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SCIENTIFIC ARTICLE

Evaluation of Bispectral Index time delay in response to anesthesia induction: an observational study

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KEYWORDS
Bispectral index monitor;
Depth of anesthesia;
Awareness;
Time delay

Abstract
Background and objectives: According to the manufacturer, the Bispectral Index (BIS) has a processing time delay of 5–10 s. Studies addressing this have suggested longer delays. We evaluated the time delay in the Bispectral Index response.
Methods: Based on clinical data from 45 patients, using the difference between the predicted and the real BIS, calculated during a fixed 3 minutes period after the moment the Bispectral Index dropped below 80 during the induction of general anesthesia with propofol and remifentanil.
Results: The difference between the predicted and the real BIS was in average 30.09 ± 18.73 s.
Conclusion: Our results may be another indication that the delay in BIS processing may be much longer than stated by the manufacture, a fact with clinical implications.

PALAVRAS-CHAVE
Monitor do índice bispectral;
Profundidade da anestesia;
Consciência;
Tempo de atraso

Avaliação do tempo de atraso do índice bispectral na resposta à indução da anestesia: estudo observacional

Resumo
Justificativa e objetivos: De acordo com o fabricante, o índice bispectral (BIS) tem um tempo de processamento de cinco a dez segundos. Estudos que avaliaram esse tempo de processamento sugeriram atrasos mais longos. Nós avaliamos o tempo de atraso na resposta do BIS.

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Métodos: Com base em dados clínicos de 45 pacientes, calculamos a diferença entre o tempo de atraso previsto e real do índice bispectral durante um período fixo de três minutos após o momento em que o BIS caiu abaixo de 80 durante a indução da anestesia geral com propofol e remifentanil.
Resultados: A diferença entre o BIS previsto e real foi em média 30,09 ± 18,73 segundos.
Conclusão: Nossos resultados sugerem que o atraso no processamento do índice bispectral pode ser muito maior que o declarado pelo fabricante, um fato com implicações clínicas.

Introduction

The Bispectral Index™ (BIS; Aspect Medical Systems Inc., Newton, MA) is a useful tool to assess the adequacy of the level of hypnosis during general anesthesia, although limitations were described.[1,2] The BIS index is derived utilizing a composite of measures from components of quantitative Electroencephalogram (EEG) signal processed using bispectral, power spectral, and time domain analysis.[3–5] These measures were combined via an algorithm to optimize the correlation between the EEG and the clinical effects of anesthesia, and quantified using the BIS index range.[3–5] This algorithm is proprietary, meaning that it is known only by the manufacturer and was never disclosed. The final result is a numerical index ranging from 0 to 100, with 0 being the value associated with the EEG isoelectric (flat) and 99 to the brain activity of a patient awake and alert.

The BIS index has a processing time delay, which, accordingly to the manufacturer is a delay of approximately 5–10 s.[3] However, these values have been disputed. Anecdotal reports have shown that cutting off the BIS sensor with a scissor so that the BIS four-electrodes sensor remain attached to the forehead but no longer communicating with the monitor, resulted in the monitor displaying a BIS value for longer than 10 s. This was showed in an educational video posted online by the Washington University in Saint Louis.[6] This video received wide attention and was used by BIS detractors to question its accuracy.[7] A more accurate evaluation of a possible time delay in BIS processing was done in studies using processed EEG that was fed to depth of anesthesia monitors. Two studies using this method reported BIS delays as long as 66 s.[8,9]

In a previous work,[10] we identified a time delay between BIS signal and modeled BIS of approximately 120 s. In this study, the modeled BIS was obtained accordingly to an interaction model structure[11] which relates the BIS values (drug effect) to the effect-site concentrations of propofol and remifentanil. The time delay was calculated using the difference between BIS signal and modeled BIS in a random value of BIS. We concluded that the time delay depends not only on the dynamics of the patient but may also be influenced by the BIS processing time delay, which was proven to vary.[8]

The present study aims to evaluate the time delay in the BIS response, based on clinical data from 45 patients, using the difference between the predicted and the actual BIS, calculated during a fixed 3 min period after the moment the BIS dropped below 80 during the induction of general anesthesia with propofol and remifentanil.

Methods

Under institutional review board approval and written informed consent, consecutive adult patients undergoing routine neurosurgical procedures were anesthetized as described below. Exclusion criteria were: any alterations in mental status or BIS < 90 before induction, significant cardiovascular, renal, hepatic or respiratory pathology and obesity (BMI > 35 $kg.m^{-2}$). Procedures done by the same anesthesiologist over a 5 month period were included.

Data acquisition protocol

In the operating room, after arrival, patients were monitored with Electrocardiogram (ECG), noninvasive Blood Pressure (BP), Oxygen Saturation via Pulse Oximetry (SpO_2) and BIS. After a placement of standard monitors and placement of an intravenous line in the dorsum of the hand, an infusion of an equilibrated electrolytic solution was started at 400 $mL.h^{-1}$ and infused at this rate through the entire surgery. Patients were pre-oxygenated with 100% O_2 for 3 min. Our clinical practice for neurosurgical procedures consists of opioid-propofol anesthesia using a Target Controlled Infusion (TCI) system. Anesthesia began with the administration of 1% propofol at 200 $mL.h^{-1}$ using an infusion pump (Asena Alaris GH). Once propofol reached the venous catheter, the tourniquet was released. The level of conscious was assessed every 10 s using the Observer's Assessment of Alertness/Sedation Scale (OAA/S).[12] At Loss Of Consciousness (LOC), which was defined as loss of eye opening in response to name calling repeatedly in a loud voice, i.e., a score of 3 in the OAA/S, the propofol effect-site target was set to the individual effect-site concentration at which LOC occurred, and remifentanil infusion started (Asena Alaris TIVA) with an initial plasma target of 2.5 $ng.mL^{-1}$

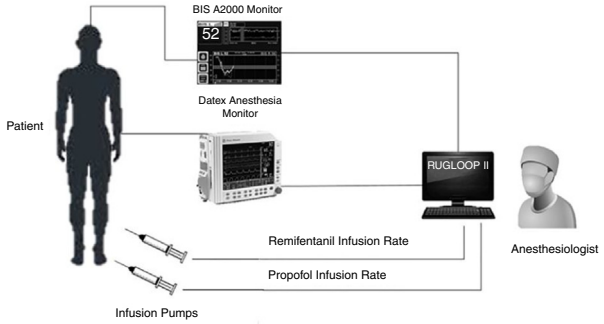

Figure 1 Anesthesia setup.

and titrated during surgery (Fig. 1). Manual ventilation was started, rocuronium was then administered at 0.6 mg.kg^{-1}. Laryngoscopy and intubation were performed and drug's infusion was changed according to patient's need so as to maintain a target range for BIS (45–60), mean arterial pressure and heart rate within ± 30% of the respective baseline values.

Bispectral index modeling

Patients were monitored with an A-2000XP BIS monitor (Aspect Medical Systems, Newton, MA) using a BIS-Sensor (Aspect Medical Systems) placed according to the instructions of the manufacturer on the forehead, and an AS3 Datex monitor (Datex-Engstrom, Helsinki, Finland) connected by RS-232 interface to a PC using Rugloop II software (DEMED, Temse, Belgium) for data capture at 5 s intervals. Rugloop II (via RS-232 interface) was used to control the propofol and the remifentanil infusion pump to record the data. Along with BIS response, infusion rate of propofol and remifentanil were recorded.

In order to model the BIS response, the drug effect itself has also to be modeled. This way, the drug behavior in human body was modeled considering three phases: pharmacokinetic phase (infused dose to plasma concentration), pharmacodynamic phase (plasma concentration to effect-site concentration), and finally translation between effect-site concentration and measurable effect (BIS). The overall model structure is showed in the block diagram from Fig. 2. The infusion rates were used to calculate the plasma and effect concentration of both drugs using two PKD models. For propofol, the PKD parameters from Schnider[13] were used, whereas for remifentanil the parameters from Minto[14,15] were employed. Bruhn et al.[16] presented an interaction model structure to relate the EEG parameter values (including BIS) to the effect concentrations of propofol and remifentanil. The results for these modulations were already published.[10]

BIS time delay calculation

The BIS time delay for each patient was calculated as the average of the differences between the predicted response of the pharmacodynamic model and the actual BIS signal of the patient, measured from the first time BIS signal dropped below 80 until the moment both signals intersect (Case 1). In the first step of the surgical procedure, only propofol is administered, associating a characteristic decrement in the modeled BIS function. At the time the propofol infusion stops and the remifentanil begins, the modeled BIS changes its behavior to fit the interaction between both drugs. A BIS value of 80 is a standard threshold where the hypnotic effect has clearly started but the patient is still conscious.

For the cases where an interception did not occur (Case 2), the endpoint was defined as 5 min after the beginning of anesthesia induction. This time limit was selected to be an instant prior maintenance phase, in which the real BIS value is stable.

We also considered the cases where both, modeled and real BIS, almost overlap (Case 3).

Data analysis

A sample size calculation was performed considering the results previously obtained (time delay 0.63 ± 0.28 min)[10] versus the BIS monitor processing time delay of 10 s (or 0.17 min), with 95% power, $\alpha = 0.1$ (Sample size paired *t* test, StatsDirect V3). A minimum sample size of 41 pairs/patients was obtained. Considering a 10% exclusion rate, a final sample size of 45 patients was established.

Data distribution is expressed as mean ± SD. Statistical analysis were performed using Matlab 2014a (Mathworks, Inc., Natick, MA) and IBM SPSS Statistics (IBM Corporation, NY). A *p* lower than 0.05 was considered statistically significant.

Results

A total of 45 neurosurgical patients were included in this study. Demographics for all 45 patients were: 51 ± 15 years of age (minimum and maximum, 20 and 79 years old, respectively), 70 ± 13 kg, 163 ± 9 cm, 17 males and 28 females.

Propofol and remifentanil effect-site concentrations for each patient during the first 15 min at induction of anesthesia are illustrated in Fig. 3A. Loss of consciousness, represented as the time when remifentanil has started to be administered, occurred within 15 min in all patients.

The BIS values captured from the Rugloop software and the BIS values modeled for each patient during the first 15 min at induction of anesthesia are presented in Fig. 3B. There is a time delay between the real BIS signal and the

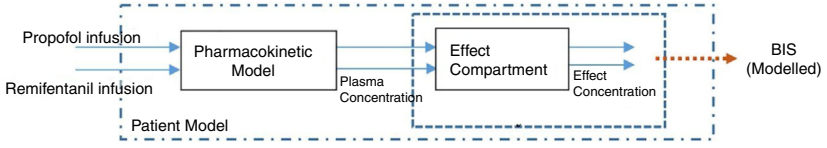

Figure 2 Block diagram of BIS modulation.

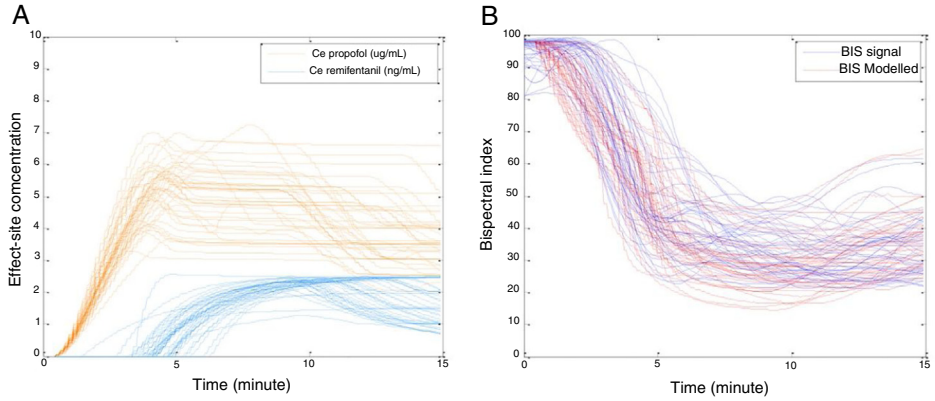

Figure 3 Data results from all 45 patients: (A) Effect-site concentration of propofol and remifentanil for each patient during the first 15 min of anesthesia induction; (B) Real versus modeled BIS values.

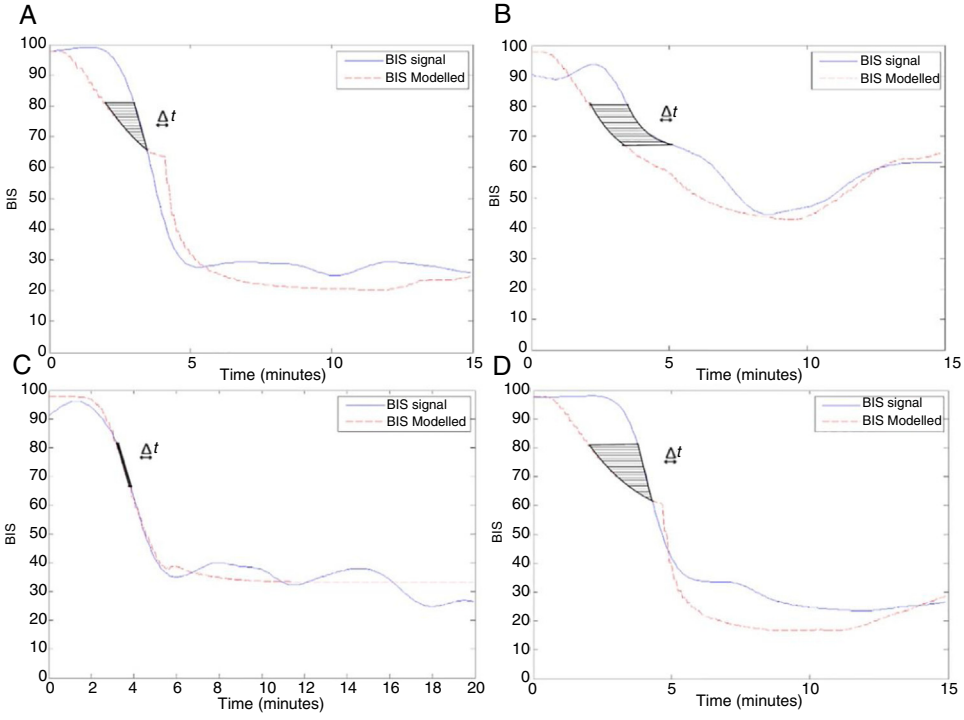

Figure 4 Time delay (Δt) between the real and the modeled BIS for: (A) Patient no. 5; (B) Patient no. 19; (C) Patient no. 22 and (D) Patient no. 27.

modeled BIS, i.e. the model predicts the BIS responses earlier than it really is.

In Fig. 4 are represented the BIS time delay (Δt) of four different patients. As observable from the comparative behavior of the real and the modeled BIS there are three major groups of results in this study. The majority of the registered cases ($n = 40$) fits as Fig. 4A and D where the signals intercept. In Fig. 4B are presented the data of a patient in which real and modeled BIS signal did no intersect. There were 5 cases in total. In the cases similar to Fig. 4C, modeled and real BIS almost overlap ($n = 2$), resulting in almost no time delay (in general lower than 5 s).

In Fig. 5 are represented the BIS time delay between the BIS signal and the predicted BIS for each patient.

Time delays were 30.09 ± 18.73 s (0.50 ± 0.31 min) and there are only 2 cases where the delay is in fact less than 10 s apart, 4.7 and 5.3 s, for patients 22 and 25, respectively.

Discussion

All but one of the currently approved depth-of-anesthesia monitors use EEG derived indexes.[17] Since the EEG is a complex signal, calculation of a derived index after processed analysis is time consuming resulting in some processing time delay. Clinically, the existence of such delay is relevant. BIS monitor adds a variable time delay to display the BIS index value, which was suggested, in our study, as 30.09 ± 18.73 s.

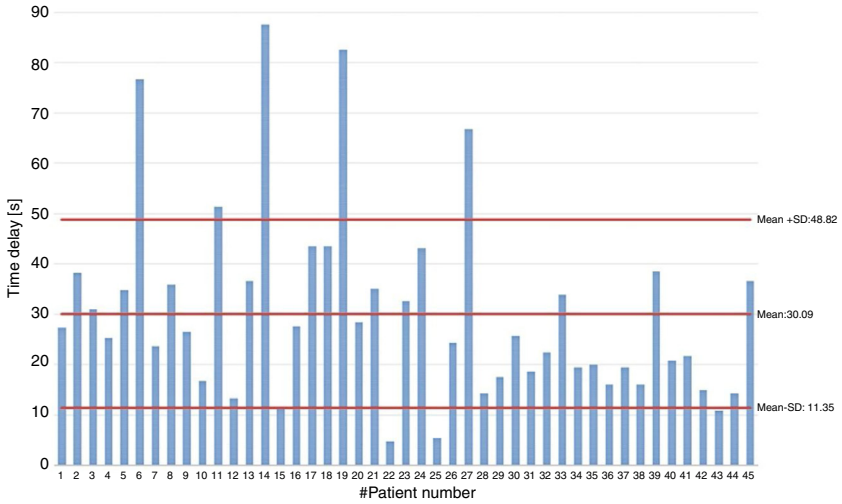

Figure 5 Time delay (Δt) between the real and the modeled BIS for all patients.

This time delay was calculated from the data of 45 patients aged between 20 and 79 years old. Purdon et al.[18] described significant age-dependent changes in the characteristics of the effects of anesthesia on the EEG with increasing age, however, the BIS index value from the BIS monitor is validated for clinical use regardless of age. Additionally, does not exist, neither on the manufacturer nor on literature indications that the EEG-based index is influenced by age.

The significance of a possible BIS index time delay can be illustrated by the fact that a patient under general anesthesia could be aroused by a noxious stimulus, skin incision, for instance, while depth of anesthesia monitor could keep displaying a value compatible with adequate anesthesia. The moment the anesthesiologist was alerted by a rise in the index value the patient could have already suffered pain and psychological trauma, resulting in a case of intraoperative awareness. Awareness under general anesthesia, although infrequent, is of significant concern to patients. It can be devastating and associated with posttraumatic stress disorders.[19,20] The BIS index was initially introduced aiming at preventing awareness and its efficacy at doing it was demonstrated.[21,22] It is not known how much time with a BIS value above 60 is necessary for awareness to occur, but it has been claimed that at least 5 min with a BIS above 60 is necessary to create awareness with recall.[21,23] Interestingly, one large randomized trial performed to assess BIS in preventing awareness reported two cases of patients with who developed awareness.[21] In both cases, a BIS reading greater than 60 occurred, lasting for 5 and 9 min respectively.[21] In view of tis data, it seems quite unlikely that the possible time delay suggested by our results (30.09 ± 18.73 s) would be sufficient to create awareness with recall; however, one cannot be sure of this and ideally depth of anesthesia monitors should have no delay at all.

If a delay in displaying a high BIS value above 60 could increase the risk of awareness, a delay in displaying a low BIS value, below 45, could also have clinical implications. Patients with at least 5 min with BIS value below 40 had a hazard ratio for death of 1.41 within 4 years of follow-up when compared to patients whose BIS was always above 40.[24] Also, cumulative time with a BIS value below 45 was shown to be independently associated with mortality at one year following surgery.[25,26] Therefore, it can be hypothesized that the occurrence of cumulative periods of time with undetected BIS below 45 or 40 could impact adversely on patient's outcome. That could indeed happen as a result of summing up several periods of time with undetected low BIS due to a time delay in BIS processing.

It is, therefore, important that the clinician is informed about the exact delay in the processing time of depth of anesthesia indexes. There has always been an interest among the anesthesiology research community to investigate the time delay for different monitors. However, few studies were performed trying to objectively measure the processing time delay. The reason is because it is not easy to implement a tool or to design a method capable of accurately measuring the delay. In the study performed by Pilge et al.[9] using artificially generated EEG signals, the time delay to detect the transition from ''general anesthesia'' to ''awake'' was 30 s, with some cases showing a delay as long as 66 s (for decreasing index values). The fastest response in BIS was seen in the transition between ''awake'' (BIS 98) to ''general anesthesia'' (BIS 52) with a delay of 14 s.[9] This study has received criticism due to the fact that it analyzed computer generated EEG signals and not real raw EEG signals. A subsequent study from the same investigators tried to overcome that criticism by analyzing real EEG recorded from patients subjected to anesthesia.[8] The calculated delay for the BIS was identical to the 60 s reported in the first study. Simulating a sudden wake-up reaction by changing the input signal from ''general anesthesia'' to ''awake BIS'', showed a delay of 25 s.[8] Both studies from these authors also examined the processing delay of other monitors, finding processing time delays for the Cerebral State® monitor (Danmeter, Odense, Denmark) and the Narcotrend® monitor (version 4.0, MonitorTechnik, Bad Bramstedt, Germany).

The results from our study suggest the existence of a delay in processing BIS index longer than that stated by the manufacture but in agreement with the results from previous studies addressing this delay.[8–10] Our results also highlight the importance of relying on the observation of the EEG

waves that are displayed in real time. In addition, one should state that our suggested time delay may be related to the fact that the pharmacokinetic model (ke0) do not correctly predict the effect/concentration delay, or due to the inter-patient variability which can be greater than expected.

Further investigation to find the influence of the suppression rate in the time BIS delay deserves also a deep study. Also, should be evaluating the effect of altering the ke0 of the PKD model to 0.21 in the estimation of the effect-site target and the plasma concentrations. Additionally, the time delay in other measurable effect such as the State Entropy (SE) of the EEG can give a complementary information.

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Conflicts of interest

The authors declare no conflicts of interest.

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References

1. Lobo FA, Schraag S. Limitations of anaesthesia depth monitoring. Curr Opin Anaesthesiol. 2011;24:657–64.
2. Dahaba AA. Different conditions that could result in the bispectral index indicating an incorrect hypnotic state. Anesth Analg. 2005;101:765–73.
3. Covidien. [Online]. Available: http://www.covidien.com/rms/brands/BIS.
4. Nunes RR, Chaves IM, de Alencar JC, et al. Bispectral index and other processed parameters of electroencephalogram: an update. Rev Bras Anestesiol. 2012;62:105–17.
5. Rampil IJ. A primer for EEG signal processing in anesthesia. Anesthesiology. 1998;89:980–1002.
6. Dryden J. Preventing memories of surgery 2011. [Online]. Available: https://www.youtube.com/watch?v=fHAkVSyOym8.
7. Lang J. Awakening Atl.; 2013.
8. Zanner R, Pilge S, Kochs EF, et al. Time delay of electroencephalogram index calculation: analysis of cerebral state, bispectral, and Narcotrend indices using perioperatively recorded electroencephalographic signals. Br J Anaesth. 2009;103:394–9.
9. Pilge S, Zanner R, Schneider G, et al. Time delay of index calculation: analysis of cerebral state, bispectral, and narcotrend indices. Anesthesiology. 2006;104:488–94.
10. Ferreira AIL, Nunes CS, Gabriel J, et al. The influence of two different drug infusion profiles on the pharmacodynamics model performance. In: Jaffray D, editor. World congress on medical physics and biomedical engineering, June 7–12, 51. Toronto, Canada: IFMBE Proceedings; 2015. p. 874–80.
11. Minto CF, Schnider TW, Short TG, et al. Response surface model for anesthetic drug interactions. Anesthesiology. 2000;92:1603–16.
12. Chernik DA, Gillings D, Laine H, 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.
13. Schnider TW, Minto CF, Gambus PL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology. 1998;88:1170–82.
14. Minto CF, Schnider TW, Egan TD, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology. 1997;86:10–23.
15. Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. Anesthesiology. 1997;86:24–33.
16. Bruhn J, Bouillon TW, Radulescu L, et al. Correlation of approximate entropy, bispectral index, and spectral edge frequency 95 (SEF95) with clinical signs of ''anesthetic depth'' during coadministration of propofol and remifentanil. Anesthesiology. 2003;98:621–7.
17. Shepherd J, Jones J, Frampton GK, et al. Clinical effectiveness and cost-effectiveness of depth of anaesthesia monitoring (E-Entropy, Bispectral Index and Narcotrend): a systematic review and economic evaluation. Health Technol Assess (Rockv). 2013;17:1–124.
18. Purdon PL, Pavone KJ, Akeju O, et al. The Ageing Brain: age-dependent changes in the electroencephalogram during propofol and sevoflurane general anaesthesia. Br J Anaesth. 2015;115:i46–57.
19. Myles PS, Williams DL, Hendrata M, et al. Patient satisfaction after anaesthesia and surgery: results of a prospective survey of 10,811 patients. Br J Anaesth. 2000;84:6–10.
20. Leslie K, Chan MTV, Myles PS, et al. Posttraumatic stress disorder in aware patients from the B-Aware trial. Anesth Analg. 2010;110:823–8.
21. Myles PS, Leslie K, McNeil J, et al. Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial. Lancet. 2004;363:1757–63.
22. Johansen JW. Update on bispectral index monitoring. Best Pract Res Clin Anaesthesiol. 2006;20:81–99.
23. Luginbühl M, Schnider TW. Detection of awareness with the bispectral index: two case reports. Anesthesiology. 2002;96:241–3.
24. Leslie K, Myles PS, Forbes A, et al. The effect of bispectral index monitoring on long-term survival in the B-aware trial. Anesth Analg. 2010;110:816–22.
25. Kertai MD, Pal N, Palanca BJA, et al. Association of perioperative risk factors and cumulative duration of low bispectral index with intermediate-term mortality after cardiac surgery in the b-unaware trial. Anesthesiology. 2010;112:1116–27.
26. Lindholm M-L, Träff S, Granath F, et al. Mortality within 2 years after surgery in relation to low intraoperative bispectral index values and preexisting malignant disease. Anesth Analg. 2009;108:508–12.