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Auditory stimuli as a contributor to consciousness while under general anesthesia

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ABSTRACT

Background: The incidence of intraoperative awareness under general anesthesia approaches 1% in high-risk patients. Anesthesiologists commonly utilize processed electroencephalograms (EEG) in order to monitor "depth" of anesthesia, the most common of which is the Bispectral Index (BIS). The B-aware and B-Unaware trials, which were designed to test the efficacy of the BIS monitor, noted an auditory component in 16 of 17 confirmed cases of intraoperative awareness. Implicit auditory memory formation has been documented under general anesthesia. Small studies have documented a significant effect of noise on BIS scores during monitored anesthesia care.

Methods: Twenty-two patients undergoing general anesthesia received earplugs after the induction of anesthesia. Every ten minutes the earplugs were reinserted or removed. Noise levels were recorded every 0.125 s and both average and maximal BIS scores were recorded every minute. Non-parametric analysis of both populations (with and without earplugs) was performed. A mixed effects model with one degree of freedom (with and without earplugs) was generated to take into account the effect of anesthetic agents on BIS scores.

Results: 3009 min of data were recorded. The median and range (25–75%) BIS scores were 39 (29–46) and 39 (28–44) with and without earplugs in place, respectively. Earplugs were associated with lower BIS scores ($p = 0.0183$). The mixed effects model confirmed this relationship ($p < 0.001$). Subgroup analysis of BIS scores in which the potential for awareness existed (maximum BIS > 60 in any one minute epoch) showed a 32% reduction in the incidence of maximal BIS scores exceeding 60 ($p = 0.0012$). There was no relationship between ambient noise level and average maximal BIS score ($R^2 = 0.003$).

Conclusions: Our study suggests that earplugs may reduce the incidence of BIS scores >60 in patients undergoing total intravenous anesthesia and that auditory stimuli may affect EEG interpretation. Because of the low cost and safety of noise reduction, as well as the catastrophic implications of intraoperative awareness, further studies to explore the effects of auditory stimuli on awareness and anesthesia are warranted.

Introduction

One of the major objectives of general anesthesia – the achievement of unconsciousness – is the most difficult to monitor. While blood pressure, heart rate, and oxygenation have been monitored in various forms for over one hundred years, there has not, until recently, been a practical means of actually monitoring the state of the brain during anesthesia. Traditional means of gauging anesthetic depth focused on the ability to predict patient movement, which is thought to be spinally-mediated [1–4], and not memory development during anesthesia and surgery. While the overall incidence of intraoperative awareness is low, it may approach 1% in "high risk" environments [5–7]. The psychological ramifications of awareness can be severe [8–12], with up to 70% of patients displaying the criteria for post-traumatic stress disorder postoperatively [13].

Thus, there has been significant interest in the development of novel methods for the anesthesiologist to monitor for and prevent intraoperative awareness. The advent of *processed* electroencephalography (EEG) monitoring, in which both open-source and proprietary algorithms are utilized to (a) process EEG waveforms and (b) derive a number related to the "depth" of anesthesia (or the probability of awareness), allowed anesthesiologists to measure anesthetic depth during surgery.

The most widely used processed EEG monitor is the Bispectral Index (BIS, Covidien, Mansfield, MA) monitor, which reduces EEG signals from three left frontal leads to a single number that is statistically correlated with an increased likelihood of awareness [14]. The B-Aware trial, a large ($n = 2463$), prospective, randomized trial suggested that a BIS range of 41–60 may reduce the incidence of intraoperative awareness in "high risk" patients [5], although the

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more recent B-Unaware [15] (n = 1941) and BAG-RECALL [16] (n = 5713) trials did not confirm these results.

Interestingly, in the B-Aware [5] and B-Unaware [15] trials, an auditory component was noted in 16 of 17 confirmed cases of awareness (four of which were exclusively auditory in nature) [5,15]. The nature of awareness was not reported in the BAG-RECALL study. The formation of implicit auditory memories has been well-documented in patients under general anesthesia with BIS scores in ranges traditionally associated with general anesthesia (41–60) [17,18], and BIS scores have been associated with the incidence of recall during sedation [19]. Nevertheless, the effects of noise reduction on BIS scores have not been specifically evaluated in patients undergoing general anesthesia.

We hypothesize that auditory stimuli are a major component of both consciousness and, more relevantly, memory formation in the setting of anesthesia. The purpose of this manuscript is to evaluate the evidence to support this hypothesis as well as to present pilot data collected at our institution designed to preliminarily test this hypothesis.

The hypothesis and theory

Auditory stimuli and current anesthetic practice

Current anesthetic practice completely ignores the possibility that auditory stimuli may play a role in anesthetic depth and/or the probability of memory formation. By contrast, a multitude of variables, some of which are obvious (age, level of surgical stimulation), and some of which are not obvious (use of particular vasopressor medications [20], whether or not one is pregnant [21], and even the color of one's hair [22]) have been shown to be related to anesthetic depth. Thus, while anesthesiologists typically take into account such factors as patient age, level of surgical stimulation, intraoperative use of analgesia agents in their efforts to titrate anesthetic agents, auditory stimuli are not measured, nor accounted for.

Auditory stimuli in sedation and general anesthesia

In 1997, Pearson et al. examined the effect of earplugs on BIS scores in five sedated critically-ill patients and found no effect [23]. In a subsequent study by Kim et al., 30 patients were sedated to a predetermined value (BIS 75 or BIS 80). Background noise was then added at graded intervals – BIS values at 80 dB were higher than at 50 dB [24]. Kang et al. randomized 63 patients to silence, music, or noise (up to 81 dB) and showed BIS increases of 8 points at noise levels of 80 dB or more [25]. More recently, Tharahirunchot et al. showed that the use of earplugs during lithotripsy reduced the amount of propofol required to maintain moderate, BIS-guided sedation [26].

The high incidence of an auditory component of awareness under general anesthesia (89% of definite cases of awareness from the B-Aware and B-Unware trials) is not surprising: brainstem auditory potentials are notoriously resistant to the effects of anesthesia, and can be used for intraoperative neuromonitoring despite complete anesthesia [27]. Not all components of the auditory nervous system are resistant to the effects of anesthesia – mid-latency auditory evoked potentials (MLAEPs) can be reduced by anesthetic agents [28–30], and MLAEPs have been shown to correlate with BIS scores [31].

Implicit memory formation

Most awareness trials focus on *explicit* memory (recognition and recall). Higher BIS values have also been implicated in the formation of implicit memories (recognition only). In a non-randomized study in which patients received headphones during general anesthesia with BIS monitoring, implicit memory formation was noted in patients who were kept within a BIS range of 41–60, but not those kept between 21 and 40 [18]. A randomized study comparing BIS-guided (goal 50–60) versus end-tidal anesthetic gas (ETAG) concentration-guided anesthesia in 128 patients anesthetized with sevoflurane showed no difference in the ability of patients to recall fifteen words read to them while under general anesthesia. When asked to recognize these words, as well as distinguish them from distracters, the BIS >50 group was significantly better at recognizing words read to them than the ETAG-guided group (37.1% vs. 31.5% hit rate, p = 0.001) [32].

Empirical data

Data collection

After Institutional Review Board approval was obtained, twenty-two patients receiving general anesthesia for spinal neurosurgical procedures were consented for this study. All patients received continuous infusions of propofol and an opioid (sufentanil or remifentanil) as their primary anesthetic, with other intravenous medications (e.g., lidocaine) administered at the discretion of the neuroanesthesiologist. No patient received volatile anesthesia.

For each case, a Tenma DT-8851 industrial noise level meter (Tenma, Springboro, OH; accurate to 0.1 dB) was placed on the top of the anesthesia machine and programmed to record the average and maximal ambient noise levels every 0.125 s. The internal clocks of both the BIS monitor and the Tenma sound recording software were synchronized.

Upon entering the operating room, monitoring via a BIS VISTA™ (platform version 2.03, application version 3.00) monitor was initiated and recording from the Tenma DT-8851 sound meter commenced. Following induction of anesthesia and positioning, Flent's Quiet! Please earplugs (Apothecary Products, Inc., Burnsville, MN; Model number 68,002; noise reduction rating −29 dB) were placed in the subjects' ears. Every ten minutes earplugs were either removed (if in place) or replaced (if not in place). Average and maximum BIS scores were recorded every minute. Recordings continued until the completion of surgery; however, data from the last 30 min of anesthesia (assumed to be a period of progressively reduced anesthesia) were not included in the final analysis.

A study coordinator was present for the entire anesthetic in all 22 cases. The BIS monitor was not hidden from the anesthesia provider, as BIS monitoring is common practice during total intravenous anesthesia (TIVA) at our institution. No guidelines for anesthetic management, including goal BIS, were required by the study protocol.

Data analysis

For the purposes of statistical analysis, BIS scores, which are complex in derivation, were treated as ordinal variables. Thus, initial comparisons between groups were made using medians and ranges, comparisons between populations were made using the Kolmogorov–Smirnov test, and comparisons between groups using arbitrary cutoffs (range of 5) were made using the Z-test. Comparisons between groups in the range of potential awareness were made using the Wald–Wolfowitz runs test. Univariate paired tests comparing BIS scores with and without earplugs was made using the Mann–Whitney U-test.

A secondary analysis was performed using NONMEM software (version 6.2.0, ICON Development Solutions, Ellicott City, MD) with