Intraoperative nociception monitoring

Department of Anesthesiology and Pain Medicine, Chungbuk National University College of Medicine, Cheongju, Korea

Hoon Kang

Monitoring depth of anesthesia has been an aim of anesthesia for several decades. Monitoring of clinical parameters, such as cardiovascular signs, sweating, and pupil signs has been routinely used. Many attempts have been made to develop systems for the accurate assessment of anesthetic depth. There have been some products available for monitoring hypnosis and sedation, and some partially acceptable measures for nociception monitoring have become available. Most of them are based on cerebral function monitoring (electroencephalogram) and autonomic responses. Awareness, with or without recall, is due to inadequate hypnosis, inadequate analgesia or increased levels of surgical stimulation at any stage during anesthesia. The ability to distinguish consciousness from unconsciousness and to detect nociception for a variety of anesthetic agents at equipotent doses is an essential element of a monitor and clinical end-point. Given the best sign of awareness is considered patient movement for any reason, neuromuscular blockade makes the assessment of depth of anesthesia difficult. While a reliable monitor ensuring unconsciousness and painlessness is required, several systems have been investigated. Although the intraoperative anesthetic state results from the balance between the effects of surgical stimulation and the effects of anesthetic agents on the central nervous system, it remains unclear if any of the current methods for monitoring anesthetic adequacy completely reflects this balance. (Anesth Pain Med 2015; 10: 227-234)

Key Words: Analgesia, Anesthesia, Hypnosis, Monitoring, Nociception.

INTRODUCTION

Of the problems which may arise in general anesthesia, that of assessing the depth of anesthesia is particularly important, because patients who suffer awareness or actual pain as a result of inadequate anesthesia, may experience considerable distress. Thus, there is a need for an objective method of assessing the depth of anesthesia (hypnosis and analgesia). It should be independent of traditional clinical signs such as heart rate and arterial pressure, of anesthesia and graded to allow the detection of awareness. In addition, it should be applicable to all of the anesthetic agents currently available, and it should respond appropriately to changes in the level of nociceptive stimulation.

Clinical signs such as cardiovascular signs (heart rate and arterial pressure), sweating or eye movement form the basis for the administration of successful anesthetics and, despite some inadequacies, have been the only practical and universally accepted indicators of adequate management of anesthesia. This article provides an overview of the implications of monitoring the hypnotic and analgesic components of anesthesia and clinical validations of the currently available monitoring systems, with technical problems concerned. Currently, most of the monitoring systems are based on electroencephalography (EEG), electromyography (EMG) or autonomic responses. Some of them are already on the market and used clinically but others are currently only used for experimental purposes. However, it is very difficult to assess the various techniques that have been proposed to monitor hypnosis and analgesia during anesthesia, while the state of anesthesia is not fully defined. In addition, mechanisms underlying action of most anesthetic drugs are poorly understood.
DEFINITION OF ANESTHESIA
AND AWARENESS

The anesthetic state consists of numerous features such as respiration rate and systolic arterial pressure of the patients. The conceptual framework of this state can be explained by four components: unconsciousness, analgesia, loss of reflexes and muscle paralysis. It is difficult to define anesthesia, because the nature of this state is still poorly understood. The poor understanding this phenomenon is so fundamental that there is no consensus even on whether anesthesia is a binary or continuous event. Some anesthetists think that anesthesia is a binary or continuous event [1] and that there is no such thing as “depth of anesthesia”; rather, it is either present or absent. Most anesthetists, however, regard anesthesia as a continuum, with different responses to different stimuli at different levels of anesthesia. Neuromuscular blockade and the suppression of automatic activity should not be considered components of anesthesia, but rather desirable supplements to the anesthetic state [1-3].

The requirements for this state differ by patient, each of whom would probably define anesthesia according to the presence or absence of that requirement. In other words, surgeons want the patient not to move, but the patient wants to be oblivious to any unpleasant event (pain, wakefulness or memory) during and after the operation. Thus, if a patient moves his legs in response to a painful stimulus during an operation without awareness or recall of intraoperative events, the surgeon may believe that the anesthesia was inadequate, while the patient may believe that was present throughout the operation.

If a patient becomes aware of his surroundings or of intraoperative events, awareness is said to have occurred due to inadequate anesthesia (inadequate hypnosis or inadequate analgesia) or an increased level of surgical stimulus at any stage during an anesthetic. Awareness has been defined as the ability to recall, with or without prompting, any events occurring during the period in which the patient is considered fully unconscious [4], or responsiveness to auditory stimuli without recall of the stimulus [5].

However, awareness is not always accompanied by recall. Patients who suffer awareness under anesthesia, particularly those who suffer pain during surgery, may experience considerable distress [6,7], which can lead to long-term psychological problems such as depression, personality changes and sleep disturbances, on their own or as part of post-traumatic stress disorder [8]. The incidence of conscious awareness is reported to be about 0.2% [9]. Anesthetists are probably more aware of the problem and its serious effects than in previous decades, and thus are also more likely to report the problem. Nonetheless, the incidence does seem to be decreasing.

To control anesthesia, all of the features (reflex and hence the triad components of anesthesia) must be controlled. Although a single anesthetic agent can do this, the supplied dose must be relatively high to control all of these features. Such a high dose could also lead to undesirable side-effects that are not associated with the anesthetic state. Better control can be achieved by supplying several drugs, each aimed towards a specific feature. The supplied dosage of each drug only needs to be sufficient to control the features influenced by that drug, which leads to lighter and better controlled anesthesia. An example of this approach was the introduction of muscle relaxant drugs.

METHODS OF ASSESSMENT OF ANESTHETIC
DEPTH (HYPNOSIS AND ANALGESIA)

Previously, clinical observation was the only means of assessing the depth of anesthesia. However, in the past decade, technological advances have enabled more objective techniques. While the best indicator of inadequate anesthesia remains patient movement, due to inadequate hypnosis or analgesia, movement does not always indicate awareness because it may sometimes be due purely to spinal reflexes. Moreover, the administration of drugs to paralyze the patient abolishes this useful clinical sign.

Several methods have been evaluated to assess the effects of sedative and hypnotic drugs: movement of the patient, eye movement, the diameter and reactivity of pupils to light, autonomic signs such as sweating and hemodynamic signs. However, there are many factors that make measuring depth of anesthesia difficult by these methods: neuromuscular blocking agents interfering with ability to move in response to pain, beta-blockers with vasodilating properties masking autonomic signs of light anesthesia. Hemodynamic signs are also poor in predicting anesthetic depth [10]. The electrophysiological techniques such as the spontaneous EEG, and its processed derivatives, Fast Fourier Transformation (FFT) [11], Median Frequency (MF) and Spectral Edge Frequency (SEF), have also been assessed as measures of depth of anesthesia. The raw EEG, however, is very difficult to analyze quickly in real-time.
by anesthetists, and MF and SEF have produced different study results with large variability and overlap in their values during consciousness and unconsciousness [12-14]. Lower esophageal contractility has also been proved to be unsuitable as it was not good in detecting awareness [15]. Furthermore, in spite of its correlation with the end-tidal concentration of volatile anesthetics [16], lower esophageal contractility was not related to blood concentration of intravenous anesthetics [17].

Clinical signs

Clinical signs result from stimulation of the sympathetic nervous system. One of the early attempts to classify depth of anesthesia using these parameters was by Guedel in 1937. Unfortunately this classification is no longer particularly meaningful, because it was specific to ether, and relied on signs that may no longer be valid during in anesthetic practice. Administration of beta-blockers, neuromuscular blocking agents, anticholinergics, and opioids, which cause vasodilation, paralysis, mydriasis, and miosis, respectively will all interfere with the signs required by that classification.

Thus, clinical signs, despite their inadequacy, are currently the only practical, universally accepted method of assessing the anesthetic state [18,19]. As such, they are successfully used to guide the administration of thousands of anesthetics every day. However, their interpretation is both subjective and variable. A reproducible, individualized description of the anesthetic state, based on clinical signs and validated against the goals of anesthesia, may allow the use of this technique as a gold standard. If another method should prove superior, it should be accepted as the new standard and the zone of surgical anesthesia should be refined accordingly.

More sophisticated trials have focused on the signs of sympathetic stimulation as indicators of anesthetic depth. “The patient response to surgical stimulation” score is commonly used, and uses pulse rate, systolic blood pressure and tear formation to generate a score [20]. Unfortunately the score is nonspecific, and is affected by vasoactive drugs, and conditions such as hypoxia and hypercarbia.

Neurophysiological techniques (electroencephalogram)

1. Auditory evoked potential and bispectral index

Unprocessed EEGs are difficult to assess, except perhaps by neurophysiologists, which makes it unsuitable for use as an anesthesia monitor in the hands of anesthetists. To be practical and useful, EEG data need to be processed and analyzed, and some variables based on EEG analyses have shown promise. Frequency analysis forms the basis of several EEG parameters, and is done by Fourier transformation of the EEG signal. This produces a spectral array of power within the different frequencies present in the signal, which can be presented visually as a compressed or density spectral array.

Further analysis of a spectral array can provide more information. The most commonly used methods are the MF and the SEF, being the frequencies below which 50% and 95% of the EEG power lies. As anesthesia deepens there is a shift towards the lower frequencies, so that these values tend to decrease with increasing anesthetic concentration and thus with increasing anesthetic depth. Unfortunately there is a large overlap between the values observed in conscious and unconscious subjects, so these values are limited in their ability to predict whether an individual patient is awake or unconscious [21].

Monitoring systems in this category include MF, SEF, bispectral index (BIS), auditory evoked potential (AEP)/auditory evoked potential index (AEPindex) and spectral entropy. They have been alleged to detect awareness during anesthesia. MF and SEF, produced by processing of EEG information, appear inadequate for assessing depth of anesthesia [22-24].

While there is no universally accepted method of monitoring the depth of anesthesia, the BIS and AEPindex might have been more promising than other techniques [13,14], because they provided anesthetists with objective and real-time indices from the anesthetised patients. In order to assess clinical value as anesthetic depth monitors, they were broadly investigated in the patients anesthetized with various volatile or intravenous anesthetics.

The AEP is derived by averaging the EEG signal recorded following repeated auditory stimuli. The AEP has been suggested to reflect the level of anesthesia (hypnosis and sedation) during general anesthesia using volatile and intravenous anesthetics. These effects are similar for equipotent doses of halothane [25], enflurane [25,26], isoflurane [27], etomidate [28], althesin [29] and propofol [17]. The effects of anesthetics are partially reversed by surgical stimulation, which affects the AEP [30]. The AEP has been shown to be a reliable detector of potential awareness during inhalational anesthesia in a limited number of studies [31,32].

Ketamine is a strong dissociative intravenous anesthetic. One study has shown no change in the AEP during ketamine anesthesia compared to the awake state [33], suggesting that ketamine anesthesia preserves primary processing of auditory
stimuli in the primary auditory cortex. One study using benzodiazepines demonstrated marked changes in latencies and amplitudes of the AEP [34]. However in another study [35] the AEP showed little change following induction of general anesthesia, suggesting the AEP did not accurately monitor the depth of anesthesia during induction and maintenance of anesthesia with benzodiazepines. Anesthesia with different anesthetic agents has been reported previously to produce dissimilar effects on the BIS [36]. In the maintenance period in which patients are normally considered to be steady-state anesthetic conditions, several patients receiving ketamine showed extremely high BIS scores which would normally be interpreted to suggest that the patient is awake. This phenomenon has been demonstrated in the previous studies [14,37,38] which have also demonstrated a large variability and overlapping in BIS values at the different stages of sedation or anesthesia with a variety of anesthetic agents in spite of some other studies [39-43] suggesting good correlation of BIS with the degree of sedation. The explanation for considerable difference in BIS values between these studies may primarily be a result of the use of different anesthetic agents, different anesthetic methods, or premedication, etc. In previous studies, BIS was reported to be closely associated with blood concentration of propofol [13,44]. In contrast, AEPindex was shown to be related less to blood concentration of propofol [13].

The BIS, a derived variable of the EEG, has been proved to reflect the depth of anesthesia. The correlation of the BIS with anesthetic depth has been broadly demonstrated in intravenous and volatile anesthesia. As a numerical index based on the AEPs, the AEPindex has been shown to be a reliable indicator of potential awareness during intravenous anesthesia [13,14].

Nitrous oxide, a weak hypnotic and good analgesic, did not appear to alter AEP markedly in some comparative studies, compared with other volatile anesthetics [31,32]. Similarly, this unique effect of nitrous oxide on AEP may also be identical for the BIS. In reality there were some reports in which nitrous oxide was shown to have no effect on the BIS in subanesthetic concentration [45,46]. This may suggest that the BIS and AEP do not accurately monitor the depth of anesthesia with nitrous oxide. Because of its limited potency as a hypnotic, nitrous oxide, when used alone or in inadequate combination with other agents, may cause a potential awareness. It cannot provide adequate anesthetic depth by itself, but it is commonly used as a sole agent or supplement for minor procedures in some clinical fields such as dentistry and obstetrics. Whereas nitrous oxide has been reported to have little effects on both BIS and AEP, there is still a need for better methods of monitoring hypnotic effect of nitrous oxide, guaranteeing a lack of awareness.

Awareness of surgical stimuli is a terrifying and painful experience; the patient, unable to communicate, hears conversations and feels surgical manipulations. In less well understood forms of awareness, long-term psychiatric morbidity may result. On the imaginary line from fully conscious through anesthesia, we do not know exactly where conscious awareness ends (and thus anesthesia begins), or whether unconscious awareness ends somewhere on the anesthesia part of the line. Although the intraoperative anesthetic state, as we see it, results from the balance between the effects of surgical stimulation and the effects of anesthetic dose on the central nervous system (CNS), it is not known whether any of the methods proposed as monitors of anesthetic adequacy truly reflect this balance, if they monitor it completely or what levels of CNS activity are appropriate during general anesthesia and surgery. The BIS, a mathematical value processed from the EEG bispectrum, was shown to be a significant predictor of patient responses to incision [47]. However, in one publication, the BIS was not able to predict movement in response to laryngeal mask airway (LMA) insertion [48]. Surgical stimulation has been known to affect the AEP [30] and EEG [49].

2. Spectral entropy

Spectral entropy (GE Healthcare, Helsinki, Finland) is another variable derived from both the EEG and EMG signals of the forehead. There are two different values calculated in this system: state entropy (SE) and response entropy (RE). A detailed explanation about the system was published elsewhere [50]. The SE measures the hypnotic component of anesthesia with volatile or intravenous anesthetics [51-53]. While response entropy and the RE-SE difference are alleged to measure the analgesic component of anesthesia using EMG, both parameters of SE also detected patients’ movement to nociceptive stimuli during anesthesia with sevoflurane [54].

Autonomic responses

1. Surgical plethysmographic index

The surgical plethysmographic index (surgical pleth index; SPI), previously called the surgical stress index, was developed based on autonomic variables (plethysmographic pulse wave amplitude and heart beat interval) to detect responses to surgical stimuli during general anesthesia. This nocicep-
tion-detecting function was evidenced by opioid consumption [55,56]. The SPI also monitors the hypnotic component of anesthesia regardless of the analgesic component. However, there are several confounding factors for the SPI, which include concomitant medication, volume status, pacemaker action, arrhythmias and posture changes.

2. Analgesia nociception index

The analgesia nociception index (ANI) represents a variable derived from analysis of the heart rate variability (HRV). The HRV is derived from a standard electrocardiography (ECG) signal. The ANI values are changed by surgical stimulations during anesthesia, such as skin incision or induction of pneumoperitoneum [57]. This system was shown to be dependent upon remifentanil effect site concentration [58]. However, the system was not able to predict patient movement in response to nociceptive stimulation, and also showed a large inter-individual variability in values after surgical stimulation.

Different drugs have been used to achieve each of the four anesthetic components: sensory blockade, motor blockade, reflex blockade and mental block. However, little effort has been made to define methods for monitoring each component. Depth of anesthesia must be associated with a balance between anesthetic depression and surgical stimulation from which an arousal response sufficient for the individual to respond to nociceptive stimuli could result, although the issue of surgical stimulation producing arousal to a conscious state has not been fully documented. With the introduction of neuromuscular blockade, the assessment of depth of anesthesia became more difficult because the drug removed some of the conventional signs of a light level of anesthesia such as patient movement that is generally considered the most useful indicator of inadequate anesthesia. Even with a standard anesthetic technique composed of oxygen, nitrous oxide, opioid, inhalational agent and neuromuscular blockade, there is a possibility that many patients may be conscious without clinical signs of inadequate anesthesia based on autonomic function during surgery, despite the amnesic effect of any recall. Wakefulness during anesthesia in paralyzed patients has been studied by some study groups, who used the isolated forearm technique intermittently throughout a prolonged period of surgery [59-64]. However, it cannot be routinely applicable for paralyzed patients because of some significant disadvantages (lack of reliability due to ischemic pain, frequent movement of the unparalyzed arm and ethical issues), but rather may have some value as an investigative tool.

From the discussion above it is clear that there is no widely accepted method available with which to make a detection of awareness during anesthesia in paralyzed patients deprived of movement. Thus, there is a need for improved techniques that allow objective assessments of the depth of anesthesia in such patients. In order to answer this need we should know how a response to verbal stimulation can be elicited in paralyzed patients in more sophisticated and objective ways. Since the CNS is the main site of general anesthetics, it is reasonable that all approaches to assessment of the depth of anesthesia have been focused on the brain. It has been suggested that neuromuscular blocking agents do not decrease anesthetic requirements [65-67]. However, other studies have shown different results, suggesting that the depth of anesthesia is affected by neuromuscular blocking agents [68-70].

There have been some reports investigating the effects of neuromuscular blocking agents on depth of anesthesia monitored by BIS. Flaishon et al. [71] showed that BIS might be able to provide a reliable method for predicting the probability of recovery of consciousness from anesthesia using thiopental or propofol in paralyzed patients. In their report, although they did not mention the direct effect of neuromuscular blocking agent on BIS, it was recognizable that the capability of BIS to predict the probability of a patient being aware was not affected by neuromuscular blockade. In contrast, Messner et al. [72] were very doubtful of the capability of BIS to indicate the level of consciousness in a paralyzed state because in their study using volunteers neuromuscular relaxation decreased BIS to very low values in a fully conscious state, which would generally be accepted as indicating an unconscious state. It implies that BIS might not be a sensitive measure of the depth of sedation or a detector of awareness in subjects who were totally paralyzed with a muscle relaxant.

In association with the causes of the marked reduction in BIS by neuromuscular blocking agents during consciousness, Messner et al. [72] suggested a close correlation of BIS with electromyographic activity. The authors postulated that the decrease in BIS after neuromuscular blockade with succinylcholine might be closely related with disappearance of electromyographic activity. However, a nondepolarizing agent, alcuronium, given prior to the administration of succinylcholine, did not have any effect on BIS. There is another report.
analyzing the causes of decrease in BIS following the administration of neuromuscular blocking agents. Bruhn et al. [73] also did not exclude the possibility of interference of EMG with BIS monitoring in unparalyzed state. They observed the reduction in BIS after vecuronium was administered intravenously in a patient at constant target concentrations of propofol and remifentanil. But it should be noted that there was already paradoxical increase in BIS presumably due to muscle rigidity by remifentanil before the decrease in BIS by vecuronium. The findings by Messner et al. and Bruhn et al. provide good contrasts with our results which showed that the administration of mivacurium did not have further effect on already reduced mean values of BIS by anesthetic induction with propofol and fentanyl [74].

There was an investigation which was not supportive of the role of neuromuscular blockade in increasing the depth of anesthesia. Greif et al. [75] documented that BIS was not changed by the degree of neuromuscular relaxation. They were against the theories that the reduction of electromyographic activity [72,73] or afferent signal from muscle [68,69] could decrease BIS. The reasons for the differences in the adequacy of BIS among study groups in indicating the depth of anesthesia during paralysis cannot be explained clearly. Of the possible reasons that can cause the differences, the neuromuscular blocking agent used in each study appears unlikely to explain the differences because the inconsistent effects with the same muscle relaxants were demonstrated. Some of the previous reports studying the effects of neuromuscular blockade on BIS obtained inconsistent results with vecuronium [71,73]. In other previous studies investigating the relationship between muscle relaxant and anesthetic requirement or depth of anesthesia, pancuronium was also shown to have conflicting effects [65,68,69].

CONCLUSIONS

Assessing the depth of anesthesia has long been an aim of anesthesia for several decades. If a patient becomes aware of his surroundings or of intraoperative events, awareness is said to have occurred. Presumably, it may result from inadequate hypnosis, inadequate analgesia or an increased level of nociceptive stimulus at any stage during anesthesia. The ability to distinguish consciousness from unconsciousness and to provide similar values for different anesthetic agents at equipotent doses is an essential feature of any monitor of the depth of anesthesia, and is the clinical end-point used. While a reliable monitor that ensures unconsciousness and painlessness is required, several systems for monitoring depth of anesthesia have been investigated. Although the intraoperative anesthetic state results from a balance between the effects of surgical stimulation and the effects of anesthetic dose on the CNS, it is not known whether any of the methods proposed as monitors of anesthetic adequacy truly reflect this balance, if they monitor hypnosis and analgesia separately or what levels of CNS activity are appropriate during general anesthesia and surgery.

REFERENCES

1. Prys-Roberts C. Anaesthesia: a practical or impractical construct. Br J Anaesth 1987; 59: 1341-5.
2. Gray TC. A reassessment of the signs and levels of anaesthesia. Ir J Med Sci 1960; 419: 499-508.
3. Pinsker MC. Anesthesia: a pragmatic construct. Anesth Analg 1986; 65: 819-20.
4. Brice DD, Hetherington RR, Uting JE. A simple study of awareness and dreaming during anaesthesia. Br J Anaesth 1970; 42: 535-42.
5. Desiderio DP, Thorne AC. Awareness and general anaesthesia. Acta Anaesthesiol Scand Suppl 1990; 92: 48-50.
6. Mirakhur RK, Morgan M. Intravenous anaesthesia: a step forward. Anaesthesia 1998; 53 Suppl 1: 1-3.
7. Doze VA, Shafer A, White PF. Propofol-nitrous oxide versus thiopental-isoflurane-nitrous oxide for general anaesthesia. Anesthesiology 1988; 69: 63-71.
8. Suttner S, Boldt J, Schmidt C, Piper S, Kulme B. Cost analysis of target-controlled infusion-based anesthesia compared with standard anesthesia regimens. Anesth Analg 1999; 88: 77-82.
9. Liu WH, Thorp TA, Graham SG, Attikhen AR. Incidence of awareness with recall during general anaesthesia. Anaesthesia 1991; 46: 435-7.
10. Hug CC Jr. Does opioid “anaesthesia” exist? Anesthesiology 1990; 73: 1-4.
11. Levy WJ, Shapiro HM, Maruchak G, Meathe E. Automated EEG processing for intraoperative monitoring: a comparison of techniques. Anesthesiology 1980; 53: 223-36.
12. Schwender D, Daunderez M, Schmid C, Pippel S, Klasing S, Finsterer U, Peter K. Spectral edge frequency of the electroencephalogram to monitor “depth” of anaesthesia with isoflurane or propofol. Br J Anaesth 1996; 77: 179-84.
13. Doi M, Gajraj RJ, Mantzaridis H, Kenny GN. Relationship between calculated blood concentrations of propofol and electrophysiological variables during emergence from anaesthesia: comparison of bispectral index, spectral edge frequency, median frequency and auditory evoked potential index. Br J Anaesth 1997; 78: 180-4.
14. Gajraj RJ, Doi M, Mantzaridis H, Kenny GN. Analysis of the EEG
19. Hug CC Jr. Lipid solubility, pharmacokinetics, and the EEG: are you better off today than you were four years ago? Anesthesiology 1985; 62: 221-6.

20. Smajic J, Praso M, Hodzic M, Hodzic S, Stabovic-Okayovic A, Smajic N, et al. Assessment of depth of anesthesia: PRST score versus bispectral index. Med Arh 2011; 65: 216-20.

21. Raeder J, Gupta A, Pedersen FM. Recovery characteristics of sevoflurane- or propofol-based anesthesia for day-care surgery. Acta Anaesthesiol Scand 1997; 41: 988-94.

22. Schneider G, Sebel PS. Monitoring depth of anesthesia. Eur J Anaesthesiol 1997; 14: 988-94.

23. White PF, Boyle WA. Relationship between hemodynamic and electroencephalographic changes during general anesthesia. Anesth Analg 1989; 68: 177-81.

24. Drummond JC, Brann CA, Perkins DE, Wolfe DE. A comparison of median frequency, spectral edge frequency, a frequency band power ratio, total power, and dominance shift in the determination of depth of anesthesia. Acta Anaesthesiol Scand 1991; 35: 693-9.

25. Thornton C, Heneghan CP, James MF, Jones JG. Effects of halothane or enflurane with controlled ventilation on auditory evoked potentials. Br J Anaesth 1984; 54: 315-23.

26. Smajic J. Praso M, Hodzic M, Hodzic S, Stabovic-Okayovic A, Smajic N, et al. Assessment of depth of anesthesia: PRST score versus bispectral index. Med Arh 2011; 65: 216-20.

27. Schneider G, Sebel PS. Monitoring depth of anesthesia. Eur J Anaesthesiol Suppl 1997; 15: 21-8.

28. White PF, Boyle WA. Relationship between hemodynamic and electroencephalographic changes during general anesthesia. Anesth Analg 1989; 68: 177-81.

29. Thornton C, Heneghan CP, Navaratnarajah M, Jones JG. Effect of isoflurane on the auditory evoked response in man. Br J Anaesth 1989; 63: 411-7.

30. Jones JG, Konieczko K. Hearing and memory in anaesthetised patients. Br Med J (Clin Res Ed) 1986; 292: 1291-3.
Bispectral analysis of the electroencephalogram correlates with patient movement to skin incision during propofol/nitrous oxide anesthesia. Anesthesiology 1994; 81: 1365-70.

48. Doi M, Gajraj RJ, Mantzaridis H, Kenny GN. Prediction of movement at laryngeal mask airway insertion: comparison of auditory evoked potential index, bispectral index, spectral edge frequency and median frequency. Br J Anaesth 1999; 82: 203-7.

49. de Beer NA, van Hooff JC, Cluitmans PJ, Korsten HH, Grouws RJ. Haemodynamic responses to incision and sternotomy in relation to the auditory evoked potential and spontaneous EEG. Br J Anaesth 1996; 76: 685-93.

50. Vierrio-Oja H, Maja V, Sarkela M, Talja P, Tenkanen N, Tolvanen-Laakso H. Description of the entropy algorithm as applied in the Datex-Ohmeda S5 entropy module. Acta Anaesthesiol Scand 2004; 48: 154-61.

51. Bruhn J, Bouillon TW, Radulscu I, Hoeft A, Bertaccini E, Shafer SL. Correlation of approximate entropy, bispectral index, and spectral edge frequency 95 (SEF95) with clinical signs of “anesthetic depth” during propofol and remifentanil anesthesia. Anesthesiology 2003; 98: 621-7.

52. Ellerkmann RK, Liermann VM, Alves TM, Wenningmann I, Brun J, Bouillon TW, Radulscu L, Hoefl A, Bertaccini E, Shafer SL. Auditory perception under anaesthesia. Anaesthesiology 1994; 81: 1365-70.

53. Schmidt GN, Bischoff P, Standl T, Hellstern A, Teuber O, Schulte J, Brunn J, Bouillon TW, Shafer SL. Electromyographic activity and spectral entropy during isoflurane anesthesia for laparoscopic abdominal surgery. J Clin Monit Comput 2012; 26: 289-94.

54. Seitsonen ER, Korhonen IK, van Gils MJ, Huiku M, Lötjönen JM, Korttila KT, et al. EEG spectral entropy, heart rate, photoplethysmography and motor responses to skin incision during sevoflurane anaesthesia. Acta Anaesthesiol Scand 2005; 49: 284-92.

55. Gruenewald M, Meybohm P, Ilies C, Hesse J, Reinhart K, Hanss R, Scholz J, et al. Influence of different remifentanil concentrations on the performance of the surgical stress index to detect a standardized painful stimulus during sevoflurane anaesthesia. Br J Anaesth 2009; 103: 586-93.

56. Struys MM, Vanpeteghem C, Huiku M, Uateia K, Blyaert NB, Mortier EP. Changes in a surgical stress index in response to standardized pain stimuli during propofol-remifentanil infusion. Br J Anaesth 2007; 99: 359-67.

57. Jeanne M, Clement C, De Jonckheere J, Logier R, Tavernier B. Variations of the analgesic nociception index during general anaesthesia for laparoscopic abdominal surgery. J Clin Monit Comput 2012; 26: 289-94.

58. Gruenewald M, Ilies C, Herz J, Schoenherr T, Fudickar A, Höcker J, et al. Influence of nociceptive stimulation on analgesic nociception index (ANI) during propofol-remifentanil anaesthesia. Br J Anaesth 2013; 110: 1024-30.

59. Tunstall ME. Detecting wakefulness during general anaesthesia for caesarean section. Br Med J 1977; 1: 1321.

60. Tunstall ME. The reduction of amnesic wakefulness during caesarean section. Anaesthesia 1979; 34: 316-9.

61. Russell IF. Auditory perception under anaesthesia. Anaesthesia 1979; 34: 211.

62. Schultetus RR, Hill CR, Dharamraj CM, Banner TE, Berman LS. Wakefulness during Caesarean section after anesthetic induction with ketamine, thiopental or ketamine and thiopental combined. Anesth Analg 1979; 65: 723-8.

63. Russell IF. Comparison of wakefulness with two anaesthetic regimens. Total i.v. balanced anaesthesia. Br J Anaesth 1986; 58: 965-8.

64. Russell IF. Midazolam-alfentanil: an anaesthetic? An investigation using the isolated forearm technique. Br J Anaesth 1993; 70: 42-6.

65. Fahey MB, Sessler DI, Cannon JE, Brady K, Stoen R, Miller RD. Atracurium, vecuronium and pancuronium do not alter the minimum alveolar concentration of halothane in humans. Anesthesiology 1989; 71: 53-6.

66. Sessler DI, Olofsson CI, Chow F. Low csophageal contractility predicts movement during skin incisions; Vecuronium does not decrease the MAC of halothane. Anesth Analg 1988; 67: S201.

67. Richmond CE, Matson A, Thornton C, Doré CJ, Newton DE. Effect of neuromuscular block on depth of anaesthesia as measured by the auditory evoked response. Br J Anaesth 1996; 76: 446-8.

68. Schwartz AE, Navedo AT, Berman MF. Pancuronium increases the duration of electroencephalogram burst suppression in dogs anaesthetised with isoflurane. Anesthesiology 1992; 77: 686-90.

69. Forbes AR, Cohen NH, Eger EI 2nd. Pancuronium reduces halothane requirement in man. Anesth Analg 1979; 58: 497-9.

70. Johansen JW, Flaishon R, Sebel PS. Esmolol reduces anaesthetic requirement for skin incision during propofol/nitrous oxide/morphine anesthesia. Anesthesiology 1997; 86: 364-71.

71. Flaishon R, Windsor A, Sigl J, Sebel PS. Recovery of consciousness after thiopental or propofol. Bispectral index and isolated forearm technique. Anesthesiology 1997; 86: 613-9.

72. Messner M, Beese U, Romstock J, Dinkel M, Tschaikowski K. The bispectral index declines during neuromuscular block in fully awake persons. Anesth Analg 2003; 97: 488-91.

73. Bruhn J, Bouillon TW, Shafer SL. Electromyographic activity falsely elevates the bispectral index. Anesthesiology 2000; 92: 1485-7.

74. Kang H, Na HS. The assessment of effect of neuromuscular blocking agent on depth of anesthesia using the BIS and AEPindex. Chungbuk Medical Journal 2006; 16: 153-60.

75. Greif R, Greenwald S, Schweitzer E, Lacy S, Rajek A, Caldwell JE, et al. Muscle relaxation does not alter hypnotic level during propofol anesthesia. Anesth Analg 2002; 94: 604-8.