Original Article

Changes in the Bispectral Index in Response to Loss of Consciousness and No Somatic Movement to Nociceptive Stimuli in Elderly Patients

Ning Yang[1,2], Yun Yue[1], Jonathan Z Pan[3], Ming-Zhang Zuo[2], Yu Shi[2], Shu-Zhen Zhou[2], Wen-Ping Peng[2], Jian-Dong Gao[1]

[1]Department of Anesthesiology, Beijing Chao-Yang Hospital, Capital Medical University, Beijing 100020, China
[2]Department of Anesthesiology, Beijing Hospital, Beijing 100730, China
[3]Department of Anesthesiology and Perioperative Care, Brain and Spinal Injury Center, University of California, San Francisco, CA 94110, USA

Abstract

Background: Bispectral index (BIS) is considered very useful to guide anesthesia care in elderly patients, but its use is controversial for the evaluation of the adequacy of analgesia. This study compared the BIS changes in response to loss of consciousness (LOC) and loss of somatic response (LOS) to nociceptive stimuli between elderly and young patients receiving intravenous target-controlled infusion (TCI) of propofol and remifentanil.

Methods: This study was performed on 52 elderly patients (aged 65–78 years) and 52 young patients (aged 25–58 years), American Society of Anesthesiologists physical status I or II. Anesthesia was induced with propofol administered by TCI. A standardized noxious electrical stimulus (transcutaneous electrical nerve stimulation, [TENS]) was applied (50 Hz, 80 mA, 0.25 ms pulses for 4 s) to the ulnar nerve at increasing remifentanil predicted effective-site concentration (Ce) until patients lost somatic response to TENS. Changes in awake, prestimulus, poststimulus BIS, heart rate, mean arterial pressure, pulse oxygen saturation, predicted plasma concentration, Ce of propofol, and remifentanil at both LOC and LOS clinical points were investigated.

Results: BIS_{LOC} in elderly group was higher than that in young patient group (65.4 ± 9.7 vs. 57.6 ± 12.3) ($t = 21.58$, $P < 0.0001$) after TCI propofol, and the propofol Ce at LOC was 1.6 ± 0.3 μg/ml in elderly patients, which was significantly lower than that in young patients (2.3 ± 0.5 μg/ml) ($t = 7.474$, $P < 0.0001$). As nociceptive stimulation induced BIS to increase, the mean of BIS maximum values after TENS was significantly higher than that before TENS in both age groups ($t = 8.902$ and $t = 8.019$, $P < 0.0001$). With increasing Ce of remifentanil until patients lost somatic response to TENS, BIS_{LOS} was the same as the BIS_{LOC} in elderly patients (65.6 ± 10.7 vs. 65.4 ± 9.7), and there were no marked differences between elderly and young patient groups in BIS_{awake}, BIS_{LOS}, and Ce of remifentanil required for LOS.

Conclusion: In elderly patients, BIS can be used as an indicator for hypnotic-analgesic balance and be helpful to guide the optimal administration of propofol and remifentanil individually.

Trial Registration: CTRI Reg. No: ChiCTR-OOC-14005629; http://www.chictr.org.cn/showproj.aspx?proj=9875.

Key words: Bispectral Index; Elderly; Nociceptive Stimuli; Propofol; Remifentanil

Introduction

Several electroencephalogram (EEG)-based index systems have been studied and used in clinical practice such as bispectral index (BIS) patient safety index, Narcotrend and entropy. These devices are monitors of hypnotic level derived from the processed EEG. Since BIS was first approved by the US Food and Drug Administration, it has been studied extensively in clinical trials and used widely in anesthesia practice. It was considered a useful tool to guide anesthesia in elderly patients.[1-3] But it was still controversial whether BIS could be used in the assessment of the level of pain and

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.176083

Address for correspondence: Prof. Yun Yue, Department of Anesthesiology, Beijing Chao-Yang Hospital, Capital Medical University, Beijing 100020, China
E-Mail: yueyun@hotmail.com

Received: 03-11-2015 **Edited by:** Li-Shao Guo
How to cite this article: Yang N, Yue Y, Pan JZ, Zuo MZ, Shi Y, Zhou SZ, Peng WP, Gao JD. Changes in the Bispectral Index in Response to Loss of Consciousness and No Somatic Movement to Nociceptive Stimuli in Elderly Patients. Chin Med J 2016;129:410-6.

adequacy of analgesia.[4-9] Some researchers think that BIS primarily measures the degree of sedation and sleep and does not reliably reflect the autonomic response to pain. In addition, BIS changes during nociceptive stimulation can be affected by many other variables such as sedatives, anesthetics, opioids (which decrease BIS by reducing cortical activity),[10] and neuromuscular blocking agents (which decrease BIS by reducing electromyogram [EMG] activity).[11,12] It was known that age-related changes in structure and function can influence anesthetic-induced changes in the EEG,[3,13-17] but there are little published data that studied the effectiveness of BIS on the evaluation of analgesia in nonparalyzed elderly patients. Therefore, we designed this prospective clinical study to compare the changes of BIS at awake state, LOC, and Loss of somastic response (LOS) in elderly and young patients under propofol-remifentanil anesthesia without muscle relaxation.

Methods

Ethical approval for this study (Ethical Committee No. ChiECRCT-20140044) was provided by the Chinese Ethics Committee of Registering Clinical Trials. One hundred and four consented patients were enrolled. They were divided into two groups: Young patients (25–58 years, n = 52) and elderly patients (65–78 years, n = 52). Exclusion criteria included recent administration of sedative or opioid drugs, body weight <80% of >120% of ideal weight, age <18 years, and impairment of cardiac, respiratory, hepatic, or renal function, known allergy to propofol or its lipid emulsion, general anesthesia 7 days before surgery, history of mental disorders, and American Society of Anesthesiologists (ASA) physical status III or above. BIS was monitored with a BIS XP (A-2000, Aspect Medical System, USA, software version 3.22, BIS Quattro Sensor). Noninvasive arterial blood pressure, pulse oxygen saturation (SpO_2), electrocardiogram, and tidal volume were monitored routinely.

After insertion of a peripheral venous line for fluid and drug administration, anesthesia was induced with target-controlled infusion (TCI) of propofol to achieve LOC, followed by TCI remifentanil until patients reached LOS to transcutaneous electrical nerve stimulation (TENS). The protocol is as follows: A TCI of propofol (Diprivan 1% pre-filled syringe 10 mg/ml, AstraZeneca UK Limited.) was administered using the Diprifusor™ (software version 2.0, Graseby 3500 Syringe Pump, Smiths Medical, Watford, UK), which uses the Marsh pharmacokinetic model. Remifentanil was administered using a microcomputer-controlled pump (SLGO High-Tech Development CO, Beijing, China), which uses the Minto pharmacokinetic model. These systems display both the predicted plasma concentration (Cp) and predicted effective-site concentration (Ce). The propofol infusion was started so as to provide Cp of 1.2 μg/ml and increase by 0.3 μg/ml every 30 s until the Modified Observer's Assessment of Alertness and Sedation (MOAA/S) became 1 [Table 1].[18] This point was defined as LOC. Values of BIS, Cp, and Ce of propofol were recorded at this point. This Ce of propofol was kept stable for 3 min. Thereafter, Ce of propofol was left unchanged for the study period, followed by remifentanil target infusion. The Cp of remifentanil was started at 2.0 ng/ml and increased by 0.3 ng/ml every 30 s until no purposeful movement was observed after TENS (50 Hz, 80 mA, 0.25 ms pulses for 4 s), which was applied to the ulnar nerve using a peripheral nerve stimulator. This technique is easy to perform with good reliability and reproducibility and is often used in lieu of skin incision, which is considered as a standard method in pain research.[19-21] Twisting or jerking the head was considered a purposeful movement but twitching or grimacing was not. This point was defined as a loss of somastic response to a nociceptive stimulus. In case of movement, electrical tetanic stimulation was stopped immediately. After BIS values and remifentanil concentrations were recorded, surgery proceeded as planned. The protocol was the same in both young and elderly group [Figure 1].

Table 1: Responsiveness scores of the MOAA/S

Responsiveness	Score
Responds readily to name spoken in normal tone	5 (alert)
Responds lethargically to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Responds only after painful trapezius squeeze	1
Does not respond to painful trapezius squeeze	0

MOAA/S: Modified Observer's Assessment of Alertness/Sedation Scale.

All parameters were averaged the minute before the induction with propofol ($parameter_{awake}$) and were compared with the value before noxious stimulus ($parameter_{pre}$), the peak value after noxious stimuli ($parameter_{max}$), and the lowest value during the noxious stimuli ($parameter_{min}$). All patients were spontaneously breathing, but if necessary, ventilation was mechanically supported. At the end of the study, patients received 0.5 mg/kg rocuronium as the neuromuscular blocking drug. Targeted final Ce of remifentanil before intubation was left to the discretion of the anesthesiologist. Intubation for subsequent surgery was performed thereafter. We interviewed patients within 24 h postsurgery using modified Brice interview including five questions about intraoperative awareness and recall.[22,23] The five questions were: (1) what was the last thing you remember before anesthesia; (2) what was the first thing you remember after waking up; (3) did you remember anything between going under anesthesia and waking up; (4) did you dream during your procedure; and (5) what was the worst thing about your operation.

Statistical analysis was performed using SPSS 22.0 (IBM Corp., New York, USA). Differences in patient characteristics were analyzed using t-test (for age, weight, and height) or Chi-square test (for male-female distribution). A $P < 0.05$ was considered to be statistically significant. One-way analysis of variance and paired t-test were used to compare

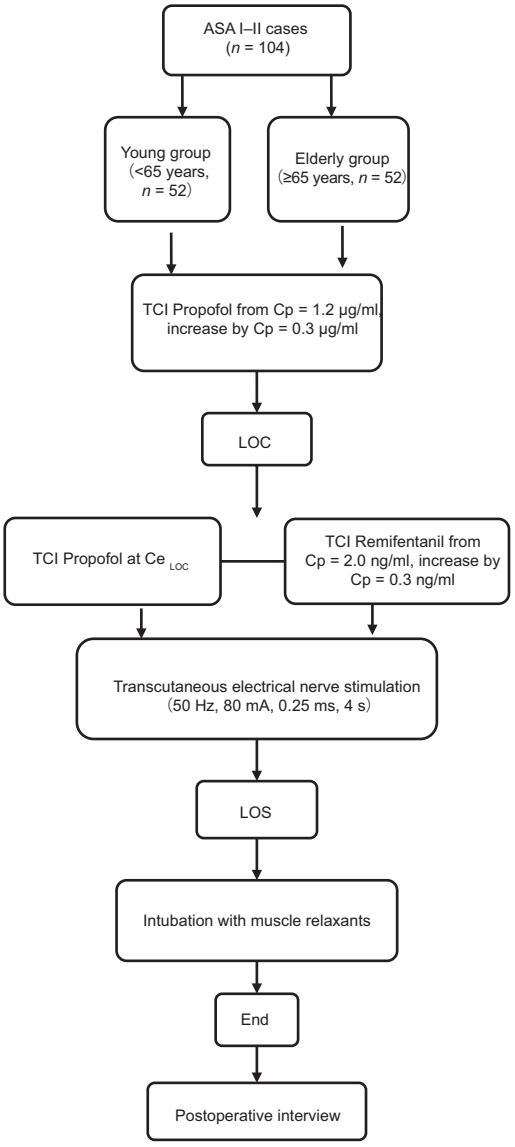

Figure 1: Diagrams of the experimental protocol. LOC: Loss of consciousness, defined as MOAA/S score =1; LOS: Loss of somatic response to a painful stimulus, defined as there is no purposeful movement such as twisting or jerking the head, but twitching or grimacing was not considered as movements due to painful stimulus. ASA: American Society of Anesthesiologists; MOAA/S: Modified Observer's Assessment of Alertness and Sedation.

BIS values and hemodynamic variables at awake, LOC, and LOS states after continuous data normality test.

Results

All studies were completed without significant clinical complications, and no intraoperative awareness and recall occurred during the pain stimulation. No significant differences were found between the groups with respect to sex ratio, weight, and height [Table 2]. Induction of anesthesia was uneventful in all patients. Most patients had respiratory depression before they lost response to a pain stimulus.

Table 2: Characteristics of the patients

Groups	*n*	Male/female (*n*)	Age (years)	Weight (kg)	Height (cm)
Young	52	22/30	43 ± 9	64 ± 11	164 ± 7
Elderly	52	25/27	70 ± 4*	67 ± 10	165 ± 8

*P<0.0001, compared with young group (t = 16.98). Data are presented as means ± standard deviation (SD).

Response to increasing predicted effective-site concentration of propofol and remifentanil before nociceptive stimulation

Bispectral index

Before anesthesia induction, there was no difference in the BIS_{awake} between young and elderly groups (97.4 ± 0.6 vs. 97.5 ± 1.1). After anesthetized patients reached LOC with gradually increased Ce of propofol, there was a significant decrease in BIS (t = 20.31, P < 0.0001). The mean BIS_{LOC} value of elderly was higher than that of young patients (65.4 ± 9.7 vs. 57.6 ± 12.3) (t = 3.147, P < 0.005) [Table 3], but mean Ce of propofol required to achieve LOC was 1.6 ± 0.3 for elderly, lower than young patients that was 2.3 ± 0.5 (t = 7.474, P < 0.0001) [Table 4]. For both age groups, when Ce of propofol was left unchanged for maintaining patients at LOC status, and followed by TCI remifentanil, BIS decreased markedly. Before first TENS was applied, BIS_{pre} decreased significantly lower than BIS_{LOC} (t = 6.102, P < 0.0001), and both BIS_{LOC} and BIS_{pre} were higher in elderly patients than that of young patients (t = 3.147, P < 0.0001) [Figure 2a].

Central hemodynamics

For both age groups, heart rate (HR) and mean arterial pressure (MAP) decreased when patients' consciousness changed from awake status to LOC. The amplitude of MAP reduction was more than HR; there was no difference between $parameter_{LOC}$ and $parameter_{pre}$ [Table 5]. The mean MAP_{awake}, MAP_{LOC}, and MAP_{pre} of elderly patients were higher than that of young patients [Figure 2b]. There was no significant difference in HR between elderly and young patients at above end points [Figure 2c].

Response to nociceptive stimulation

Bispectral index

During nociceptive stimulation, BIS was increased markedly. The mean BIS_{max} was higher than BIS_{pre} around 23% in elderly patients and 38% in young patients, even higher than BIS_{LOC} (t=2.333, P<0.001). But all patients had clinical signs of deep sleep. When TENS was interrupted and Ce of remifentanil was increased gradually, BIS values fell back. The mean BIS_{MIN} value was lower than BIS_{pre} (t = 5.025, P < 0.0001), while Ce of remifentanil was increased until patients lost somatic response to TENS. However, BIS_{LOS} was still higher than BIS_{pre} and was close to BIS_{LOC} for both age groups [Table 3]. Furthermore, BIS values and Ce of remifentanil required at LOS for elderly

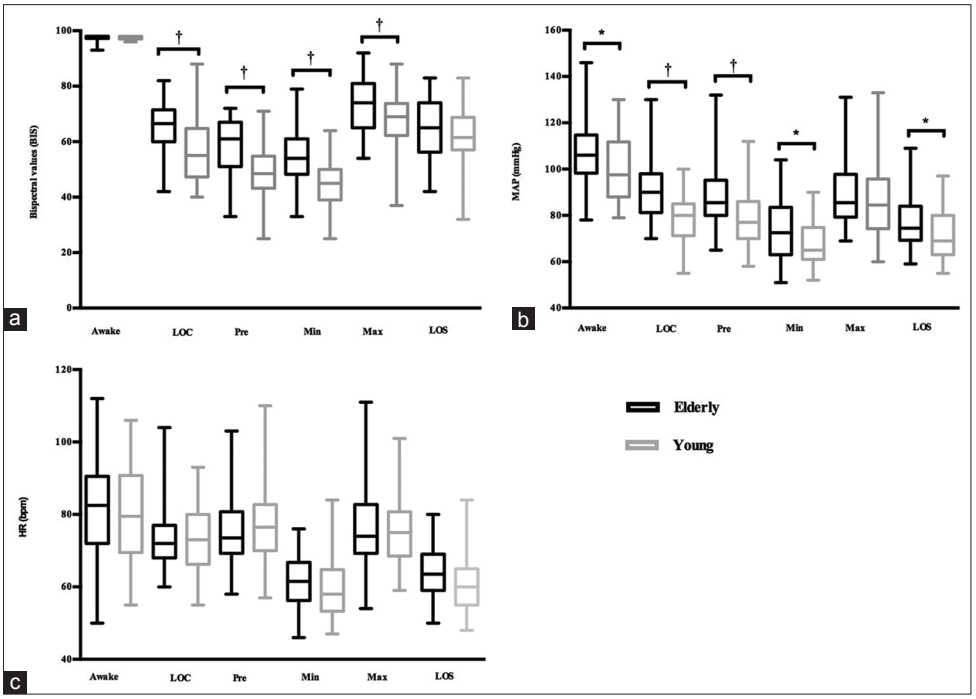

Figure 2: Parameter changes before and after nociceptive stimuli. Boxplots of bispectral index (a), mean arterial blood pressure (b), and heart rate (c) for elderly versus young patients; Awake: Status before anesthesia induction; Pre: Prenociceptive stimulus; Min: Lowest values during nociceptive stimulation; Max: Highest values after nociceptive stimulation; LOS: Loss of somatic response to nociceptive stimulus. Data are presented as mean and standard deviation. *$P < 0.05$, †$P < 0.01$ (ANOVA with Tukey's multiple comparisons test).

Table 3: Bispectral index values at different end points

Group	*n*	Awake	LOC	Pre	Min	Max	LOS
Young	52	97.4 ± 0.6	57.6 ± 12.3‡	49.2 ± 8.8††	44.5 ± 8.3‡‡	68.0 ± 10.1§§	61.5 ± 11.3†
Elderly	52	97.5 ± 1.1	65.4 ± 9.7*	59.2 ± 9.6‖	54.3 ± 9.7**	73.1 ± 10.4¶	65.6 ± 10.7§

Data are presented as means ± standard deviation (SD). *$P = 0.0023$, compared with young group ($t = 3.147$), $P<0.0001$, compared with awake ($t = 21.58$); †$P<0.0001$, compared with awake ($t = 20.91$), Pre ($t = 6.570$), Min ($t = 10.49$), Max ($t = 7.285$); ‡$P<0.0001$, compared with awake ($t = 20.31$); §$P<0.0001$, compared with awake ($t = 21.58$), Pre ($t = 3.490$), Min ($t = 6.883$), Max ($t = 5.607$); ‖$P<0.0001$, compared with LOC ($t = 6.102$), young group ($t = 4.863$); ¶$P<0.0001$, compared with Pre ($t = 8.019$), $P = 0.0343$, compared with young group ($t = 2.154$); **$P<0.0001$, compared with Pre ($t = 5.025$), young group ($t = 4.855$); ††$P<0.001$, compared with LOC ($t = 3.966$); ‡‡$P<0.0001$, compared with Pre ($t = 4.666$), LOC ($t = 3.966$); §§$P<0.0001$, compared with Pre ($t = 8.902$), $P<0.001$, compared with LOC ($t = 2.333$). LOC: Loss of consciousness; LOS: Loss of somatic response to nociceptive stimulus; Pre: Prenociceptive stimulation; Min: Minimum values after nociceptive stimulation; Max: Maximum values after nociceptive stimulation.

were very close to that for young patients (3.8 ± 1.3 ng/ml vs. 3.9 ± 1.1 ng/ml) [Table 4]. BIS_{pre}, BIS_{min}, and BIS_{max} of elderly patients were significantly higher than that of young patients [Figure 2a].

Central hemodynamics

Under the anesthesia with propofol and increasing Ce of remifentanil infusion, HR and MAP declined and mean $parameter_{min}$ was lower than $parameter_{pre}$ ($t = 9.26$, $P < 0.0001$). Then repeated TENS induced increase in HR and MAP, and mean $parameter_{max}$ was close to $parameter_{pre}$ and $parameter_{LOC}$. When Ce of remifentanil was titrated up to make patients achieve LOS status, HR and MAP dropped lower than that of LOC and prestimulation [Table 5], but these decreases were acceptable in the clinical range for elderly and young patients. MAP_{min} and MAP_{LOS} of elderly patients were significantly higher than that of young patients [Figure 2b]. There was no significant difference in HR between elderly and young patients at above end points [Figure 2c].

Table 4: Effective concentration of propofol and remifentanil

Group	*n*	Propofol at LOC (μg/ml)		Remifentanil at LOS (ng/ml)	
		Cp	Ce	Cp	Ce
Young	52	4.2 ± 0.6	2.3 ± 0.5	5.5 ± 1.0	3.9 ± 1.1
Elderly	52	3.3 ± 0.4*	1.6 ± 0.3†	5.3 ± 1.3	3.8 ± 1.3

Data are presented as means ± standard deviation (SD). *$P<0.0001$, compared with the young group ($t = 7.727$); †$P<0.0001$, compared with the young group ($t = 7.474$). Cp: Predicted plasma concentration; Ce: Predicted effect-site concentration; LOC: Loss of consciousness; LOS: Loss of somatic response to nociceptive stimulus.

Discussion

Several investigators have studied the sensitivity of BIS as a measure of sedation and anesthesia in adult and elderly patients receiving propofol infusion.[24-26] Furthermore, some studies demonstrate a potential link between the BIS

Table 5: Cardiovascular response

Parameters	Group	*n*	Awake	LOC	Pre	Min	Max	LOS
HR (bpm)	Young	52	79.7 ± 12.8	73.1 ± 8.8*	76.6 ± 10.2¶	59.6 ± 8.8$^{‖}$	76.2 ± 9.7^{Δ}	60.8 ± 8.4†
	Elderly	52	81.4 ± 13.1	73.4 ± 9.2‡	75.2 ± 9.3	61.7 ± 7.4$^{#}$	75.8 ± 10.7^{ΔΔ}	64.0 ± 7.3§
MAP (mmHg)	Young	52	99.8 ± 14.3	78.7 ± 11.5$^{‖‖}$	79.0 ± 12.8	67.3 ± 19.5$^{##}$	84.7 ± 14.1§§	71.9 ± 11.3¶¶
	Elderly	52	107.4 ± 13.9**	89.9 ± 12.3††	87.2 ± 13.7	72.9 ± 12.9$^{▲}$	88.9 ± 14.2$^{▲▲}$	77.2 ± 11.6‡‡

Data are presented as means ± standard deviation (SD). *P = 0.0119, compared with awake (t = 2.889); $^{†}P$<0.0001, compared with awake (t = 5.437), LOC (t = 5.437), Pre (t = 6.570), Max (t = 15.65); P = 0.0057, compared with Min (t = 2.925); $^{‡}P$ = 0.0046, compared with awake (t = 3.532); $^{§}P$<0.0001, compared with awake (t = 7.670), Pre (t = 9.420), Max (t = 9.321), P = 0.007, compared with LOC (t = 4.137), P = 0.0019, compared with Min (t = 3.336); $^{‖}P$<0.0001, compared with Pre (t = 13.31); $^{¶}P$ = 0.0024, compared with LOC (t = 3.242); ^{Δ}P = 0.029, compared with LOC (t = 2.029), P<0.0001, compared with Min (t = 18.43); $^{▲}P$<0.0001, compared with Pre (t = 9.102), P = 0.0110, compared with young group (t = 2.605); $^{#}P$<0.0001, compared with Pre (t = 24.31); **P = 0.018, compared with young group (t = 2.975); $^{††}P$<0.0001, compared with awake (t = 6.207), young group (t = 4.375); $^{‡‡}P$<0.0001, compared with awake (t = 10.71), LOC (t = 4.498), Pre (t = 5.650), Max (t = 7.955), P = 0.0040, compared with Min (t = 3.055), P = 0.0429, compared with young group (t = 2.058); $^{§§}P$ = 0.016, compared with LOC (t = 2.526), P = 0.0079, compared with Pre (t = 2.801), P<0.0001, compared with Min (t = 9.884); $^{‖‖}P$<0.0001, compared with awake (t = 7.563); $^{¶¶}P$<0.0001, compared with awake (t = 10.000), Max (t = 6.090), P<0.05, compared with LOC (t = 2.437), P = 0.0019, compared with Pre (t = 3.336), P = 0.0106, compared with Min (t = 2.684); ^{ΔΔ}P<0.0001, compared with Min (t = 11.38); $^{▲▲}P$<0.0001, compared with Min (t = 11.08); $^{##}P$<0.0001, compared with LOC (t = 7.531), Pre (t = 9.268). LOC: Loss of consciousness; LOS: Loss of somatic response to nociceptive stimulus; HR: Heart rate; MAP: Mean arterial blood pressure; Pre: Prenociceptive stimulation; Min: Minimum values after nociceptive stimulation; Max: Maximum values after nociceptive stimulation.

value and nociceptive procedures,[4,5,10] and most of them conclude that nociceptive stimulation causes a significant increase in the BIS.[4,27] The most possible explanation is that nociceptive stimulus can increase the EMG activity of the facial muscles, especially the corrugator supercilii muscles, which is a specific facial expression of pain.[28] There is an overlap between the EMG activity and cortical activity that could influence the signals received by BIS device so that pain stimulation may increase BIS values by increasing EMG activity. Besides EMG activity, BIS changes during nociceptive stimulation can be affected by sedatives, opioids, and muscle relaxants.[11,12]

Previous studies indicate that BIS is correlated with depth of sedation independently of age, which means BIS is not affected by age-related EEG changes.[29,30] Our current study suggests when patients lost consciousness by titration of propofol according to clinical signs (MOAA/S = 1), the BIS values were higher in elderly than young patients and Ce of propofol required in elderly was lower than young patients. The underlying reason could be due to cortical thinning and reductions in brain volume that are associated with aging and dementia, and most likely reflect a reduced functional capacity in affected brain structures. Therefore, it was confirmed by the present study that due to age-related alterations in structure and function that influence anesthetic-induced changes in the EEG activity, elderly patients are more sensitive to the hypnotic, for example, propofol, than younger people.[2,13-17] Recently, Purdon *et al*.[31] observed propofol induced a specific age-related alpha band changes in elderly patients compared with young patients. Our results are consistent with their findings that BIS provided elevated index readings during unconsciousness in elderly patients. Therefore, by achieving a desired target index value (between 40 and 60 are thought to reflect a level of unconsciousness suitable for surgery),[32,33] the anesthetics would likely be overdosed and lead to burst suppression in elderly patients.[34,35] Although BIS could not reflect the degenerative changes in EEG in aged patients, it can indicate the sensitivity of individuals to hypnotic agents. In order to monitor brain states of elderly patients receiving general anesthesia and sedation, it is very important to capture the BIS values responding to the clinical signs at LOC, which will be used as a sedative baseline for subsequent titration of opioids. From this study, we agree with some authors' suggestion that interpretation of the unprocessed EEG could be an alternative approach to a single numerical index.[36-38]

In this study, we show nociceptive stimulation significantly induced BIS increase when Ce of remifentanil was not titrated up to adequate analgesic level, then BIS value dropped, until patients had no somatic response to TENS, especially in elderly. BIS_{LOS} was higher than $BIS_{PRE,}$ but almost the same as BIS_{LOC} (65.6 vs. 65.4), and both the BIS values and Ce of remifentanil required were close between elderly and young patients. The reason might be that adequate anti-nociceptive effects successfully suppress transmission of noxious stimuli in the spinal cord (the same neural input may otherwise result in patient movement) and decrease the overall variability of BIS.[10,39] In addition, adequate anesthesia can inhibit the EMG activity induced by TENS.[40] It suggests that combined with clinical signs, BIS can help to identify adequate sedation and analgesia for the individual patient. This means after titration to Ce of propofol to achieve and maintain LOC (based on clinical signs), BIS_{LOS} and BIS_{LOC} should not vary markedly when adequate Ce of remifentanil were administrated. This is thus very helpful to guide anesthesia titration in elderly patients to avoid over sedation. It is particularly important in aged patients with hypertension or bradycardia in whom HR and MAP are not suitable as an indicator of nociception balance.

The current study shows that there is no difference in BIS signals between elderly and young patients at awake state, and verifies recent findings on the fundamental role of EMG in the BIS algorithm. In addition to awake EEG, measurement of muscle activity may also be required in BIS monitoring algorithm to generate values that reflect the awake status of the subject.[41]

Limitations

In this work, considering clinical safety, we have chosen ASA physical status I or II young and aged patients to enroll in our study. Some results may be limited in applying to the real clinical situation. For example, aged patients usually have multiple comorbidities and may present with high perioperative risks.

Due to clinical feasibility, we used predicted values for concentrations of propofol and remifentanil generated by TCI systems instead of real measured values. The pharmacokinetic or pharmacodynamic differences among the populations of different age and races should be considered. In order to observe somatic response to pain stimulation, we did not administer muscle relaxants to any patients, but the BIS values of paralyzed patients will be different from unparalyzed patients.[11,12] The results will be more persuasive to measure EEG using two or more methods at the same time.

In conclusion, elderly patients are more sensitive to the propofol, compared with young patients. They required lower predicted Ce of propofol to reach LOC at higher BIS values under constant propofol TCI. BIS may prove to be useful in monitoring the hypnotic-analgesic balance. Besides processed EEG monitor (BIS) and clinical signs of the depth of sedation, unprocessed EEG could be a supplementary measure for optimizing propofol-remifentanil anesthesia in elderly patients in future.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Fahlenkamp AV, Krebber F, Rex S, Grottke O, Fries M, Rossaint R, *et al.* Bispectral index monitoring during balanced xenon or sevoflurane anaesthesia in elderly patients. Eur J Anaesthesiol 2010;27:906-11. doi: 10.1097/EJA.0b013e32833d1289.
2. Kazama T, Ikeda K, Morita K, Kikura M, Doi M, Ikeda T, *et al.* Comparison of the effect-site k(eO)s of propofol for blood pressure and EEG bispectral index in elderly and younger patients. Anesthesiology 1999;90:1517-27.
3. Liu SH, Wei W, Ding GN, Ke JD, Hong FX, Tian M. Relationship between depth of anesthesia and effect-site concentration of propofol during induction with the target-controlled infusion technique in elderly patients. Chin Med J 2009;122:935-40. doi: 10.3760/cma.j.issn.0366-6999.2009.08.011.
4. Ekman A, Brudin L, Sandin R. A comparison of bispectral index and rapidly extracted auditory evoked potentials index responses to noxious stimulation during sevoflurane anesthesia. Anesth Analg 2004;99:1141-6. doi: 10.1213/01.ane.0000130618.99860.48.
5. Sebel PS, Lang E, Rampil IJ, White PF, Cork R, Jopling M, *et al.* A multicenter study of bispectral electroencephalogram analysis for monitoring anesthetic effect. Anesth Analg 1997;84:891-9. doi: 10.1097/00000539-199704000-00035.
6. Dierckens E, Fleyfel M, Robin E, Legrand A, Borel M, Gambier L, *et al.* Is entropy a monitor for the guidance of intraoperative analgesia? Ann Fr Anesth Reanim 2007;26:113-8. doi: 10.1016/j.annfar.2006.09.004.
7. Takamatsu I, Ozaki M, Kazama T. Entropy indices vs. the bispectral index for estimating nociception during sevoflurane anaesthesia. Br J Anaesth 2006;96:620-6. doi: 10.1093/bja/ael050.
8. Coleman RM T-LY, Gélinas C CM, Atallah M, Parenteau-Goudreault E, et al. Changes in the bispectral index in response to experimental noxious stimuli. ISRN Pain 2013; 1: 1-8.doi:10.1155/2013/583920.
9. Ellerkmann RK, Grass A, Hoeft A, Soehle M. The response of the composite variability index to a standardized noxious stimulus during propofol-remifentanil anesthesia. Anesth Analg 2013;116:580-8. doi: 10.1213/ANE.0b013e31827ced18.
10. Lysakowski C, Dumont L, Pellegrini M, Clergue F, Tassonyi E. Effects of fentanyl, alfentanil, remifentanil and sufentanil on loss of consciousness and bispectral index during propofol induction of anaesthesia. Br J Anaesth 2001;86:523-7. doi: 10.1093/bja/86.4.523.
11. Dahaba AA, Mattweber M, Fuchs A, Zenz W, Rehak PH, List WF, *et al.* The effect of different stages of neuromuscular block on the bispectral index and the bispectral index-XP under remifentanil/propofol anesthesia. Anesth Analg 2004;99:781-7. doi: 10.1213/01.ane.0000132997.19872.bc.
12. Vivien B, Di Maria S, Ouattara A, Langeron O, Coriat P, Riou B. Overestimation of bispectral index in sedated intensive care unit patients revealed by administration of muscle relaxant. Anesthesiology 2003;99:9-17. doi: 10.1097/00000542-200307000-00006.
13. Fjell AM, Westlye LT, Grydeland H, Amlien I, Espeseth T, Reinvang I, *et al.* Accelerating cortical thinning: Unique to dementia or universal in aging? Cereb Cortex 2014;24:919-34. doi: 10.1093/cercor/bhs379.
14. McGinnis SM, Brickhouse M, Pascual B, Dickerson BC. Age-related changes in the thickness of cortical zones in humans. Brain Topogr 2011;24:279-91. doi: 10.1007/s10548-011-0198-6.
15. Morrison JH, Baxter MG. The ageing cortical synapse: Hallmarks and implications for cognitive decline. Nat Rev Neurosci 2012;13:240-50. doi: 10.1038/nrn3200.
16. Marr RA, Thomas RM, Peterson DA. Insights into neurogenesis and aging: Potential therapy for degenerative disease? Future Neurol 2010;5:527-41. doi: 10.2217/FNL.10.33.
17. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, *et al.* The influence of age on propofol pharmacodynamics. Anesthesiology 1999;90:1502-16. doi: 10.1097/00000542-199906000-00003.
18. Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, *et al*. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: Study with intravenous midazolam. J Clin Psychopharmacol 1990;10:244-51.
19. Kopman AF, Lawson D. Milliamperage requirements for supramaximal stimulation of the ulnar nerve with surface electrodes. Anesthesiology 1984;61:83-5. doi: 10.1097/00000542-198407000-00015.
20. Ortolani O, Conti A, Chan YK, Sie MY, Ong GS. Comparison of propofol consumption and recovery time in Caucasians from Italy, with Chinese, Malays and Indians from Malaysia. Anaesth Intensive Care 2004;32:250-5.
21. Saidman LJ, Eger EI 2nd. Effect of nitrous oxide and of narcotic premedication on the alveolar concentration of halothane required for anesthesia. Anesthesiology 1964;25:302-6.
22. Enlund M. TIVA, awareness, and the brice interview. Anesth Analg 2006;102:967. doi: 10.1213/01.ANE.0000190856.16254.A4.
23. Mashour GA, Kent C, Picton P, Ramachandran SK, Tremper KK, Turner CR, *et al.* Assessment of intraoperative awareness with explicit recall: A comparison of 2 methods. Anesth Analg 2013;116:889-91. doi: 10.1213/ANE.0b013e318281e9ad.
24. Liu J, Singh H, White PF. Electroencephalographic bispectral index correlates with intraoperative recall and depth of propofol-induced sedation. Anesth Analg 1997;84:185-9. doi: 10.1097/00000539-199701000-00033.
25. Kearse LA Jr., Rosow C, Zaslavsky A, Connors P, Dershwitz M, Denman W. Bispectral analysis of the electroencephalogram predicts conscious processing of information during propofol sedation and hypnosis. Anesthesiology 1998;88:25-34. doi: 10.1097/00000542-199801000-00007.
26. Gan TJ, Glass PS, Windsor A, Payne F, Rosow C, Sebel P, *et al.* Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. BIS Utility Study Group. Anesthesiology 1997;87:808-15.

27. Coleman RM, Tousignant-Laflamme Y, Ouellet P, Parenteau-Goudreault É, Cogan J, Bourgault P. The use of the bispectral index in the detection of pain in mechanically ventilated adults in the intensive care unit: A review of the literature. Pain Res Manag 2015;20:e33-7.
28. Prkachin KM. Assessing pain by facial expression: Facial expression as nexus. Pain Res Manag 2009;14:53-8.
29. Renna M, Venturi R. Bispectral index and anaesthesia in the elderly. Minerva Anestesiol 2000;66:398-402.
30. Arnold G, Kluger M, Voss L, Sleigh J. BIS and entropy in the elderly. Anaesthesia 2007;62:907-12. doi: 10.1111/j.1365-2044.2007.05149.x.
31. Purdon PL, Pavone KJ, Akeju O, Smith AC, Sampson AL, Lee J, *et al.* The ageing brain: Age-dependent changes in the electroencephalogram during propofol and sevoflurane general anaesthesia. Br J Anaesth 2015;115 Suppl 1:i46-57. doi: 10.1093/bja/aev213.
32. Rosow C, Manberg PJ. Bispectral index monitoring. Anesthesiol Clin North America 2001;19:947-66, xi. doi: 10.1016/S0889-8537(01)80018-3.
33. Kelley S. Monitoring Consciousness. 2nd ed. Norwood, MA, USA: Aspect Medical Systems; 2007. p. 1-46.
34. Bruhn J, Bouillon TW, Shafer SL. Bispectral index (BIS) and burst suppression: Revealing a part of the BIS algorithm. J Clin Monit Comput 2000;16:593-6. doi: 10.1023/A:1012216600170.
35. Besch G, Liu N, Samain E, Pericard C, Boichut N, Mercier M, *et al.* Occurrence of and risk factors for electroencephalogram burst suppression during propofol-remifentanil anaesthesia. Br J Anaesth 2011;107:749-56. doi: 10.1093/bja/aer235.
36. Bennett C, Voss LJ, Barnard JP, Sleigh JW. Practical use of the raw electroencephalogram waveform during general anesthesia: The art and science. Anesth Analg 2009;109:539-50. doi: 10.1213/ane.0b013e3181a9fc38.
37. Avidan MS. I. International Consortium for EEG Training of Anesthesia Practitioners (ICE-TAP). Available from: http://www.icetap.org. [Last accessed on 2015 Dec 28].
38. Purdon PL, Sampson A, Pavone KJ, Brown EN. Clinical electroencephalography for anesthesiologists: Part I: Background and basic signatures. Anesthesiology 2015;123:937-60. doi: 10.1097/ALN.0000000000000841.
39. Iselin-Chaves IA, Flaishon R, Sebel PS, Howell S, Gan TJ, Sigl J, *et al.* The effect of the interaction of propofol and alfentanil on recall, loss of consciousness, and the bispectral index. Anesth Analg 1998;87:949-55. doi: 10.1097/00000539-199810000-00038.
40. Paloheimo M. Quantitative surface electromyography (qEMG): Applications in anaesthesiology and critical care. Acta Anaesthesiol Scand Suppl 1990;93:1-83.
41. Schuller PJ, Newell S, Strickland PA, Barry JJ. Response of bispectral index to neuromuscular block in awake volunteers. Br J Anaesth 2015;115 Suppl 1:i95-103. doi: 10.1093/bja/aev072.