ORIGINAL RESEARCH PAPER

Anaesthesiology

MONITORING THE DEPTH OF ANAESTHESIA-REVIEW

KEY WORDS: General anaesthesia, total i.v. anaesthesia, electroencephalogram.

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ABSTRACT

Monitoring depth of anesthesia is a newer advance in the monitoring of anesthesia. Accurate assessment of the depth of anesthesia contributes to tailoring drug administration to the individual patient. Depth of anaesthesia monitors might help to individualize anaesthesia by permitting accurate drug administration against the measured state of arousal of the patient. In addition, the avoidance of awareness or excessive anaesthetic depth might result in improved patient outcomes. Various depth of anaesthesia monitors based on processed analysis of the EEG or mid-latency auditoryevoked potentials are commercially available as surrogate measures of anaesthetic drug effect. However, not all of them are validated to the same extent.

INTRODUCTION:

General anaesthesia is a state of drug-induced,reversible loss of consciousness. Implicit in this description (and consistent with patient expectations) is that from the time of induction of anaesthesia to emergence, patients will not be conscious of their surgery or their surroundings.Unintended awareness ('awareness')occurs when general anaesthesia has failed,and it arises more commonly than is generally perceived. Awareness is unpleasant, feared by patients, and is a cause of psychological harm to both the patient and the anaesthetist.Most episodes of awareness are avoidable.[1] Approximately 3.2 million general anaesthetics are given each year in the UK, and the overall rate of awareness is estimated to be between 1 and 2 per 1000 cases.[1 – 3]. General anesthesia (GA) is defined as a drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation 4. GA takes an important role in surgical procedures where an anesthetic overdose may lead to drug-associated toxicities, coma and even death; on the other hand a light anesthetic dose may lead to the well-known event of intraoperative awareness, which can cause sleep disorders, depression, night terrors, hospitals fears and post-traumatic stress disorder [5-7]. In this context, monitoring depth of anesthesia has become an important issue in anesthesiology.
Unfortunately, we cannot yet measure consciousness. There is acceptance amongst a majority of experts in the field of awareness that the isolated forearm technique, which measures responsiveness to command as a surrogate for consciousness, is the 'gold standard' technique against which other monitors should be validated. However, only 50% of patients who respond to command with an isolated forearm can later recall doing so.Modern depth of anaesthesia monitors can provide insight into the effects of delivered anaesthetic agents on the brain. This information can help to guide the rational administration of anaesthetic agents and to optimize drug delivery to the needs of individual patients. Commercially available monitors currently are of two types, those that measure spontaneous cortical electrical activity (electroencephalogram, or EEG) and those that measure stimulusevoked electrical activity (evoked potentials). Common to these is an attempt to convert the frontal EEG signal into a user-friendly,dimensionless index of depth of anaesthesia from 0 to 100 (with 0 representing no electrical activity, and 100 fully awake and responsive).In general terms, during anaesthesia, the EEG shifts from a high-frequency, low-amplitude signal (_10 mV) to a more regular,lower frequency, higher amplitude signal.

DISCUSSION:

Electroencephalographic signal (EEG) reflects the activity of the central nervous system and it has been widely used for monitoring depth of anesthesia. In general terms, the EEG of an anesthetized patient changes from high frequency, low amplitude when awake to low frequency, high amplitude when anesthetized; it is also noted that, during the anesthesia procedure the degree of EEG disorder is reduced. Therefore, the concept of entropy was introduced in EEG signal processing. Entropy is related to the complexity of a signal, and has been considered a promising measure of states of consciousness [5]. State Entropy (SE) and Response Entropy (RE) are indices provided by Datex-Ohmeda S/5TM entropy module (General Electric, Finland), which is currently a reference in EEG monitoring during general anesthesia [8-9].

Controversies in depth of anaesthesia monitoring

Depth of anaesthesia monitors do not measure consciousness, and are not currently recommended for every patient undergoing general anaesthesia. Since the outputs from DOA monitors generally decline with increasing concentrations of anaesthetic (albeit with variation across agents and between subjects), their use is to some extent justified when there is no other means of measuring agent concentrations in the body [as is currently the case with total i.v. anaesthesia (TIVA)]. However, if used in this way, DOA monitors become a crude measure that the anaesthetic is having some effect, rather than it is having a sufficient effect. There are pitfalls for the inexperienced with these devices in the interpretation of artifacts,many of which are because of electrical interference or poor electrode placement, and the sometimes-unstable numbers that are displayed, so they should not be used for the first time in a high-risk patient.

TIVA is often regarded as an independent risk factor for awareness because of the risk of interruption of drug supply, and the lack of an equivalent measure to ETAG. However, there is no hard evidence that the incidence of awareness is higher with TIVA than with a volatile anaesthetic technique. BIS correlates well with measured plasma concentrations of propofol, and ETAG concentrations.A monitor of depth of anaesthesia may help in guiding drug delivery to the effect site during TIVA, particularly where additional risk factors for awareness exist, or where population-derived assumptions may not apply as well to individuals at the fringes of the pharmacokinetic models (e.g. the obese, children, and the elderly).

Minimal sedation (anxiolysis) is a drug-induced state during which patients respond normally to verbal commands. Although cognitive function and physical coordination may be impaired, airway reflexes and ventilatory and cardiovascular functions are unaffected. Moderate sedation (conscious sedation) is a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light

tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.Deep sedation is a drug-induced depression of consciousness during which patients can not be easily aroused but respond purposefully following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate.

Cardiovascular function is usually maintained. General anesthesia is a drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.

Electroencephalogram (EEG) is a surface recording of the summed cortical electrophysiological activity and is altered by the level of consciousness. EEG-based monitoring could, in theory, directly monitor the neurological response to anesthetic agents, and account for the inherent variation in anesthetic sensitivity. In reality, measuring the EEG in the clinical setting and turning it into a reliable tool for monitoring anesthetic depth is challenging. Despite these challenges, several methods of EEG acquisition and processing have been developed and approved for clinical use. which measures the amount of disorder in the EEG (state entropy), in addition to frontalis electromyogram (response entropy)1; and auditory evoked potential (AEP),which measures the latency of cortical response to auditory stimulation.1 While these devices have potential clinical utility, they also have inherent limitations. EEG remains a crude measure of anesthetic effects on the brain in that the threshold and type of EEG changes that identify lack of awareness are still not known with complete certainty for every patient. The signals are prone to interference by artifact and all of the devices depend upon algorithms developed using a certain patient population.The transition from a state of wakefulness to a state of general anesthesia is accompanied by profound changes in the brain's spontaneous electrical activity recorded from electrodes placed on the scalp (electroencephalogram or EEG). The clinical monitoring is simple and is commonly used by the variety of physicians. Only the advances in computer hardware and signal processing algorithms have enabled the processing of EEG signals.

Accidental awareness under general anesthesia (AAGA) is a potentially devastating complication due to inadequate depth of anesthesia. AAGA is estimated to occur in 0.2% of adults receiving general anesthesia and potentially greater in children.[10-11]. The main fac tors contributing to awareness are equipment failure, intentional light anesthesia used to limit physiologic instability (e.g., hemodynamically unstable and trauma patients), and high anesthesia requirement of the patient. Total intravenous anesthesia (TIVA) has a particularly high risk of awareness, as there is no real-time measure like exhaled agent concentration to measure the anesthetic load in vivo [12]. It is thought that EEG-based depth of anesthesia monitoring may act as a "safety net" against AAGA, especially with TIVA. Several studies have compared BIS™ to the Patient State Index (PSI) and Entropy, and reported comparable effectiveness in predicting the depth of anesthesia.[13-15].To date, there is one large-scale study investigating the use of BIS during propofol TIVA. Zhang et al. conducted an RCT of 5,228 patients with propofol TIVA and found that the risk of awareness was significantly lower in the BIS-guided cohort (0.14%) compared to the BISblinded cohort (0.65%) [16]. Depth of anesthesia monitoring may also be used to prevent excessively deep anesthesia,which may be associated with delayed emergence from anesthesia and increased risk of perioperative complications. Several studies have reported that BIS monitoring is associated with lower anesthetic requirement with both intravenous and volatile agents[17-19] and similar findings have also been reported with Entropy™ and with AEP monitoring.[20-21] Punjasawadwong et al. conducted a meta-analysis of the anesthetic equirement with and without BIS monitoring,which reached the same conclusion [22]. It is thought that by minimizing the amount of anesthetic agent administered, depth of anesthesia monitoring may result in faster recovery from anesthesia. Gan et al. found that BIS monitoring is associated with significantly quicker emergence from anesthesia as well as shorter stay in PACU.12 Similar findings were subsequently reported in several other studies,13,17,18 and meta-analyses 22-[23].

BIS monitoring may also reduce the incidence of vasomotor complications as a result of unnecessarily deep anesthesia. Jildenstål et al. reported that AEP-guided anesthesia was associated with significantly lower vasopressor requirement. [24]. Low BIS index as well as "double low" events (low BIS and low mean arterial blood pressure [MAP], typically defined as casebased time-weighted average BIS and MAP below the sample mean) have been associated with increased mortality [25-26]. While the concept of 'triple low' (low BIS, low MAP, and low-end tidal anesthetic concentration) has also been introduced, the combination of low BIS and lowend tidal concentration is suggestive of sensitivity to anesthetic agent, rather than excessively deep anesthesia [27].

Lastly, it has been proposed that excessively deep anesthesia in high-risk (pre-existing neurocognitive disorders, cerebral vascular disease,frailty, etc.) patients is associated with the development of postoperative delirium and postoperative cognitive dysfunction [28]. Postoperative delirium (POD) is associated with increased morbidity and mortality, as well as long-term cognitive and functional decline. Several studies have demonstrated that BIS-guided anesthesia is associated with a significantly lower risk of POD [29-31] On the other hand, the ENGAGES trial recently published by Wildes et al. reported that despite lower anesthetic requirement and less EEG suppression in the BIS cohort, there was no significant difference in the risk of delirium, but they did report significantly lower 30-day mortality.16 MacKenzie et al. conducted a meta-analysis of 13 studies and reported lower risk of POD with depth of anesthesia monitoring [32].

The quality of EEG records is mainly influenced by internal or external sources of electromagnetic waves. Numerous sources of interference can mislead EEG measurements. The common sources of interference are the electrical activity of head muscles , cardiac pacemaker [33], hot air blanket systems [34] and the electrocoagulation needles [35]. The EEG activity is also influenced by anesthetic agents. However, ketamine does not change the BIS index even when patients are unconscious[36]. Ketamine has no effects on AEP [37]. The effects of nitrous oxide on EEG or BIS value are varied and therefore unpredictable [38-40,]. So, the current EEG or AEP-based anesthetic monitoring devices are not able to reliably assess the patient's depth of anesthesia when ketamine or nitrous oxide is used.

Physiological conditions, such as age [41], race [42], gender [43], low body temperature [44], acid-base imbalances [345], low blood glucose [46] or cerebral ischemia 47] also have a significant effect on patient can influence the EEG. The changes in the patient's age or general health may require adjustment of anesthetic agents. This variability in drug concentration is caused by variability of physiological effects of drugs on the differences in pharmacodynamics and

pharmacokinetics. Neuromuscular blocking agents have the effects on muscle electrical activity and indirectly on the signal quality of EEG measurement [46]. AEP are the responses of the auditory pathway to sound stimuli. An AEP is calculated by repeatedly applying an auditory stimulus to the patient and averaging EEG periods that immediately follow each stimulus[6].Compared to the raw EEG, AEP is less sensitive to artifacts. However, there still have no direct measure of consciousness available in clinical practice and thus no gold standard against which to test EEG or AEP derived indices of anesthetic depth [47].

Clinical signs

The most commonly used scoring system is Evans's score [48]. This score assesses autonomic activity related to systolic blood pressure, heart rate, sweating and tears. This system is simple and not requiring specialized equipment. However, these parameters are not specific and the scores can vary widely among individuals. ASA task force members on practice advisory for intraoperative awareness and brain function monitoring have been recommended physicians should be used these clinical signs to assess intraoperative consciousness [49]. Additionally, conventional monitoring systems including electrocardiogram, noninvasive blood pressure, capnography and end tidal anesthetic analyzer are valuable and should be used to help assessment of these clinical signs.

Skin conductance

Measuring skin resistance level and changes in the resistance of the skin is a simple and noninvasive method for evaluating the sympathetic nerve activity. The measurement of skin conductance is a quantification of the clinical sign of sweat production. Skin conductance is initially low and increases as anesthetic depth is increased. There has a correlation between electrical skin impedance, predicted plasma concentrations of propofol and the MOAAS scale [50]. The individual variability of the measurement values constitutes a problem in the interpretation of skin resistance measurements. In addition, several factors affecting sweating can reduce the accuracy of this monitoring.

Isolated forearm technique

Isolated forearm technique is a method detecting awareness during clinical practice. The tourniquet is applied to the patient's upper arm before administration of the muscle relaxant, and is inflated above systolic blood pressure to exclude its effect. Movement of the arm indicated wakefulness or light anesthesia, although not necessarily explicit awareness. However, the incidence of movement with this technique can vary with the choice of anesthetic drugs [51]. Other limitations of this technique are the limited time available before the patients are unable to move their arms, level of sedation/anesthesia needed to prevent the movement of patient's arm, and the nonspecific response may be misinterpreted.

Heart rate variability

Clinically, the beat to beat variability of heart rate may provide information which would be useful for monitoring depth of anesthesia. Three components of the heart rate variability are low, medium and high frequency fluctuations. Heart rate increases during inspiration and decreases during expiration through the parasympathetic reflex. This is called as the respiratory sinus arrhythmia (RSA). The reduction of the RSA is observed during anesthesia together with increase during recovery. Some monitors use the heart rate variability at respiratory frequency or RSA as a method assessing anesthetic depth [52]. However, the vagal tone depends on an intact of autonomic nervous system and healthy myocardial conducting system. Additionally, several factors influencing the heart rate variability in the perioperative setting are conduction abnormalities, autonomic neuropathy and sepsis as well as some medications such as beta-blockers and atropine.

The Ramsay scale was developed in 1970 in order to promote adequate sedation in intensive care units. It is internationally one of the most frequently cited sedation assessment tools. The Ramsay scale mainly involves a positive approach to the patient, designed to cause minimal disturbance to sleep. The level of sedation in mechanically ventilated patients is most often assessed with the Ramsay scale. This sedation scale divides into six score responses [53].

1 Anxious, agitated, restless
2 Cooperative, tranquil, oriented
3 Drowsy, response to verbal command
4 Asleep, brisk response to light glabellar tap and loud auditory stimulus
5 Asleep, sluggish response to light glabellar tap and loud auditory stimulus
6 No response to stimulus

To date, the reliability of the Ramsay scale remains controversial. Many studies show that there are insufficient evidences to support the reliability of the Ramsay sedation scale as a measure of sedation assessment [54-55]. In contrast, several studies demonstrate that the inter-observer reliability of the level of sedation measurements, performed in daily clinical practice within a large team of physicians, proved to be almost perfect [56-57]. However, the Ramsay scale is largely outdated and has been superseded by more appropriate, practical scoring tools. The Modified Observer Assessment of Alertness/Sedation scale (MOAA/S) is a six-point scale ranging from 5 to 0. It entails a positive action that involves eliciting a response to increasingly intense stimuli[58]. Patients are considered to have loss of consciousness at the transition between level 3 and level 2.

5 Responds readily to name spoken in normal tone
4 Lethargic response to name spoken in normal tone
3 Response only after name is called loudly and/or repeatedly
2 Response only after mild prodding or shaking
1 Response only after painful trapezius squeeze
0 No response after painful trapezius squeeze

To date, the author also uses the MOAA/S for sedation for various gastrointestinal endoscopic procedures [59-61]. Generally, the MOAA/S and the Ramsay scale are not interchangeable with the definitions of the levels of sedation. There is evidence of a correlation between the MOAA/S score and the Bispectral (BIS) measurement in several studies [62]. The monitoring of stress response during surgery is important, because prolonged surgical stress can lead to increased morbidity and delayed postoperative recovery [63]. An appropriate depth of sedation is routinely adjusted by titration of sedative concentration. Generally, the changes in heart rate and arterial blood pressure were used as signs of increased nociception during sedation but their specificity and sensitivity is not very high [64].

Depth of anesthesia monitoring may be a useful tool to help the clinician prevent the complications of too little or too much anesthesia. Whereas, anesthetic gas measurement may be sufficient for preventing awareness during inhalation anesthesia, tools like EEG-based depth monitoring add insight into anesthetic effect during TIVA. Excessive anesthetic dosages are well known to cause hemodynamic instability,but we are learning there may be other consequences of too much anesthesia such as neurocognitive dysfunction. Depth of anesthesia monitoring becomes more compelling if it can be used to guide the clinician to the "sweet spot" where anesthetic dose is sufficient to prevent awareness but not greater than needed. Some patients are especially vulnerable to anesthetic dosage complications and it is likely we have not yet identified all of those patient

populations. RCTs to date examining anesthetic depth monitoring have focused on large populations undergoing general anesthesia rather than focusing on at-risk populations, where the impact of depth monitoring would be more readily apparent. If benefits are demonstrated in at-risk populations, the cost-effectiveness arguments for using the technology in these populations would further improve.

CONCLUSION:

The threshold of evidence that supports a device as a monitoring standard is not clear.Pulse oximetry could not be shown to improve outcome, yet it is a well-established monitoring standard. Although the potential benefit of improved outcomes may be difficult to show,the potential to cause harm for example, by failing to detect awareness, is important to understand. It is not difficult to argue that once depth of anesthesia monitoring technology is proven more reliable, our monitoring recommendations should address the appropriate role for this technology in clinical practice. There are cases in which current technology could misinterpreted EEG patterns. If the anesthesiologists are not aware of this situation, is likely that they deepen what is already deep anesthesia.It is important to realize that unexpectedly high quantitative EEG indices values are relatively common and may result in dangerous anesthetic drug overdose

REFERENCES:

1. Sebel PS, Bowdle TA, Ghoneim MM et al. The incidence of awareness during anesthesia: multicenter United States study. Anesth Analg 2004;99:833–9
2. Myles PS, Leslie K, McNeil J, Forbes A, Chan MT. Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial. Lancet 2004; 363: 1757–63
3. Avidan MS, Zhang L, Burnside BA et al. Anesthesia awareness and the bispectral index. N Eng J Med 2008; 358: 1097–108
4. Bein B. Entropy. Best Pract Res Clin Anaesthesiol. 2006;20(1):101–9.
5. Schmidt GN, Bischoff P, Standl T, Hellstern A, Teuber O, et al. (2004) Comparative evaluation of the Datex-Ohmeda S/5 Entropy Module and the Bispectral Index monitor during propofol-remifentanil anesthesia. Anesthesiology 101(6): 1283-1290.
6. Ellerkmann RK, Liermann M, Alves T, Wenningmann I, Kreuer S, et al. (2004) Spectral Entropy and bispectral index as measures of the EEG effects of sevoflurane. Anesthesiology 101: 1275-1282.
7. Viertiö-Oja H, Maja V, Särkelä M, Talja P, Tenkanen N, et al. (2004) Description of the EntropyTM algorithm as applied in the Datex- Ohmeda S/5TM Entropy Module. Acta Anaesthesiol Scand 48(2): 154- 161.
8. Wheeler P, Hoffman WE, Baughman VL, Koenig H (2005) Response entropy increases during painful stimulation. J Neurosurg Anesthesiol 17(2): 86-90.
9. Bennett C, Voss LJ, Barnard JPM, Sleigh JW (2009) Practical use of the raw electroencephalogram waveform during general anesthesia: The art and science. Anesth Analg 109(2): 539-550.
10. Mihai R, Scott S, Cook TM. Litigation related to inadequate anaesthesia:an analysis of claims against the NHS in England 1995–2007. Anaesthesia 2009; 64:829–35
11. Brice DD, Hetherington RR, Utting JE. A simple study of awareness and dreaming during anaesthesia. Br J Anaesth 1970; 42: 535–42
12. Bruhn J, Myles PS, Sneyd R, Struys MMRF. Depth of anaesthesia monitoring: what's available, what's validated and what's next? Br J Anaesth. 2019;97:85–94.
13. Soehle M, Ellerkmann RK, Grube M, et al. Comparison between bispectral index and patient state index as measures of the electroencephalographic effects of sevoflurane. Anesthesiology. 2008; 109:799–805.
14. Aho AJ, Kamata K, Jantti V, et al. Comparison of bispectral index and entropy values with electroencephalogram during surgical anaesthesia with sevoflurane. Br J Anaesth. 2015;115:258–266.
15. Zhang C, Xu L, Ma YQ, et al. Bispectral index monitoring prevent awareness during total intravenous anesthesia: a prospective, randomized, double-blinded, multi-center controlled trial. Chin Med J (Engl). 2011; 124:3664–3669.
16. Gan TJ, Glass PS, Windsor A, et al. Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. BIS Utility Study Group. Anesthesiology. 1997;87:808–815.
17. Bocskai T, Loibl C, Vamos Z, et al. Cost-effectiveness of anesthesia maintained with sevoflurane or propofol with and without additional monitoring: a prospective, randomized controlled trial. BMC Anesthesiol. 2018;18:100.
18. Quesada N, Judez D, Martinez Ubieto J, et al. Bispectral Index Monitoring Reduces the Dosage of Propofol and Adverse Events in Sedation for Endobronchial Ultrasound. Respiration. 2016;92:166–175.
19. Rusch D, Arndt C, Eberhart L, et al. Bispectral index to guide induction of anesthesia: a randomized controlled study. BMC Anesthesiol. 2018;18:66.
20. Riad W, Schreiber M, Saeed AB. Monitoring with EEG entropy decreases propofol requirement and maintains cardiovascular stability during induction of anaesthesia in elderly patients. Eur J Anaesthesiol. 2007;24:684–688.
21. Punjasawadwong Y, Phongchiewboon A, Bunchungmongkol N. Bispectral index for improving anaesthetic delivery and postoperative recovery. Cochrane Database Syst Rev. 2014(6):Cd003843.
22. Chiang MH, Wu SC, Hsu SW, Chin JC. Bispectral index and non-bispectral index anesthetic protocols on postoperative recovery outcomes. Minerva Anestesiol. 2018;84:216–228.
23. Zorrilla-Vaca A, Healy RJ, Wu CL, Grant MC. Relation between bispectral index measurements of anesthetic depth and postoperative mortality: a meta-analysis of observational studies. Can J Anaesth. 2017;64:597–607.
24. Maheshwari A, McCormick PJ, Sessler DI, et al. Prolonged concurrent hypotension and low bispectral index ('double low') are associated with mortality, serious complications,and prolonged hospitalization after cardiac surgery. Br J Anaesth. 2017;119:40–49.
25. Kertai MD, White WD, Gan TJ. Cumulative duration of "triple low" state of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia is not associated with increased mortality. Anesthesiology. 2014;121:18–28.
26. McCormick PJ, Levin MA, Lin HM, Sessler DI, Reich DL. Effectiveness of an electronic alert for hypotension and low bispectral index on 90-day postoperative mortality: a prospective, randomized trial. Anesthesiology. 2016;125:1113– 1120.
27. Soehle M, Dittmann A, Ellerkmann RK, Baumgarten G, Putensen C, Guenther U. Intraoperative burst suppression is associated with postoperative delirium following cardiac surgery: a prospective, observational study. BMC Anesthesiol. 2015;15:61.
28. Chan MT, Cheng BC, Lee TM, Gin T. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. J Neurosurg Anesthesiol. 2013;25:33–42.
29. Radtke FM, Franck M, Lendner J, et al. Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. Br J Anaesth. 2013;110 Suppl 1:i98–105.
30. Whitlock EL, Torres BA, Lin N, et al. Postoperative delirium in a substudy of cardiothoracic surgical patients in the BAGRECALL clinical trial. Anesth Analg. 2014;118:809–817.
31. MacKenzie KK, Britt-Spells AM, Sands LP, Leung JM. Processed electroencephalogram monitoring and postoperative delirium: a systematic review and meta-analysis. Anesthesiology. 2018;129 417–427.
32. Wildes TS, Mickle AM, Ben Abdallah A, et al. Effect of electroencephalography- guided anesthetic administration on postoperative delirium among older adults undergoing major surgery: the ENGAGES randomized clinical trial. JAMA. 2019;321:473–483.
33. Vivien B, Langeron O, Riou B. Increase in bispectral index (BIS) while correcting a severe hypoglycemia. Anesth Analg. 2002; 95: 1824-1825.
34. Messner M, Beese U, Romstock J, Dinkel M, Tschaikowsky K. The bispectral index declines during neuromuscular block in fully awake persons. Anesth Analg. 2003; 97: 488-491.
35. Palanca BJ, Mashour GA, Avidan MS. Processed electroencephalogram in depth of anesthesia monitoring. Curr Opin Anesthesiol. 2009; 22: 553-559. PMid:19652597
36. Johansen JW, Sebel PS. Development and clinical application of lectroencephalographic bispectrum monitoring. Anesthesiology. 2000; 93: 1336-1344.
37. Consales G, Chelazzi C, Rinaldi S, De Gaudio AR. Bispectral index compared to Ramsay score for sedation monitoring in intensive care units. Minerva Anestesiol. 2006; 72: 329-336.
38. Powers KS, Nazarian EB, Tapyrik SA, et al. Bispectral index as a guide for titration of propofol during procedural sedation among children. Pediatrics. 2005; 115: 1666-1674.
39. Klockars JG, Hiller A, Ranta S, et al. Spectral entropy as a measure of hypnosis in children. Anesthesiology. 2006; 104: 708-717.
40. Wehrmann T, Grotkamp J, Stergiou N, et al. Electroencephalogram monitoring facilitates sedation with propofol for routine ERCP: a randomized controlled trial. Gastrointest Endosc. 2002; 56: 817-824
41. Chen SC, Rex DK. An initial investigation of bispectral monitoring as an adjunct to nurse-administered propofol sedation for colonoscopy. Am J Gastroenterol. 2004; 99: 1081-1086.
42. Drake LM, Chen SC, Rex DK. Efficacy of Bispectral monitoring as an adjunct to nurse-administered propofol sedation for colonoscopy: a randomized controlled trial. Am J Gastroenterol. 2006; 101: 2003-2007.
43. DeWitt JM. Bispectral index monitoring for nurse-administered propofol sedation during upper endoscopic ultrasound: a prospective,randomized controlled trial. Dig Dis Sci. 2008; 53: 2739-2745.
44. Kreuer S, Biedler A, Larsen R, Altmann S, Wilhelm W. Narcotrend monitoring allows faster emergence and a reduction of drug consumption in propofol-remifentanil anesthesia. Anesthesiology. 2003; 99: 34-41.
44. Panousis P, Heller AR, Burghardt M, Bleyl JU, Koch T. The effects ofelectromyographic activity on the accuracy of the Narcotrend monitor compared with the Bispectral index during combined anesthesia. Anaesthesia. 2007; 62: 868-874.
46. Amornyotin S, Chalayonnawin W, Kongphlay S. Deep sedation for endoscopic retrograde cholangiopancreatography: a comparison between clinical assessment and NarcotrendTM monitoring. Med Devices: Evid Res. 2011; 4: 43-49. PMid:22915929
47. Weber F, Zimmermann M, Bein T. The impact of acoustic stimulation on the AEP Monitor/2 derived composite auditory evoked potential index under awake and anesthetized conditions. Anesth Analg. 2005; 101: 435-439.
48. Plourde G. Auditory evoked potentials. Best Pract Res Clin Anesthesiol. 2006; 20: 129-139.
49. Horn B, Pilge S, Kochs EF, Stockmanns G, Hock A, Schneider G. A combination of electroencephalogram and auditory evoked potentials separates different levels of anesthesia in volunteers. Anesth Analg. 2009; 108: 1512-1521.
50. Gajraj RJ, Doi M, Mantzaridis H, Kenny GNC. Comparison of bispectral EEG analysis and auditory evoked potentials for monitoring depth of anesthesia during propofol anesthesia. Br J Anaesth. 1999; 82: 672-678.
51. Nishiyama T, Hanaoka K. The A-line ARX index may be a more sensitive detector of arousal than the bispectral index during propofol-fentanyl-nitrous oxide anesthesia: a preliminary investigation. Can J Anesth. 2004; 51: 539-544. 52 Drover DR, Lemmens HJ, Pierce ET, et al. Patient state index. Anesthesiology. 2002; 97: 82-89. PMid:12131107
53. Pilge S, Blum J, Kochs EF, Schoniger SA, Kreuzer M, Schneider G. Does the Cerebral State Index separate consciousness from unconsciousness? Anesth Analg. 2011; 113: 1403-1410.
54 Hoymork SC, Hval K, Jensen EW, Raeder J. Can the Cerebral State Monitor

replace the Bispectral index in monitoring hypnotic effect during propofol/remifentanil anesthesia? Acta Anaesthesiol Scand. 2007; 51: 210-216.
55. Bruhn J, Lehmann LE, Ropcke H, et al. Shannon entropy applied to the measurement of the electroencephalographic effects of desflurane. Anesthesiology. 2001; 95: 30-55.
56. Zanner R, Pilge S, Kochs EF, Kreuzer M, Schneider G. Time delay felectroencephalogram index calculation: analysis of cerebral state, bispectral, and Narcotrend indices using perioperatively recorded electroencephalographic signals. Br J Anaesth. 2009; 103: 394-399.
57. Pilge S, Zanner R, Schneider G, et al. Time delay of index calculation: analysis of cerebral state, bispectral, and Narcotrend indices. Anesthesiology. 2006; 104: 488-494.
58. White PF, Ma H, Tang J, et al. Does the use of electroencephalographic bispectral index or auditory evoked potential index monitoring facilitate recovery after desflurane anesthesia in the ambulatory setting? Anesthesiology. 2004; 100: 811–817.
59. Wong J, Song D, Blanshard H, et al. Titration of isoflurane using BIS index improves early recovery of elderly patients undergoing orthopedic surgeries. Can J Anaesth. 2002; 49: 13–18.
60. Jildenstal PK, Hallen JL, Rawal N, et al. Effect of auditory evoked potential-guided anaesthesia on consumption of anaesthetics and early postoperative cognitive dysfunction: a randomised controlled trial. Eur J Anaesthesiol. 2011; 28: 213–219.
61. Apfelbaum JL, Arens JF, Cole DJ, Connis RT, Domino KB, et al. (2006) Practice advisory for intraoperative awareness and brain function monitoring: a report by the american society of anesthesiologists task force on intraoperative awareness. Anesthesiology 104(4): 847-864.
62. Osterman JE, Hopper J, Heran WJ, Keane TM, van der Kolk B (2001) Awareness under anesthesia and the development of posttraumatic stress disorder. Gen Hosp Psychiatry 23(4): 198-204.
63. Errando CL, Aldecoa C (2014) Awareness with explicit recall during general anaesthesia: Current status and issues. Br J Anaesth 112(1): 1-4.
64. Sebel PS, Bowdle TA, Ghoneim MM, Rampil IJ, Padilla RE, et al. (2004) The incidence of awareness during anesthesia: A multicenter United States study. Anesth Analg 99: 833-839.