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ORIGINAL ARTICLE

Auditory evoked potential index does not correlate with observer assessment of alertness and sedation score during 0.5% bupivacaine spinal anesthesia with nitrous oxide sedation alone

Junko Ichikawa · Kumiko Taira · Keiko Nishiyama · Masato Endo · Mitsuharu Kodaka · Miwako Kawamata · Makiko Komori · Makoto Ozaki

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Abstract
Purpose The aim of this study was to evaluate the auditory evoked potential (AEP) index as a hypnosis monitor during nitrous oxide (N_2O) sedation added to spinal analgesia.
Methods Forty-five patients scheduled to undergo surgery under spinal anesthesia were recruited after giving informed consent. Adequate anesthesia levels were confirmed, and a disposable AEP index sensor (aepEX, Medical Device Management) was placed. A tight facemask was fitted, and a fresh gas flow of 100% oxygen 10 L/min was provided. AEP index monitoring was then initiated, and measurements and observer assessment of alertness/sedation (OAA/S) scores were recorded manually. N_2O was administered in stepwise increases in the end-tidal concentration of 33%, 50%, and 67%. Paired AEP index and OAA/S scores were obtained immediately before each change in N_2O concentration.
Results Sixteen patients were excluded from final analysis because of nausea, vomiting, or abnormal excitatory behaviors. The increases in N_2O concentration induced significant decreases in OAA/S scores and no substantial AEP index changes. Although OAA/S scores of 1 and 2 were observed in only two and five patients, respectively, a reduction in the OAA/S score from 5 to 1 was associated with a significant decrease in AEP index to the level indicative of moderate sedation.
Conclusion The AEP index might not be a suitable indicator of light hypnosis as defined by an OAA/S score of ≥ 3 during sedation with N_2O alone.

Keywords Auditory evoked potential index · Observer assessment of alertness and sedation score · Nitrous oxide

Introduction

With progress in anesthesia care, patients' comfort, such as quality sedation during local anesthesia, has been paid increasing attention. The bispectral index (BIS) is an excellent predictor of sedation and hypnosis produced by propofol, midazolam, isoflurane, and sevoflurane [1–3]. However, some studies have reported paradoxical BIS changes and inaccurate readings that do not always correlate with clinical measures of sedation. A previous study has shown that BIS did not seem to work well during sedation with nitrous oxide (N_2O) [4, 5] but provided accurate measures of sedation during anesthesia with a volatile agent plus N_2O [6]. N_2O is a frequently used adjunct to balanced anesthesia, decreasing the minimum alveolar concentration of volatile anesthetics and the plasma concentration of intravenously administered anesthetics required for loss of consciousness [7]. In addition, N_2O is commonly used as the sole anesthetic for sedation in dental practice and obstetrics. Although previous studies have monitored BIS changes during N_2O-induced anesthesia, the effect of N_2O on the auditory evoked potential (AEP) index remains unclear.

AEP index has been reported to be superior to the spontaneous electroencephalogram (EEG) for identifying

J. Ichikawa (✉) · K. Taira · K. Nishiyama · M. Endo · M. Kodaka · M. Kawamata · M. Komori
Department of Anesthesiology, Tokyo Women's Medical University Medical Center East, 2-1-10 Nishiogu, Arakawa-ku, Tokyo 116-8567, Japan
e-mail: htwfx872@yahoo.co.jp

M. Ozaki
Department of Anesthesiology, Tokyo Women's Medical University, Tokyo, Japan

transition from a conscious state during propofol infusion [8, 9]. Furthermore, AEP index predicts the depth of sedation and movement in response to skin incision during sevoflurane anesthesia [10]. These results suggest that AEP index might be a useful predictor of the depth of sedation as measured by the observer's assessment of alertness and sedation (OAA/S), a well-established sedation scoring system used during light sedation. Therefore, the aim of this study was to investigate the effect of N_2O on AEP index and to test the hypothesis that the AEP index correlates with sedation as measured by OAA/S during anesthesia with N_2O alone.

Methods

Participants

The protocol was approved by the institutional ethics committee for human studies of Tokyo Women's Medical University, Tokyo, Japan. Written informed consent was obtained from each patient or his or her legal guardian. Forty-five patients [aged 29–83 years; American Society of Anesthesiologists' (ASA) physical status I or II] were recruited. All patients were scheduled to undergo elective lower-extremity surgery or inguinal herniorrhaphy under spinal anesthesia. Patients were excluded if they had concurrent diseases, neurologic disorders, hearing disturbances, clinically significant obesity (body mass index >30), or a history of cardiac, pulmonary, hepatic, or renal disease. Patients were also excluded if they abused drugs or alcohol or were receiving medications potentially affecting EEG response (sedatives, hypnotics, anticonvulsants).

Anesthetic techniques

Patients fasted for at least 8 h before surgery and received no premedication. On arrival at the operating room, standard monitoring was initiated, including electrocardiography, pulse oximetry, and noninvasive measurement of arterial blood pressure. Baseline vital signs were obtained, and subsequent values were recorded at 2.5-min intervals throughout the study period. Before anesthesia, a 20-gauge venous catheter was inserted, and a crystalloid solution (500 ml) was administered intravenously within 30 min before the operation. A spinal puncture was performed at the L2 or L3 interspace using a 25-gauge Quincke needle with the patient in a lateral decubitus position, and 0.5% isobaric bupivacaine was slowly injected at a rate of 1 ml/15 s. The spinal block level was assessed by the cold sensation test 15 min after the spinal anesthesia and before the patient was returned to the ward. Clinically relevant hypotension (a decrease in systolic arterial blood pressure >30% from the baseline value) or bradycardia (heart rate <50 bpm) was treated with 4- to 8-mg incremental doses of ephedrine.

Acquisition of auditory evoked potentials

The aepEX monitor (Medical Device Management, Essex, UK) uses headphones and three electrodes, two of which are placed on the forehead and the other on a mastoid process. The midlatency AEP (MLAEP) was elicited using a binaural click with a sound intensity of 90 ± 3 dB created by a 1-ms-square wave pulse delivered to the headphones at a rate of 6.9 Hz (one click every 144 ms). The MLAEP waveform extraction from the EEG was achieved by averaging 256 EEG sweeps, each with a 144-ms duration, totaling 36.9 s. The AEP index was calculated by analysis of the MLAEP waveform. Although the time required for a full update of the signal was 36.9 s, a moving time-averaging technique allowed a faster response time to any change in the index, which was updated every 0.3 s. All electrodes were applied as recommended by the manufacturer after preparing the skin with an abrasive sensor preparation. Electrode impedances were considered acceptable if they were <5 kΩ. Electromyographic activity contamination and patient movement were considered artifacts and removed at the time of AEP data collection.

Study design

After the vital signs were stabilized and the patient had remained on the operating table in a comfortable position for at least 5 min, the spinal block level was confirmed. The patient was fitted with a tight face mask connected to a circle breathing system with a fresh gas flow of 100% oxygen 10 L/min . After at least 3 min had elapsed, AEP index monitoring was initiated. All patients breathed through a face mask connected to a semiclosed anesthetic circuit. The total fresh gas flow into the anesthetic circuit was maintained at 10 L/min. Because of concerns about a dose-dependent increase in the incidence of nausea, emesis, and excitatory behavior, N_2O was administered in an upward sequence of end-tidal concentration steps of 33%, 50%, and 67%. Each end-tidal N_2O concentration was maintained for at least 15 min before advancing to the next concentration. Paired AEP index and OAA/S scores (Table 1) were obtained immediately before each change in N_2O concentration. The AEP index corresponding to each OAA/S score was calculated by averaging three values obtained during the 45-s interval immediately before the assessment of OAA/S score.

Expired gas was collected at a rate of 200 ml/min via a sampling tube located between the face mask and the dead space, and the carbon dioxide tension and concentrations of

Table 1 Responsiveness scores of the modified observer's assessment of alertness/sedation scale (OAA/S)

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

N_2O and oxygen were measured continuously using an infrared anesthetic gas analyzer (Capnomac Ultima; Datex Instrumentarium Corp., Helsinki, Finland). Ventilation was gently assisted whenever necessary to maintain an end-tidal carbon dioxide tension within the physiological range of 30–35 mmHg. If any emotional changes (excitation, laughing, crying), behavioral abnormalities (involuntary movement, slurred speech, tachypnea), or nausea or vomiting were observed, further procedures were abandoned. Normothermia was maintained throughout the procedure.

Statistical analysis

Data are expressed as the mean ± standard deviation (SD), medians, or both. The nominal AEP index and ordinal OAA/S scores were compared at each target N_2O end-tidal concentration by a nonparametric Friedman' analysis of ranks, with a post hoc analysis correcting for repeated measurements. Seven patients had OAA/S scores of 1 or 2 while receiving 67% N_2O; the other patients only had OAA/S scores of 3, 4, or 5. AEP index was compared among the different OAA/S scores by the Friedman test, followed by the Wilcoxon signed-rank test as a post hoc analysis. The criterion for rejection of the null hypothesis was $P < 0.05$. All statistical analyses were performed using SPSS software (version 11.0; Michigan, IL, USA).

Results

Five patients were unable to tolerate the face mask at an N_2O concentration of 67% because of abnormal excitatory and violent behavior. Another 11 patients had nausea or vomiting during 50% or 67% N_2O administration. Data from these 16 individuals were excluded from the final analysis. The 29 other patients tolerated the study protocol well, and the study was conducted without major deviations from the protocol. None of the patients had clinically relevant hypotension or bradycardia requiring the administration of ephedrine. Table 2 summarizes patients' characteristics, duration of surgery, doses of local anesthetics used, and sensory block height 15 min after spinal anesthesia, which began to recede before the patients were returned to the ward.

Table 2 Patient characteristics and anesthetic data

Characteristic	Data
Age (years)	62.9 ± 14.5
Weight (kg)	63.1 ± 12.1
Sex (M/F)	16/13
ASA physical status (I/II)	5/24
Administered dose of 0.5% bupivacaine (mg)	16.3 ± 2.4
Duration of surgery (min)	91.6 ± 38.9
Level of sensory block	T8 (T5–T11)

Data are shown as the mean ± SD or median (range)

ASA American Society of Anesthesiologists

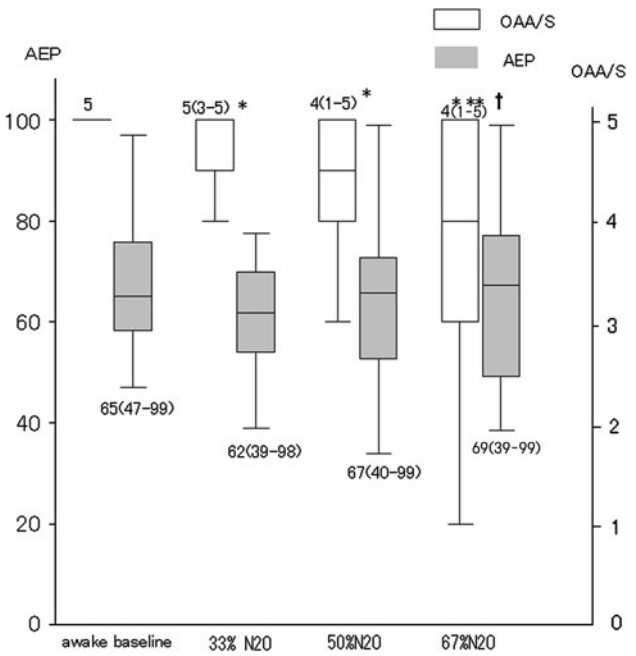

Fig. 1 The auditory evoked potential (AEP) index and observer's assessment of alertness and sedation (OAA/S) scores at the awake baseline [before nitrous oxide (N_2O) administration] and during breathing various concentrations of N_2O. *Box plots* show the median and 25th and 75th percentiles (*box boundaries*) and 10th and 90th percentiles (*whiskers*). $^*P < 0.01$ versus awake baseline, $^{**}P < 0.01$ versus N_2O 33%, $^{\dagger}P < 0.01$ versus N_2O 50%, $^{\ddagger}P < 0.01$ versus N_2O 67%

Figure 1 shows the AEP index at baseline and at each N_2O concentration studied. As the N_2O concentration increased, the OAA/S scores decreased significantly, with no significant changes in the AEP index.

Figure 2 shows the AEP index plotted against the OAA/S score. At an end-tidal concentration of 67% N_2O, OAA/S

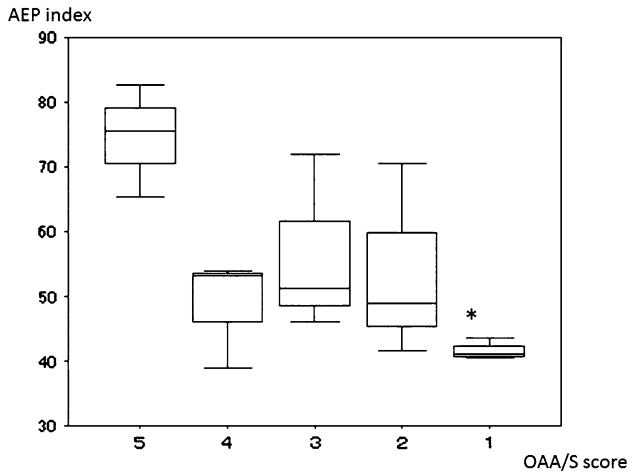

Fig. 2 Distribution of auditory evoked potential (AEP) index plotted against observer's assessments of alertness and sedation (OAA/S) scores during nitrous oxide (N_2O) sedation. Values are median (*line across the box*) and 25th and 75th percentiles (*box boundaries*) and 10th and 90th percentiles (*whiskers*). *$P < 0.05$ versus OAA/S scores 2, 3, 4, and 5

scores of 1 and 2 were observed in only two and five patients, respectively. The median AEP index significantly decreased from 74.5 (range 65.3–82.6) at an OAA/S score of 5 to 41.7 (range 40.6–43.6) at an OAA/S score of 1.

Discussion

Our study showed that: (1) increasing N_2O concentration to 67% produced the expected decrease in OAA/S score but no change in the AEP index; (2) a decrease in the OAA/S score from 5 to 1 was associated with a significant decrease in AEP index to the level indicative of moderate sedation. The first finding is consistent with the results of Sebel et al. [11], who reported that the administration of 50% N_2O to healthy volunteers did not alter brain stem AEP, and Goto et al. [6], who found that 70% N_2O hardly affected the MLAEP, even at concentrations producing unresponsiveness. On the other hand, several studies [12, 13] demonstrated an amplitude decrement in late-latency AEP with N_2O administration alone. The AEP index is simply calculated from the amplitude difference between successive 0.56-ms segments of MLAEP waveforms [14], which reflect the degree of curvature of the AEP. Because the AEP index is a MLAEP parameter, our results do not appear to be inconsistent with those of previous studies. To our knowledge, the use of AEP monitoring during N_2O administration alone has not been reported previously.

Several mechanisms may account for the lack of an apparent effect of 67% N_2O on the AEP index. First, the degree of hypnosis was simply insufficient to produce any decrease in the AEP index in our study. The maximum concentration of N_2O used in the study was only marginally higher than the minimum alveolar anesthetic concentration (MAC)-awake of N_2O (0.64 MAC, 66%) [15]. In fact, only seven patients had OAA/S scores of 1 or 2 during the administration of 67% N_2O, which means that most patients responded only to repeated and loud commands, but had not completely lost consciousness as defined by an OAA/S score of 2. Large variability and overlap in the AEP index at light hypnosis associated with OAA/S scores of 3, 4, or 5 during N_2O sedation alone would make differentiation of these anesthetic depths difficult.

Second, N_2O as a sole agent tends to activate the EEG: it increases EEG spectral power in the high beta (40–50 Hz) frequency range [5] and produces fast oscillatory activity (FOA) with frequencies as high as 35 Hz [16]. In contrast, N_2O in combination with another volatile anesthetic slows the EEG [17].The AEP index simplifies interpretation of MLAEP waveforms, which computer techniques extract from the underlying spontaneous EEG. Therefore, the AEP index may reflect the activated EEG in response to N_2O alone and would change minimally.

The third plausible mechanism for the lack of an apparent effect of 67% N_2O on the AEP index is related to regional distribution of cerebral metabolic rate. N_2O exerts a highly region-specific effect on cerebral metabolic rate, leaving the primary auditory cortex relatively unaffected [18]. The MLAEP generated as auditory signals are transmitted through the primary auditory cortex. This notion is supported by a previous study in which N_2O-induced FOA was mediated at the thalamic level [16]. In contrast, inhalation anesthetics, such as isoflurane and sevoflurane, potently suppress metabolic activity in the entire brain, including the primary auditory cortex [19, 20], and may have effects on the AEP index.

Our study had several limitations. First, we studied variables considered to be free of artifacts arising from EEG, background noises, and patient movements. Nonetheless, some variables might still have been affected by artifacts. However, such confounding factors are difficult to control in an operating room, and the study objective was to assess the usefulness of the AEP index in the clinical situation. None of the patients in this study were given ephedrine, which has been reported to cross the blood–brain barrier and act indirectly by releasing endogenous norepinephrine, potentially affecting the results of AEP monitoring [21]. Second, several studies have shown that patients appear drowsy during spinal anesthesia depending on the peak block height, without uses of sedations [22]. Possible mechanisms for this trend are the rostral spread of local anesthetics or decreased reticular activating system activity caused by interruption of afferent input. We administered N_2O 15–20 min after the installation of spinal anesthesia, and the levels of sensory blockade were around

T8 at the highest. Although the onset time of peak sensory block with plain bupivacaine is 45 min [23], and spinal anesthesia itself might have affected the study results, the sedation/hypnosis associated with spinal anesthesia does not alter the EEG enough to decrease the AEP index. The third limitation was that patients free of moderate or severe hearing impairment during ordinary conversation did not undergo conductive hearing tests. Conductive hearing loss, in which the auditory trigger is not transmitted via the auditory pathway, might have reduced AEP amplitude. The final limitation was that selection bias might have occurred. This potential is based on the fact that 16 of 45 patients were excluded from the study due to protocol deviators. The sole use of 67% N_2O for sedation during spinal anesthesia [4] is not appropriate, and procedures for sedating patients should be reconsidered in future studies.

In summary, the use of 67% N_2O alone had little effect on the AEP index, whereas the OAA/S scores were significantly reduced. Although the OAA/S score was 1 or 2 in two and five patients, respectively, a reduction in the OAS/S from 5 to 1 was associated with a significant decrease in the AEP index, indicating moderate sedation. These results suggest that the AEP index may not be suitable for assessing light hypnosis induced by N_2O alone. Further studies are required to evaluate the effect of N_2O alone on the AEP index in patients with clinically significant hypnosis.

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References

1. Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil. Anesthesiology. 1997;86:836–47.
2. Liu J, Singh H, White PF. Electroencephalographic bispectral index correlates with intraoperative recall and depth of propofol-induced sedation. Anesth Analg. 1997;84:185–9.
3. Kearse L, Ronsow C, Zaslavsky A, Connors P, Dershwitz M, Denman W. Bispectral analysis of the encephalogram predicts conscious processing of information during propofol sedation and hypnosis. Anesthesiology. 1998;88:25–34.
4. Kyung SP, Eun JH, Kyung WH, Ho YK, Tae HH. Bispectral index does not correlate with observer assessment of alertness and sedation scores during 0.5% bupivacaine epidural anesthesia with nitrous oxide sedation. Anesth Analg. 2006;104:385–9.
5. Rampil IJ, Kim JS, Lenhardt R, Negishi C, Sessler D. Bispectral EEG index during nitrous oxide administration. Anesthesiology. 1998;89:671–7.
6. Goto T, Nakata Y, Hayato S, Ishiguro Y, Nimi Y, Morita S. The midlatency auditory evoked potentials predict responsiveness to verbal commands in patients emerging from anesthesia with xenon, isoflurane, and sevoflurane but not with nitrous oxide. Anesthesiology. 2001;94:782–9.
7. Smith WD, Dutton RC, Smith NT. Measurement the performance of anesthetic depth indicators. Anesthesiology. 1996;84:38–51.
8. Schraag S, Bothner U, Gajraj R, Kenny GNC, Georgieff M. The performance of electroencephalogram bispectral index and auditory evoked potential index to predict loss of consciousness during propofol infusion. Anesth Analg. 1999;89:1311–5.
9. Doi M, Gajraj RJ, Mantzaridis H, Kenney GNC. Relationship between calculated blood concentration of propofol and electrophysiological variables during emergence from anaesthesia: A comparison of bispectral index, spectral edge frequency, median frequency and auditory evoked potential index. Br J Anaesth. 1997;78:180–4.
10. Kurita T, Doi M, Katoh T, et al. Auditory evoked potential index predicts the depth of sedation and movement in response to skin incision during sevoflurane anesthesia. Anesthesiology. 2001; 95:364–70.
11. Sebel PS, Flynn PJ, Ingram DA. Effect of nitrous oxide on visual, auditory and somatosensory evoked potentials. Br J Anesth. 1984;56:1403–7.
12. Houston HG, Mcclelland RJ, Fenwick PBC. Effect of nitrous oxide on auditory cortical evoked potentials and subjective thresholds. Br J Anaesth. 1988;61:606–10.
13. Timsit-Berthier M, Mantanus H, Dethier D, Hans D, Lamy M, Niethammer T, Pozzessere G. Quantified EEG and CNV changes during inhalation of nitrous oxide. Rev Electroencephalogr Neurophysiol Clin. 1982;12:259–67.
14. Mantzaridis H, Kenny GN. Auditory evoked potential index: a quantitative measure of changes in auditory evoked potentials during general anaesthesia. Anaesthesia. 1997;52:1030–6.
15. Dwyer R, Bennett HL, Eager EI, Heilbron D. Effects of isoflurane and nitrous oxide in subanesthetic concentrations on memory and responsiveness in volunteers. Anesthesiology. 1992;77:888–98.
16. Yamamura T, Fukuda M, Takeya H, Goto Y, Furukawa K. Fast oscillatory EEG activity induced by analgesic concentrations of nitrous oxide in man. Anesth Analg. 1981;60:283–8.
17. Yli-Hankala A. The effect of nitrous oxide in EEG spectral power during halothane and isoflurane anaesthesia. Acta Anaesthesiol Scand. 1990;34:579–84.
18. Crosby G, Crane AM, Sokoloff L. A comparison of local rates of glucose utilization in spinal cord and brain in conscious and nitrous oxide- or pentobarbital-treated rats. Anesthesiology. 1984;61:434–8.
19. Akire MT, Haler RJ, Shah NK, Anderson CT. Positron emission tomography study of regional cerebral metabolism in humans during isoflurane anesthesia. Anesthesiology. 1997;86:549–57.
20. Artru AA, Lam AM, Johnson JO, Sperry RJ. Intracranial pressure, middle cerebral artery flow velocity, and plasma inorganic fluoride concentrations in neurosurgical patients receiving sevoflurane or isoflurane. Anesth Analg. 1997;85:587–92.
21. Ishiyama T, Oguchi T, Tetsuya I, Matsukawa T, Kashimoto S, Kumazawa T. Ephedrine, but not phenylephrine, increase bispectral index values during combined general and epidural anesthesia. Anesth Analg. 2003;97:780–4.
22. Gentili M, Chau Huu P, Enel D, Hollande J, Bonnet F. Sedation depends on the level of sensory block induced by spinal anaesthesia. Br J Anaesth. 1998;81:970–1.
23. Higuch H, Hirata J, Adachi Y, Kazama T. Influence of lumbosacral cerebrospinal fluid density velocity, and volume on extent and duration of plain bupivacaine spinal anesthesia. Anesthesiology. 2004;100:106–14.