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Comparison of blood pressure and pain rating index used for depth regulation of sevoflurane anesthesia

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Abstract

Objective: The Pain Rating index (PRi) is a new parameter for regulating analgesic depth of anesthesia based on wavelet analysis. The aim of this study was to investigate the feasibility of PRi for depth regulation of sevoflurane anesthesia.

Methods: We conducted a monocentric randomized controlled study from September 2017 to June 2018 in patients undergoing anterior cervical discectomy and fusion (ACDF) (n=44). Patients were randomly allocated into two groups and assigned 22 cases to each group: systolic blood pressure group (SBP group) and pain rating index group (PRi group). In SBP group, sevoflurane inhalation concentration (Cs) was adjusted to maintain SBP values at baseline values -20%～+20%; in PRi group, Cs was adjusted to maintain PRi values between 50 and 70. The primary endpoint was anesthesia recovery time. Secondary endpoints included extubation time, sevoflurane consumption, number of intraoperative hemodynamic instability events /interventions, number of adverse events and postoperative visual analogue scale for pain.

Results: Patient demographic characteristics, surgical time and anesthesia time did not differ between groups. Anesthesia recovery time was shorter in PRi

group than in SBP group (17.5±3.8min vs 21.5±2.8 min; *P=0.001*). Extubation time was also shorter in PRi group than in SBP group (21.9±1.7min vs 24.1±2.5min; *P=0.001*). Sevoflurane consumption was lower in PRi group than in SBP group (15.5±4.1ml vs 20.0±2.5ml; *P=0.001*).

Conclusions: PRi was feasible to regulate depth of sevoflurane anesthesia, which could shorten anesthesia recovery time and extubation time, reduce sevoflurane consumption during general anesthesia in patients undergoing cervical vertebra surgery.

Keywords: Pain rating index; sevoflurane; depth of anesthesia.

Introduction

The general anesthesia mainly includes three components: sedation, analgesia and muscle relaxation, only when all three components reach appropriate state at the same time, the ideal depth of anesthesia could be obtained[1]. Currently, there are standard monitoring ways in anesthesia sedation depth and muscle relaxation depth, but the monitoring of analgesia depth is still in exploration stage[2].

The Pain Rating index(PRi) is a new parameter for monitoring analgesic depth of anesthesia based on wavelet analysis during general anesthesia. The PRi mainly extracts electroencephalograph (EEG) metadata of repeatable and regular changes in high and low frequency rhythm associated with pain signal and specifically reflect tolerance degree to pain stimulation in the cerebral cortex and subcortical center[3]. The range of PRi values is 0-100: 50-70 indicates satisfactory analgesia, <50 suggests excessive analgesia and >70 implies inadequate analgesia. The studies[4] showed that the PRi could predict hemodynamic reactivity after tracheal intubation and skin incision in pediatric patients during general anesthesia.

The previous regulation of sevoflurane anesthesia depth is mainly based on the monitoring of anesthesia sedation depth (e.g. bispectral index), but sevoflurane

has dose-dependent sedative, analgesic, muscle relaxant and autonomic reflex inhibitory actions. The current clinical trial aimed to investigate the feasibility of PRi for depth regulation of sevoflurane anesthesia. We hypothesized that PRi was feasible to regulate depth of sevoflurane anesthesia, which could shorten anesthesia recovery time and extubation time, reduce sevoflurane consumption in patients undergoing anterior cervical discectomy and fusion.

Methods

This randomized controlled trial was conducted from September 2017 to June 2018. The trial was approved by Ethical Committee (YXLL-2017-005) and registered in the Chinese Clinical Trial Registry (registration number: ChiCTR-IPR-17012092; date of registration: July 23, 2017). Written informed consent was obtained from all patients. Consecutive patients (age 40-60 years) undergoing elective anterior cervical discectomy and fusion(ACDF) surgery, with body mass index (BMI) 18-25 kg/m^2 and American Society of Anesthesiologists (ASA) physical status classification of I or II were included in the study.

The exclusion criteria were: (1) patients with history of central nervous system or respiratory system disease; (2) patients with abuse of alcohol or illicit drugs; (3) patients with history of malignant hyperthermia; (4) patients with psychiatric history or refused to sign informed consent.

A random number generator assigned the eligible patients into two groups: systolic blood pressure group(SBP group) and pain rating index group(PRi group). The main anesthesiologist was aware of patient grouping and intervention used. However, all patients and all staff who performed data collection and analysis were blinded to patient grouping and intervention used.

Non-invasive blood pressure (NIBP), pulse oxygen saturation (SpO_2), heart rate (HR) and electrocardiogram (ECG) were routinely monitored during surgery in all patients (IntelliVue MX700 bedside patient monitor; Philips, Amsterdam,

The Netherlands). For the monitoring of PRi, skin of the patient's forehead and mastoid was degreased with alcohol and EEG electrodes of multifunction combination monitor HXD-I (Beijing Easymonitor Technology, Co., Ltd., Beijing, China) were placed on Patients' forehead, 2cm above midpoint between eyebrows and above bilateral eyebrows, the reference electrodes were placed on bilateral mastoid. The electrode impedance was kept below 7.5kΩ as required by the manufacturer to ensure optimal contact.

The baseline values for SBP, HR and PRi were defined as average of three consecutive measurements immediately after patients' arrival in operating theater and recorded before anesthesia induction. During surgery, the anesthesiologist (who was aware of patient's assignment) managed level of anesthesia based on the group, patient had been allocated. However, all investigators involved in the collection, recording and analysis of data were blinded to the patient's assignment.

Calculation of PRi was conducted by the following procedure: [3,5]

For collected EEG signals, under sampling frequency, sampling accuracy and time window, vector set of each waveform signal is generated by discrete processing:

fi (x) = [x1 x2 x3 … xm-2 xm-1 xm]

i: number of EEG leads, m: number of vector elements.

Each lead EEG data acquisition window is S seconds, composed of each lead of EEG data vector Ni. Preprocessing of vector data for removal of DC components:

f (x) = f (x) – Av

Av: Direct circuit component of a vector.

For preprocessed brain wave data, wavelet analysis algorithm is applied. Wavelet algorithm definition:

If f (x) function is signal for space domain {-∞，+∞}, continuous wavelet transform algorithm formula is as follows:

$$W_c f(\tau, a) = \frac{1}{\sqrt{a}} \int_{-\infty}^{\infty} f(x) \Phi(\frac{x-\tau}{a}) dx$$

For calculation formula of wavelet frequency domain, the following expressions are used:

$$WT_x(a, \tau) = \frac{\sqrt{a}}{2\pi} \int X(\omega)\, \Psi(a\omega) e^{j\omega t} d\omega$$

The spectral analysis algorithm uses the discrete Fourier formula:

$$F(\omega) = f(\omega) = \int f(t) e^{-j\omega t}\, dt$$

The inverse transformation uses the following formula:

$$f(t) = \hat{F}(\omega) = \frac{1}{2\pi} \int F(\omega) e^{j\omega t} d\omega$$

For brain wave data, first apply binary conversion algorithm and waveform reconstruction algorithm in wavelet analysis to process specific brain wave vector data, select specific wavelet generating function, construct an n scale, from 2^0 to 2^n to conduct binary conversion algorithm:

(Wf(2^j,x))j∈z

A set of wavelet transform basis functions for bandpass filter banks can be obtained:

(Wf (2^0, x)), (Wf (2^1, x)), (Wf (2^N, x))

The power WLE of waveform potential of each wavelet base reconstruction function can be obtained

For each guided brainwave vector:

f (x) = [x1, x2, x3... xm-2, xm-1, xm]

The power spectrum function is calculated synchronously, and the formula is calculated by using fast Fourier transform:

$$X(\omega) = \int_{-\infty}^{\infty} f(x) e^{-j\omega t} dt$$

The calculation window is n, which can obtain alpha wave component of 8-13hz, the component of delta wave of 0.5-4hz, the theta component of 4-8hz, and the beta wave component of 13-30hz, as well as the dominant frequency, edge frequency and central frequency, and the initial phase pH (hz) of each frequency component.

The generating function was defined as the first derivative of smoothing function, and 64 points were constructed, scaling from 2^0 to 2^6 through dyadic wavelet transform.

The weighted items of each sub-index extracted from EEG were acquired through decomposing of different EEG data vectors on transformation characteristic weighting sequence by using multi-layer calculation and multiple regression iteration method. PRi was calculated by combining the weighted items of each sub-index (a_1,a_2.....a_n as the multiple regression weighting coefficients).

PRi = (a_1,a_2……a_n)&(i_22, i_24, i_35, i_52, i_60 ,i_70)

All patients were preoxygenated for five minutes with 100% oxygen. Then intravenous midazolam 0.05mg/kg, sufentanil 0.5ug/kg and etomidate 0.3mg/kg were administered for anesthesia induction, followed by vecuronium 0.1mg/kg for muscle relaxation. The patient's trachea was intubated and lungs were ventilated mechanically with a tidal volume of 8 to 10 mL/kg , with ventilatory rate adjusted to maintain end-tidal carbon dioxide between 30 and 35 mmHg.

For all the patients, sevoflurane (Maruishi Pharmaceutical Co., Ltd., Osaka, Japan) inhalation concentration (Cs) was started initially at 2 vol% with 2L/min of fresh gas flow. During maintenance of anesthesia, Cs range was limited between 1.5 vol% and 4 vol%, and vecuronium 0.05mg/kg was administered every forty minutes. In SBP group, Cs was adjusted to keep SBP at baseline values -20%~+20% by increasing or decreasing 0.5 vol% stepwisely. In PRi group, Cs was adjusted to keep PRi values at 50-70 by increasing or decreasing 0.5 vol% stepwisely.

The intraoperative hemodynamic instability events were defined identically for both groups. Hypertension was defined as SBP>120% baseline SBP. Hypotension was defined as SBP<80% baseline SBP. Tachycardia was defined as HR>90 beats per minute if baseline HR was below 75 beats per minute, or HR>120% baseline HR if it was >75 beats per minute. Bradycardia was defined

as HR<45 beats per minute[6, 7].

The intraoperative hemodynamic instability events were treated as follows: 0.3mg of nicardipine was administered intravenously for hypertension, 10mg of esmolol for tachycardia, 10mg of ephedrine for hypotension, and 0.5mg of atropine for bradycardia[6, 7].

At the end of surgery, sevoflurane was discontinued, and all patients received sufentanil 0.15μg/kg and tropisetron 5mg. Extubation was performed when the patient had recovered respiration and consciousness. Anesthesia recovery time and extubation time were measured by the investigators blinded to the patient's assignment. All patients were transferred to postanesthesia care unit (PACU) after extubation. In PACU, the same investigators who were blinded to the patient's assignment assessed postoperative adverse events and pain score.

Anesthesia recovery time was defined as the time from discontinuation of anesthetics to spontaneous opening of eyes. Extubation time was defined as the time from discontinuation of anesthetics to extubation.

The primary endpoint was to evaluate anesthesia recovery time in this study. The secondary endpoints included (1) sevoflurane consumption; (2) extubation time; (3) the number of intraoperative hemodynamic instability events (hypertension, hypotension, tachycardia and bradycardia); (4) the number of intraoperative interventions (hypertension, hypotension, tachycardia and bradycardia); (5) the number of intraoperative and postoperative adverse events (nausea, vomiting, agitation, respiratory depression and awareness); (6) postoperative visual analogue scale (VAS) for pain.

The primary endpoint of this study was to evaluate anesthesia recovery time. The sample size calculation was based on the results of a pilot study with 6 cases in each group. In the pilot study, anesthesia recovery time (mean±standard deviation) was 22.3±2.6min in SBP group and 18.4±3.0min in PRi group, respectively. Therefore, the effect size of 2-groups was 0.91. On the assumption that the allocation ratio of 2-groups was 1, a sample size for each group was 18,

calculated by Student's t-test, a level of significance of 0.05, and a power of 0.92. Considering a 20% dropout rate, the sample size for final enrollment was 22 in each group (total 44 patients).

Normally distributed quantitative data are presented as mean ± standard deviation (SD) and were analyzed with Student's t-test. Non-normally distributed data are expressed as median (range) and were analyzed using Brown-Forsythe test. Categorical variables are expressed as *n* (%) and were analyzed with chi-squared test. A *P*-value <0.05 was considered statistically significant in all analyses. Statistical analyses were performed using SAS 9.4 statistical software (SAS Institute, Cary, NC, USA). The above data analysis was conducted and completed by two data analysts independently.

Results

Among 56 patients assessed for eligibility, 5 patients refused to participate, and 7 patients did not meet inclusion criteria (age<40 years, n=4 and BMI>25 kg/m^2, n=3). Therefore, 44 patients were initially enrolled in this study (SBP group, n=22 and PRi group, n=22; Figure 1). There were no differences in patients'demographic data, surgical time and anesthesia time between two groups (Table 1).

Anesthesia recovery time was shorter in PRi group than in SBP group (17.5±3.8min vs 21.5±2.8min; *P=0.001*). Extubation time was also significantly shorter in PRi group than in SBP group (21.9±1.7min vs 24.1±2.5min; *P=0.001*). Sevoflurane consumption was also lower in PRi group than in SBP group (15.5±4.1ml vs 20.0±2.5ml; *P=0.001*)(Table 2).

The total incidence of intraoperative hemodynamic instability events and the incidences of each type of hemodynamic instability events (hypertension, hypotension, tachycardia and bradycardia) did not differ significantly between two groups (*P>0.05*,Table 3).

The rates of intervention with nicardipine, ephedrine, esmolol and atropine were

231 also similar between two groups (*P>0.05*,Table 3).
232 There were no significant differences between groups in the incidences of
233 postoperative nausea/vomiting or agitation (*P>0.05*,Table 4). Moreover,
234 postoperative VAS for pain was also similar between groups (*P>0.05*, Table 4).
235 No patients reported awareness during general anesthesia, and none experienced
236 postoperative respiratory depression.
237

238 **Discussion**

239 The exploration of minimum effective dose of anesthetic drug under accurate
240 regulation of anesthesia depth is a pursuit of modern anesthesiologists and
241 would help to optimize use of anesthetic drug, maintain hemodynamic stability,
242 improve quality of anaesthesia and reduce complications of anesthesia.
243 Traditional monitoring of anesthesia depth relies on clinical signs that represent
244 the reactions of the body to noxious stimuli during surgery such as blood
245 pressure or heart rate changes, body movement, sweating, lacrimation, eye
246 movement and pupillary reflex[8]. However, these indicators have poor specificity
247 and could be influenced by many factors, including other drugs used in
248 combination with general anesthetics. Thus, there is considerable interest in the
249 development of better methods for monitoring the depth of anesthesia.
250 The main findings of the present randomized controlled trial were that
251 regulation of sevoflurane anesthesia depth with PRi in patients undergoing
252 cervical vertebra surgery shortened anesthesia recovery time and extubation
253 time, reduced sevoflurane consumption, as compared with regulation by
254 monitoring of conventional clinical signs(SBP). Furthermore, the use of PRi to
255 regulate anesthesia depth was not associated with any increases in intraoperative
256 hemodynamic instability events or postoperative adverse events or any negative
257 impacts on postoperative pain scores. Taken together, our data suggested that
258 monitoring of PRi is a feasible method of regulating the depth of anesthesia and
259 might have advantages over conventional monitoring of clinical signs.

The pain is based on the existence of consciousness. During general anesthesia, the patients' consciousness disappears, and “pain” is mainly manifested as nociceptive stress response, so regulation of anesthesia depth is essentially the regulation of balance between nociceptive stimulation and anti-nociceptive effects of anaesthesia, that is, the regulation of analgesia depth. Accurate regulation of analgesia depth during general anesthesia could help to guide rational use of analgesic drugs and improve quality of anesthesia. In recent years, the exploration and development of Surgical Stress Index(SSI)[6, 7, 9-12], Tip Perfusion Index(TPI)[13] and Analgesia Nociception Index(ANI)[14-18] have greatly improved the regulation of analgesia depth. However, the clinical application of these indexes is limited due to various complex factors. At present, there is still lacking an advanced and reliable objective quantitative measure of pain used to guide clinical practice.

For two decades, depth of anesthesia monitors have been on the market to predict the hypnotic effect of intravenous as well as volatile anesthesia[19]. The new trend is to include predictions of the nociception/ antinociception balance as well. In recent years, a number of studies have found that pain can cause significant and specific changes in multi-brain region and multi-frequency EEG signals, and EEG could reflect the changes in brain caused by anesthetics[20, 21]. The newest study found that, based on acquisition of original EEG signal, using the wavelet transform to analyze EEG data, might be used to reflect degree of chronic pain in humans[22]. However, the above studies only remain at the level of theoretical research, and do not yet form a reliable and convenient quantitative indicator for clinical practice.

The PRi (range 0–100) is a new parameter for regulating analgesic depth of anesthesia based on wavelet analysis technology, which is a multi-scale refined analysis of the original EEG wave achieved using scaling and translation functions[3]. The principle of this method is to extract metadata of repeatable and regular changes in high and low frequency rhythms associated with pain signals

289 from EEG, and specifically reflect the degree of tolerance to pain stimuli in the
290 cerebral cortex and subcortical center[3, 23 ,24]. In this study, the equipment for PRi
291 analysis was multifunctional monitor HXD-I developed by Chinese researchers
292 in July 2015, which collects left and right two-channel EEG signals from
293 prefrontal lobe, and reduces the complexity of features through continuous and
294 discrete wavelet transform. The continuous wavelet transforms, binary discrete
295 wavelet transform and frequency domain reconstruction algorithm in wavelet
296 analysis were first introduced to deal with the specific EEG data vector[5]. This
297 study found that compared with SBP group , both anesthesia recovery time and
298 extubation time were significantly shortened, and sevoflurane consumption
299 decreased significantly in PRi group, suggesting that PRi was feasible in
300 regulating depth of sevoflurane anesthesia, and was better than the clinical
301 experience in its regulation.
302 We found that PRi had some limitations in this study. First, PRi value was
303 susceptible to electrotome's interference and postural changes. Secondly, PRi
304 value changed greatly and had more transient change, which led to limitation in
305 guiding clinical drug regulation. These limitations all affected its clinical
306 application in regulation of anesthesia depth, so we should continuously
307 improve monitoring parameters and anti-external interference performances.
308 This study was an exploratory single-center study, the sample size was small
309 and the type of surgery was simple. In addition, the application of vasoactive
310 drugs (such as nicardipine or ephedrine) might affect the calculation of PRi
311 value..
312
313 **Conclusion**
314 In summary, the current study confirmed that PRi was feasible to regulate depth
315 of sevoflurane anesthesia, which could shorten anesthesia recovery time and
316 extubation time, reduce sevoflurane consumption during general anesthesia in
317 patients undergoing cervical vertebra surgery. The study would also provide

ideas and clinical data for the management of accurate anesthesia and enhanced recovery after surgery

Disclaimer: I would like to declare on behalf of my co-authors that the work described was original research that has not been published previously, and not under consideration for publication elsewhere, in whole or in part.

Cconflict of interest: The authors declare that they have no conflicts of interest.

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Table 1: Demographic and clinical data

	SBP Group (n=22)	PRi Group (n=22)
Sex(m/f)	11/11	12/10
Age(y)	51±9	50±4
BMI(kg/m^2)	22.8±1.6	22.6±1.3
ASA(I/II)	15/7	17/5
Surgical time(min)	80±9	81±11
Anesthesia time(min)	116±10	115±11

Values are given as mean values ± standard deviation or absolute numbers.
BMI: Body Mass Index; ASA: American Society of Anesthesiologists; SBP: systolic blood pressure; PRi: pain rating index.
No statistically significant differences were observed between two groups.

Table 2: Anesthesia recovery time, Extubation time and Sevoflurane consumption

	SBP Group(n=22)	PRi Group(n=22)	*P* value
Anesthesia recovery time(min)	21.5±2.8	17.5±3.8[a]	0.001
Extubation time(min)	24.1±2.5	21.9±1.7[a]	0.001
Sevoflurane consumption(ml)	20.0±2.5	15.5±4.1[a]	0.001

Values are represented as mean values±standard deviation.
[a] $P<0.05$ when compared with SBP group .
SBP: systolic blood pressure; PRi: pain rating index.
Anesthesia recovery time: time from stopping the sevoflurane to eye opening.
Extubation time: time from stopping the sevoflurane to extubation.

Table 3: Hemodynamic Instability Events and Interventions

	SBP Group (n=22)	PRi Group (n=22)	*P* value
Hypertension	12(0.55)	12(0.55)	1.000
Hypotension	5(0.23)	3(0.14)	0.646
Tachycardia	5(0.23)	4(0.18)	0.725
Bradycardia	2(0.09)	1(0.05)	0.865
Total unwanted events	24(1.09)	20(0.91)	0.564
Nicardipine	4(0.18)	13(0.59)	0.075
Esmolol	5(0.23)	5(0.23)	1.000
Ephedrine	3(0.14)	3(0.14)	1.000
Atropine	2(0.09)	1(0.05)	0.865

Data are numbers of Intraoperative hemodynamic instability events and interventions during surgery.
Data in parentheses are numbers of intraoperative hemodynamic instability events and interventions per patient.
SBP, systolic blood pressure; PRi, pain rating index.
No statistically significant differences were observed between two groups.

Table 4: Intraoperative/postoperative adverse events and postoperative visual analog scale for pain

	SBP Group (n=22)	PRi Group (n=22)	*P* value
PONV	5(0.23)	4(0.18)	0.725
Agitation	4(0.18)	3(0.14)	0.901
Respiration depression	0(0)	0(0)	1.000
Awareness	0(0)	0(0)	1.000
Pain VAS_{0h}	0(0-1)	0(0-1)	1.000
Pain $VAS_{1/2h}$	1(0-4)	2(0-4)	0.865

Data are numbers of postoperative adverse events or median of VAS . Data in parentheses are numbers of postoperative adverse events per patient or range of VAS.
VAS, Visual Analogue Scale, scaled from 0 to 10 (0 means no pain and 10 means the maximum intensity of pain); PONV, postoperative nausea and vomiting; SBP, systolic blood pressure; PRi, pain rating index.
No statistically significant differences were observed between two groups.

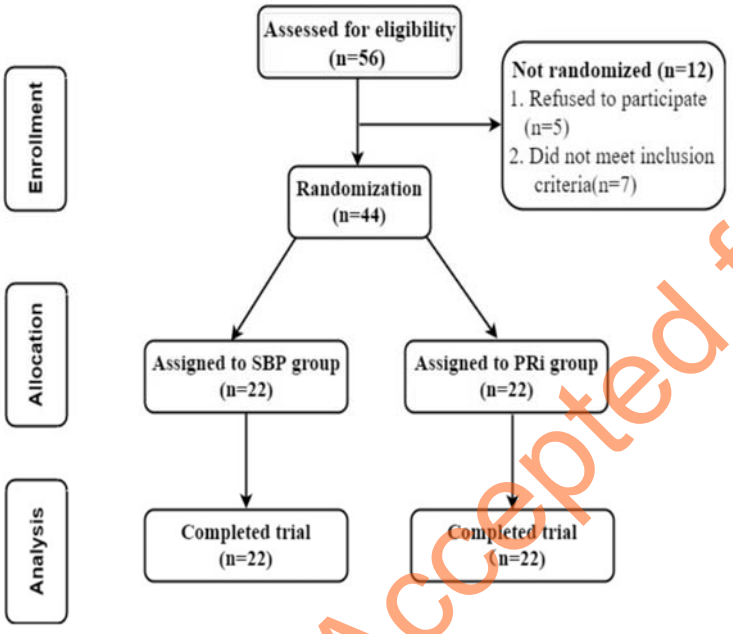

Figure 1. A participant flowchart.

SBP, systolic blood pressure; PRi, pain rating index.