospital Medical Information Network (UMIN 000042843, Principal investigator: Satoshi Hagihira, Date of registration: December 24, 2020). This manuscript adheres to the applicable CONSORT guidelines.

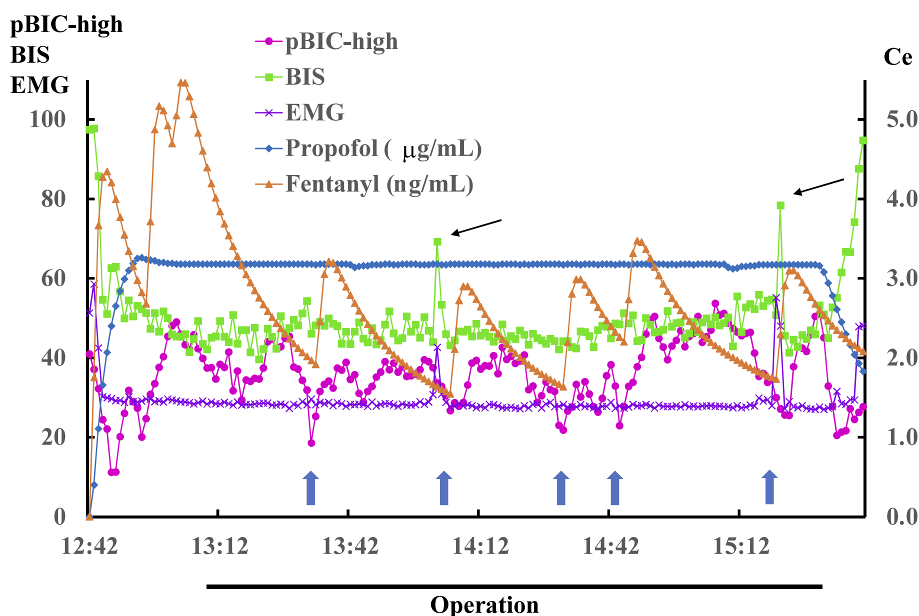

Fig. 1 An example of the changes of changes of pBIC-high, BIS and estimated effect-site concentration of propofol and fentanyl during laparoscopy assisted trans-vaginal hysterectomy for 49-year-old female patient. Left axis indicated pBIC-high (%) and BIS. Blue line indicated Ce of propofol (µg/mL; right axis), orange line indicated Ce of fentanyl (ng/mL; right axis), pink line indicated pBIC-high (%; left axis), and green line indicated BIS (no unit; left axis). Thick arrows indicated the timing of fentanyl administration and thin arrows indicated increased BIS due to EMG contamination

Building on the previous study [5], which was conducted at the beginning of surgery and aimed to assess both whether pBICs could be indicators of nociceptive input in response to intraoperative surgical stimuli, and whether fentanyl administration could restore pBICs, we designed a prospective observational study.

Patients

We recruited patients as following: (1) age 20–65 years when consent was obtained; (2) undergoing surgery in the supine position; (3) ASA physical status I–II; and (4) the patient gave free, written, fully informed consent. We excluded patients who with the following criteria: (i) head and neck surgery; (ii) high risk of drug interaction with anesthetics or sedatives; (iii) need for a surrogate; and (iv) otherwise judged by the principal investigator to be unsuitable.

Anesthetic protocols

In addition to standard monitors, including electrocardiography, noninvasive blood pressure, oximetry, and expired-gas monitoring, we used a BIS monitor (A3100C; Covidien, Boulder, CO, USA). Anesthesia was induced with propofol at 1–2 mg/kg and fentanyl at 3 g/kg. After administering 0.6 mg/kg of rocuronium, we intubated the patient's trachea. Anesthesia was maintained with air, oxygen and sevoflurane. Expiratory sevoflurane concentration, kept constant during surgery, was maintained at 1.3–1.5%. The ventilator was set to maintain expiratory carbon dioxide concentration at 35–40 mmHg. We excluded from the study patients under stable anesthesia prior to surgery but with pBICs at less than 20% (here and below: absolute percentage, not percent relative to base value).

Fentanyl was administered at 2 g/kg before the start of surgery. During the intraoperative period, fentanyl at 1 g/kg (minimum dose 50 g) was added according to the following criteria: (1) if either pBICs fell by more than 10% (in absolute value) from the highest value within the latest 5 min; (LT10; LT10-high, LT10-low) (2) if either pBICs fell below 20% (BL20; BL20-high, BL20-low).

To avoid critical status, even if neither criteria applied, fentanyl was administered if deemed necessary by the anesthesiologist. Rocuronium was administered in requirement. As a rule, no other analgesics should be administered for 10 min after fentanyl administration, and none were. When the criteria were still fulfilled 10 min after fentanyl administration, we once added fentanyl at 1 g/kg. Previous study revealed that the SDs of pBIC-low and pBIC-high at steady state were 3.21% and 3.05%, respectively. We considered difference of 10 was clinically significant. Larger difference might be clearer, however, delay of fentanyl administration might cause contamination of EMG as shown in the presented case.

When epidural anesthesia was indicated for post-operative analgesia, epidural tubing was inserted before induction and a test dose of 3 ml of 1% lidocaine was administered via epidural catheter, after which no epidural anesthetic was administered intraoperatively. When indicated for post-operative analgesia, peripheral nerve blocks were performed after surgery.

Data collection

From the BIS monitor, both raw EEG data and EEG-derived parameters were recorded to a computer using Bispectrum Analyzer (BSA) for A2000 (URL http://www7.kmu.ac.jp/anesthw/software-library) which, in real time, from the latest 3 min of EEG data, is able to calculate and display pBIC-low and pBIC-high every 10 s. The detailed method for calculating pBIC-low and pBIC-high is described in the Appendix.

When one of the criteria was met, fentanyl was administered: in figures and tables, and below, this time point is referred to as AddFent; the data point 5 min before AddFent, Pre5; and at 5 min after, Post5. If multiple criteria were met simultaneously, we included the data in all groups.

Consequently, we calculated pBICs at Post5 from 3 min 30 s to 6 min 30 s after fentanyl administration, during which time the maximum effect of fentanyl in EEG data could be detected [5].

Statistical analyses

First, fat pencil test and Kormogorov–Smirnov normality tests were performed for each parameter, and if normality was detected, it was handled as parametric, otherwise the parameter was handled as nonparametric.

Our hypothesis was that fentanyl administration when pBIC values decreased to meet our criteria would restore them. To prove our hypothesis, we made two comparisons after applied repeated measures of ANOVA (parametric) or by Friedman rank sum test (nonparametric). We compared pBICs values between AddFent and Post5 by one-sided paired t-test with Holm's correction (parametric) or by Friedman test with Holm's correction (nonparametric). Then, we conducted an equivalence test between Pre5 and Post5 with Holm's correction. We also compared BIS, systolic blood pressure (sBP) and heart rate (HR) at the same three time points by repeated measures of ANOVA (parametric) or by Friedman rank sum test (nonparametric).

EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) was used for all statistical analyses. EZR is statistical software that extends the functionality of R and R Commander [7].

As the primary outcome of LT10 is an expected increase in pBICs after fentanyl administration, we calculated the required number of samples as follows: $\alpha = 0.025$ (considering Holm's correction), $\beta = 0.20$, SD = 10.0 (from our previous study); detect difference = 7.0, one-sided using G*Power3 software [8] (Ver 3.1.9.6). In this condition, the required number of samples was 19. In this study, since fentanyl was administered based on two criteria for two pBICs, making it a total of four scenarios, it was challenging to calculate the number of cases needed to obtain the sample size of 19 for all four cases. Therefore, we estimated the number of cases to be approximately 50. We also calculated the post hoc power in each analysis, because the sample size of each group would become quite different in the current study design.

Table 1 Demographic data. Parametric data are presented as mean (SD). The unit of measure for those without a notation is case

Summary	Total
Cases	46
Age [y.o]	45.6 (9.7)
Gender [M/F]	3/43
Laparoscopic gynecological surgery [N]	35
Laparoscopic cholecystectomy [N]	4
Mastectomy [N]	4
Laparoscopic hepatectomy [N]	2
Inguinal hernia repair [N]	1
Anesthesia duration [min]	205 (62)
Operative duration [min]	143 (59)

Results

Having obtained written informed consent from each of the 56 patients, we gathered data between February and October 2021. Table 1 summarizes the demographic data, and Fig. 2 shows the CONSORT diagram. Six of the 56 patients were excluded because fentanyl was not administered intraoperatively. Furthermore, as written below 4 cases were excluded from 50 patients. Finally, we analyzed 3 men and 43 women. Four had general anesthesia only, one had general anesthesia and epidural tubing, and 41 received anesthesia and had peripheral nerve blocks after completion of surgery. Anesthesia was induced with propofol. One patient with an egg allergy was induced with thyamilal. Patients for whom we were unable to secure a peripheral venous line were given a slow induction with sevoflurane.

Altogether, we administered intraoperative fentanyl 145 times: 25 instances were judged to be LT10, but with pBICs dropping by smaller than 10% within 5 min; 18

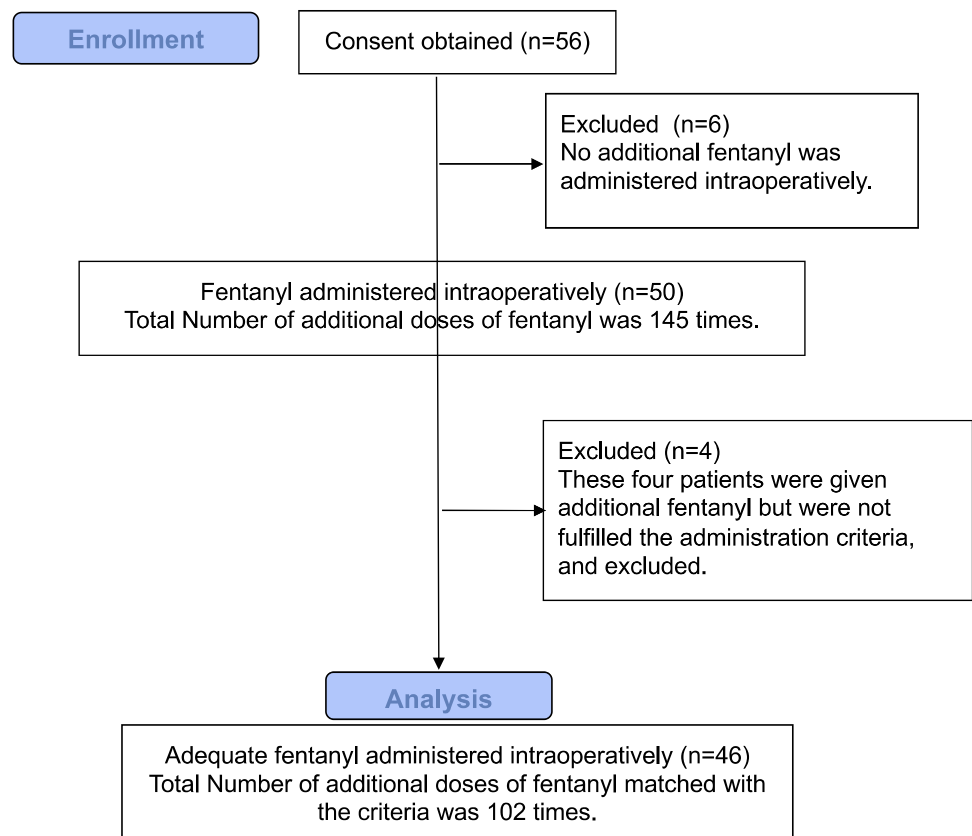

Fig. 2 CONSORT diagram

instances were judged to be BL20, but were excluded because pBICs at Pre5 were less than 20%. Subsequently, those 25, 18 instances and 4 patients who had no criteria for interventions were excluded. Analyses were performed on the remaining 102 instances. Detailed numbers of triggers for fentanyl administration are shown in Table sup1.

The fat pencil test and Kormogorov–Smirnov test revealed that all parameters could be handled as parametric. Figure 3 shows the changes of pBICs for LT10 at Pre5, AddFent, and Post5.

For LT10-high, the values were 39.8% (10.9%), 26.9% (10.5%) and 35.7% (12.5%); $F(2,82) = 129.3$, $p < 2e\text{-}16$, while for LT10-low, the values were 39.5% (6.0%), 26.8% (6.4%) and 35.0% (7.0%); $F(2,62) = 87.36$, $p < 2e\text{-}16$. Figure 4 shows the changes of pBICs for BL20 at Pre5, AddFent and Post5. For BL20-high, the values were 26.3% (5.6%), 16.5% (2.6%) and 25.7% (7.0%); $F(2,76) = 56.25$, $p = 1.02e\text{-}15$. For BL20-low, they were 26.7% (4.8%), 17.4% (1.8%) and 26.9% (5.7%); $F(2,36) = 33.37$, $p = 6.33e\text{-}09$.

In all groups, pBIC values at Post5 were significantly greater than those at AddFent. P values were as follows; 4.571e-4 (LT10-high), 2.756e-06 (LT10-low), 2.274e-09 (BL20-high), and 1.382e-06 (BL20-low). Post hoc powers were 0.99 (LT10-high), 1.0 (LT10-low), 1.0 (BL20-high), and 1.0 (BL20-low), respectively.

The results of equivalence test between Pre5 and Post5 were as follows. In this test, we calculated the 97.5% confidential interval of the difference between Pre5 and Post5. The intervals were [−5.86, −2.36] (LT10-high), [−7.09, −2.23] (LT10-low), [−2.93, 1.81] (BL20-high), and [−3.31, 3.67] (BL20-low). We set the clinically acceptable range for pBIC-low as [−6.29,6.29] and for pBIC-high as [−5.98,5.98] considering 95% confidential interval, because SD of pBIC-low and pBIC-high at steady state were 3.21% and 3.05%, respectively. Finally, except LT10-low group, pBIC values at Pre5 and those at Post5 were judged as equivalent.

For both criteria, between Pre5, AddFent, and Post5, no significant differences were detected in BIS, sBP and HR (Table 2).

Discussion

Five minutes after fentanyl administration, pBICs significantly increased and returned to Pre5 values except in LT10-low group. Thus, from the current study, since fentanyl administration restored pBICs, we assume that pBICs

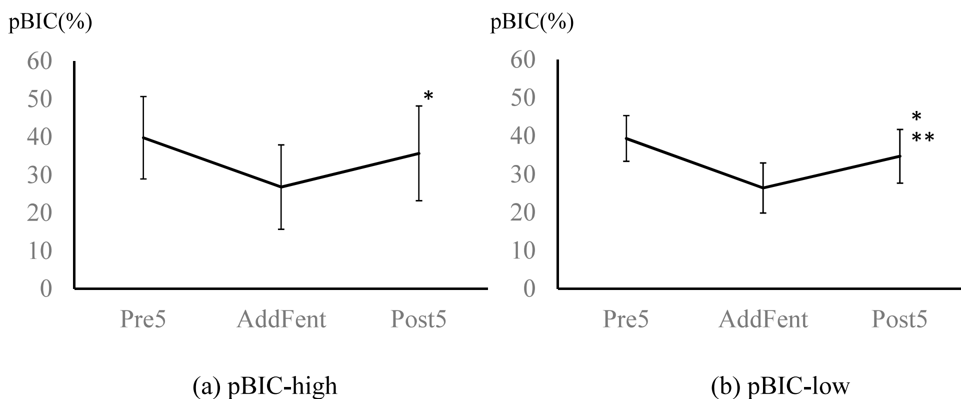

Fig. 3 During surgical anesthesia, two peaks (pBIC-high and pBIC-low) of EEG bicoherence are apparent in the bi-frequency space around the diagonal line: pBIC-low emerges at around 4 Hz, and pBIC-high at around 10 Hz. Changes in pBIC-high (Fig. 3a) and pBIC-low (Fig. 3b) in less than 10% (LT10) *$p < 0.025$ (pBIC-high; 4.571e-4, pBIC-low: 2.756e-06 vs. AddFent), **$p < 0.025$ (inferior to Pre5)

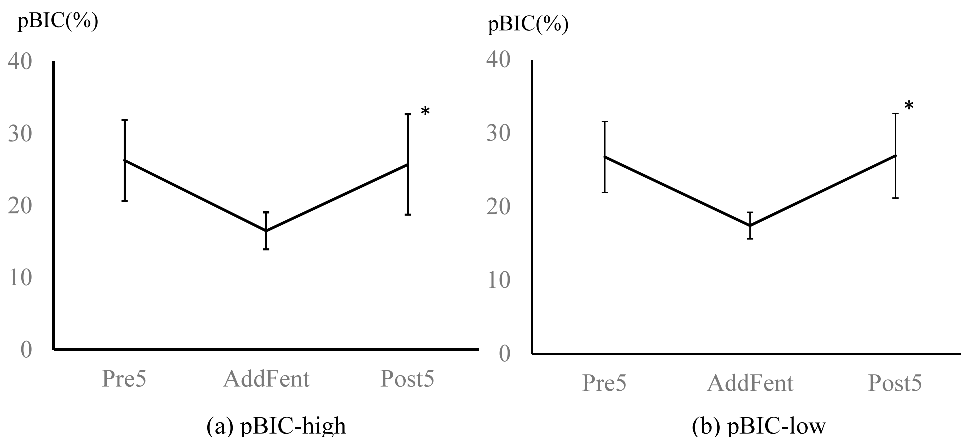

Fig. 4 Changes in pBIC-high (Fig. 4a) and pBIC-low (Fig. 4a) in below 20% (BL20) *$p < 0.025$ (pBIC-high; 2.274e-09, pBIC-low: 1.382e-06 vs. AddFent)

Table 2 Changes in BIS, heart rate and systolic blood pressure (sBP) in LT10 and BL20. Parametric data are presented as mean (SD)

LT10	pBIC-high				pBIC-low			
	Pre5	AddFent	Post5	p	Pre5	AddFent	Post5	p
BIS	42.7 (7.1)	43.2 (8.8)	42.5 (7.2)	0.882	45.4 (7.6)	45.8 (9.9)	43.9 (6.4)	0.59
HR [beats/min]	67.2 (14.0)	67.9 (14.0)	65.6 (11.5)	0.704	69.1 (11.2)	70.5 (9.9)	69.8 (10.4)	0.856
Systolic BP [mmHg]	112.7 (13.7)	117.0 (16.3)	111.9 (16.2)	0.272	114.9 (14.1)	122.2 (18.4)	116.2 (19.2)	0.193
BL20								
	Pre5	AddFent	Post5	p	Pre5	AddFent	Post5	p
BIS	47.1 (9.7)	47.2 (10.8)	44.9 (8.1)	0.425	51.2 (8.9)	50.7 (7.2)	48 (6.3)	0.299
HR [beats/min]	72 (12.0)	73.0 (15.4)	70.3 (10.2)	0.645	63.6 (8.0)	63.2 (6.8)	61.2 (5.0)	0.447
Systolic BP [mmHg]	119.9 (20.1)	124.1 (21)	117.9 (18.7)	0.37	110.8 (16.0)	113.8 (14.2)	111.2 (13.4)	0.786

decreased because analgesia was insufficient. Previous report showed that fentanyl itself had no effect on pBICs when it was administered before incision [5].

If this finding is accepted, pBICs could become useful indicators for intraoperative analgesia. Meanwhile, at the three time points measured, there were no significant changes in sBP nor HR. This suggests that pBICs are more sensitive to insufficient analgesia than hemodynamic parameters.

We also should consider the factors that might change EEG bicoherence. Previous report showed that peak height of EEG bicoherence changed with anesthetic concentration. However, we kept anesthetic concentration constant during surgery. So, this factor could be excluded. Currently, we didn't know other factors that had influence on pBICs. However, considering that brain ischemia decreased the alpha band activity, there is a possibility that pBICs might decrease when brain ischemia occurred. In the current study, hemodynamic status was fairly stable and brain ischemia could be excluded. Another possibility would be hypocapnia or hypercapnia. In the current study, expiratory carbon dioxide concentration was kept 35–40 mmHg. So, this also could be excluded. Finally, we considered noxious stimuli, in other words insufficient analgesia, would probably be the cause of the changes in pBICs in the current study.

Garcia et al. [2] described 3 types of EEG changes in response to noxious stimuli during anesthesia: beta arousal, delta arousal, alpha dropout. Alpha dropout referred to the reduction or disappearance of spindle wave that occurred during anesthesia due to noxious input, which would correspond with decrease in pBIC-high in the current study. As reported by Steriade and his colleagues [9, 10], the rhythm of spindle wave was generated by thalamo-cortico-thalamic reverberating circuit, and bispectral analysis seemed to be this activity. Bicoherence is a measure of the degree of QPC and is theoretically unaffected by EEG power (or amplitude) [3]. In practice, current method for calculating bicoherence had some influence, but often sufficient bicoherence values could be obtained even when EEG power was low. Therefore, we believed that our method could be applied to patients with originally small EEG amplitudes. We showed an example of a case that showed small power in the α-region but significantly high pBICs in Fig. supp1 accompanied with those of an average patient. Of course, it would be difficult to apply our method to patients with low pBICs even in the absence of noxious stimuli at the clinical level of anesthesia, as in the case of the patients excluded in the current study.

Hight et al. [11] suggested that alpha dropout might suggest thalamocortical depolarization and could provide a measure of nociception during surgery, which is in line with our current result. We thought that alpha power could also be an indicator of adequate analgesia in patients with large alpha power at surgical level of anesthesia. Actually, we can judge insufficiency of analgesia by watching the changing of alpha power in patients with large alpha power. However, EEG always fluctuates even without any sensory stimuli, then it seemed rather difficult to find the changes in alpha power in patients with small alpha power [12], because we should distinguish decrease of alpha power from fluctuation of alpha power. Furthermore, it seemed difficult to set adequate cutoff value of alpha power because of large inter-individual variability in absolute alpha power or alpha power/total power. Generally speaking, α power became small with increase of age [13]. Then detecting power changes in the α-region in elder patients seemed difficult. As our software also showed power spectrum in every 10 s, we might be able to judge the decrease of alpha power by qualitatively watching the changes of power spectrum, but it would only be subjective.

In the previous report [5], pBIC-low decreased after incision in all cases including delta arousal. Thus, pBIC-low decreased while delta power increased during delta arousal. Delta rhythm observed during delta arousal was thought to be generated in the midbrain [2]. On the other hand, both spindle rhythm and delta rhythm observed during surgical

level of anesthesia without noxious stimuli were generated in thalamic reticular nuclei and thalamo-cortico-thalamic reverberating circuit [9, 10]. We speculated that this reverberating circuit is the source of QPC and noxious input attenuated these rhythms generated by this circuit. That was why pBIC-low decreased even when delta arousal was observed. Alpha dropout can occur simultaneously during beta arousal and delta arousal. When the noxious stimuli were weak, alpha dropout occurred first, while delta arousal usually occurred when the noxious stimuli were intense. When delta arousal occurred, alpha dropout also occurred at about the same time. This could be seen from the changes in bicoherence and electroencephalogram (EEG) in the previous report [5].

In LT10, while we restricted the period of pBICs observation to within 5 min, we consider it necessary to administer analgesic when pBICs decreases more slowly. As the intensity of surgical stimuli varies second by second, insufficiency of analgesia is not so clearly determined. Considering that the decrement speed of Ce of fentanyl became rather slow in metabolic phase, decrease of pBICs seemed more rapid as shown in Fig. 1. We speculated that QPC would completely disappear when some amount of noxious stimuli reached to the brain. Here we assumed that QPC was 40% when analgesia was sufficient and QPC fell to 10% by noxious input, pBIC value would change to $(40+40+10)/3=30\%$, $(40+10+10)/3=20\%$ and $(10+10+10)/3=10\%$ at 1, 2 and 3 min after QPC fell to 10%. Although it took 3 min to change to the new value because pBICs were calculated from latest 3 min of EEG signal, smaller SD of pBICs made it possible to detect their changes faster. We could easily and quickly detect the decrease of pBICs from their trend changes as pBICs were updated every 10 s. The case shown in Fig. 1 also indicated that delay of fentanyl administration might cause body movement and/or hemodynamic changes due to insufficient analgesia. Then, we should consider appropriate threshold of decrement in pBICs.

In BL20, fentanyl administration was timed to when pBICs decreased to less than 20%. Bispectral analysis is a statistical technique and pBICs of lower than 15%–20% (dependent on the number of epochs used for bispectral calculation) indicate that little or no quadratic phase coupling is occurring. In the previous study [5], when anesthesia was maintained using only volatile anesthetic, post-incision pBICs decreased to less than 20% in all 24 cases. In some patients, pBICs did not rise to 30% or more even at surgical levels of anesthesia before incision. Since it was rather difficult to detect triggering decreases in such patients, we devised BL20.

In the current study, to judge the timing of fentanyl administration, we utilized the trend graph and the latest pBICs values displayed by the software. As pBICs were updated every 10 s and often fluctuated, it was quite difficult to judge whether drops in pBICs fulfilled the LT10. As a result, many misjudgments occurred. Now we are planning to develop an auto-detection system for decrease of pBICs in LT10 and BL20 for the future study.

We reviewed literature on analgesia monitors, launched to date, for intraoperative nociceptive input based on autonomic system response. For example, the Analgesia Nociception Index (ANI, MDorolis) detects painful stimuli based on heart rate variability and aims to reflect the balance between nociception and antinociception [14]. The Surgical pleth index (SPI, GE) supposedly detects autonomic nervous system responses from plethysmographic pulse wave amplitude and HR data [15]. Similarly, The Nociception Level Index (NOL, Medasense) attempts to detect nociceptive inputs from accelerometer, body temperature, and fingertip volume pulse wave variations [16]. The Pupillary pain index (PPI, IDMED) monitors pupil diameter [17]. We speculated that pBICs might be more sensitive than those monitors based on autonomic system response, because we showed that pBICs changed without any hemodynamic changes, namely autonomic responses.

EEG analysis is used by qNOX (Quantium Medical) [18]. qNOX is calculated from several EEG band powers using adaptive neuro fuzzy inference system [18]. Then we could not know its precise logic to get qNOX. Another EEG based monitor is Pain Threshold Index (PTI) (Beijing Easemonitor Technology Inc., China) [19]. PTI seemed to be calculated by EEG wavelet analysis. At present, detailed information about PTI is not available.

Recently, Laferrière-Langlois et al. [1] wrote in their review that nociception monitors remained by comparison underdeveloped and underutilized. We thought that the comparison of our current method with other commercially available nociception monitor is the future issue.

As pBICs also vary according to anesthetic concentration [4], to indicate adequate analgesia, anesthetic concentration should be kept constant when using pBICs. In line with current balanced anesthesia policies, it makes sense to keep anesthetic concentration constant and to manage analgesics during surgery.

Limitations

Application of the current method is restricted to surgical levels of anesthesia, which produce high enough changes in pBICs. And, since pBICs vary with anesthetic concentration, to use pBICs as indicators of analgesia, it is necessary to maintain constant anesthetic concentration. Of course, this is not an inconvenience if balanced anesthesia is practiced, because, once an adequate level has been determined, there is no need to change the maintenance concentration of anesthetic during surgery. In addition, it may be difficult

to observe and evaluate pBICs in patients receiving antipsychotic drugs, or to evaluate patients with cerebrovascular disorders or other cerebral function disorders which may have altered or decreased cerebral function and cerebral blood flow. Such patients were excluded from the current study.

For patients with low pBICs in stable anesthesia prior to surgery, it may be more difficult to capture pBICs fluctuations. There were no applicable cases in the present study.

Another limitation is that our method only works well when intensity of surgical stimuli is within a reasonable range. While intensity of surgical stimuli changes second by second, the effect of fentanyl in bolus reaches a peak after about 4 ~ 5 min and then gradually diminishes. After this peak, it is quite difficult to judge when to give the next fentanyl administration. It may be necessary to administer fentanyl before any surgical stimuli by predicting that the next procedure might cause sudden intense stimuli. Using pBICs, it is difficult to deal with such situations. In our sample, however, intensity of surgical stimuli was not so severe, and especially during laparoscopic surgery, remained within a reasonable range. The use of pBICs monitoring may be suitable for such types of surgery.

It is known that α power, generally, decreases as age increases. Consequently, pBICs monitoring is not suitable for elderly patients who show low α power in EEG during anesthesia.

In the current study, we included both genders but, as shown in the results, most participants were female. In future studies we hope to control for gender bias. Furthermore, to demonstrate the usefulness of including pBICs monitoring, we will design studies for relatively similar surgical procedures to compare doses of narcotics, given before and after surgery, with post-operative pain in (i) patients who receive analgesia at the anesthetist's discretion, as in the past, with (ii) patients who receive analgesia with reference to variations in pBICs. We feel confident that the results of such studies will demonstrate the usefulness of pBICs alongside the other modes of monitoring.

In the current study, we could not show that pBIC-low values in the LT10 group returned to the previous value as lower limit of confidential interval was just below our clinically significant limit, although they significantly increased from those at AddFent. Currently, we could not draw decisive conclusion of pBIC-low in LT10.

Conclusion

Decreases in pBICs indicate inadequate analgesia. These parameters, were more sensitive than hemodynamic parameters such as blood pressure or heart rate that anesthetists usually use as indicators of insufficient analgesia.

Appendix

In computing the bispectrum, the EEG signal was first divided into a series of epochs. There is no rule how to divide the signal to a series of epochs. Overlapping of epochs is often used for increase the number of epochs in restricted EEG signal. For each epoch, Fourier transform was computed after applying appropriate window function.

Bispectrum: $B(f_1,f_2)$ is calculated using the following equation.

$$TP_j(f_1,f_2) = X_j(f_1) \bullet X_j(f_2) \bullet X_j^*(f_1 + f_2)$$

$$B(f_1,f_2) = \left| \sum_j TP_j(f_1,f_2) \right|$$

Here, $X(f)$ is a frequency component calculated using Fourier transform and is a complex-value. $X^*(f)$, the conjugate of $X(f)$. $TP_j(f_1,f_2)$, is a triple product. And j indicated the j-th of TP or X.

This summation is the heart of bispectral calculation. The reason is as follows:

When a complex-value is expressed as a polar coordinate, $X(f)$ is expressed as follows:

$$X(f) = r \bullet \{\cos(ft + \theta) + i \bullet \sin(ft + \theta)\}$$

Here, ‘t’ is the time parameter. Subsequently, each frequency component of triple products is expressed as follows:

$$X(f_1) = r_1 \bullet \{\cos(f_1 t + \theta_1) + i \bullet \sin(f_1 t + \theta_1)\}$$

$$X(f_2) = r_2 \bullet \{\cos(f_2 t + \theta_2) + i \bullet \sin(f_2 t + \theta_2)\}$$

$$X^*(f_1 + f_2) = r_3 \bullet [\cos\{(f_1 + f_2)t + \theta_3\} - i \bullet \sin\{(f_1 + f_2)t + \theta_3\}]$$

Here, r_1, r_2, r_3 represent the magnitudes of $X(f_1)$, $X(f_2)$, $X(f_1 + f_2)$, and $\theta_1, \theta_2, \theta_3$ represent the phase angle of $X(f_1)$, $X(f_2)$, $X(f_1 + f_2)$.

Using the characteristics of polar coordinates, the magnitude of $TP_j(f_1,f_2)$ becomes $r_1 \bullet r_2 \bullet r_3$, and the phase angle of $TP_j(f_1,f_2)$ are calculated as follows:

$$(f_1 t + \theta_1) + (f_2 t + \theta_2) - \{(f_1 + f_2)t + \theta_3\} = \theta_1 + \theta_2 - \theta_3$$

And

$$TP(f_1 + f_2) = r_1 \bullet r_2 \bullet r_3\{\cos(\theta_1 + \theta_2 - \theta_3) + i \bullet \sin(\theta_1 + \theta_2 - \theta_3)\}$$

The fact that time parameter ‘t’ is canceled is important because it means that the phase angle of the triple product is independent of the EEG epoch that was used to calculate the frequency components.

It also follows that the form $(\theta_1 + \theta_2 - \theta_3)$ is suitable for investigating the relationship between $(\theta_1 + \theta_2)$ and θ_3. Furthermore, the equation above also shows that the size of the triple product is independent of the $\theta_1, \theta_2, \theta_3$ alignment.

Consequently, it is impossible to tell from a single epoch result whether or not a signal is phase-coupled.

Incidentally, bispectrum is the magnitude of the sum of triple products. The bispectrum value is determined by the distribution pattern of each $(\theta_1 + \theta_2 - \theta_3)$. If there was no relationship among $\theta_1, \theta_2, \theta_3$, $(\theta_1 + \theta_2 - \theta_3)$ would be randomly distributed between $[0,2\pi]$. As a result, the sum of the triple products would tend toward zero. On the other hand, bispectrum would show non-zero values if there were some relationships among $\theta_1, \theta_2, \theta_3$. Thus, bispectral analysis can detect phase coupling among the frequency components of a signal.

Because bispectrum is also influenced by the amplitudes of the frequency components, to evaluate the degree of phase coupling, it is necessary to normalize bispectrum values. Normalized bispectrum values are called bicoherence. Several methods for calculating bicoherence have been described in the literature. As described in a previous report [3], the authors hold that the following equation is most mathematically reasonable:

$$BIC(f_1,f_2) = \frac{B(f_1,f_2)}{\sum_j \left|TP_j(f_1,f_2)\right|} \bullet 100(\%)$$

$$= \frac{B(f_1 + f_2)}{\sum_j \sqrt{P_j(f_1) \bullet P_j(f_2) \bullet P_j(f_1 + f_2)}} \bullet 100(\%)$$

Since bispectrum is defined as the magnitude of the sum of complex-numbers, using the equation below, it should be scaled using the sum of the magnitudes of each complex-number:

$$\left|z_1 + z_2\right| \le \left|z_1\right| + \left|z_2\right|$$

Another important parameter is average BIC (aBIC). As defined in the previous study [4], aBIC(f) was calculated as follows:

$$aBIC(f) = \frac{1}{11}\Big[BIC(f,f) + 2\{BIC(f,f-0.5) + BIC(f+0.5,f-0.5) + BIC(f+0.5,f-1.0) + BIC(f+1.0,f-1.0) + BIC(f+1.0,f-1.5)\}\Big]$$

And maximum value among $aBIC(f) 2.0 \le f \le 6.0$ Hz was defined as pBIC-low, and the maximum value among $aBIC(f) 7.0 \le f \le 13.0$ Hz was defined as pBIC-high.

In BSA, the calculating method for bispectrum followed that of the BIS monitor. Namely, EEG signal was first divided into two-second length of epoch, each epoch was overlapped by 75% each other, Fourier transform was computed after applying Blackman window.

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Data availability The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest None.

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