## Analgesia & Resuscitation: Current Research

**Research Article**

# The Effect of Propofol Injection Pain on Auditory Evoked Potential Index and Bispectral Index

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## Abstract

**Background:** The electroencephalogram (EEG) methods are being used widely, to monitor of the depth of awareness. Among them, auditory evoked potential (AEP index) and the bispectral index (BIS) were adopted as specific EEG methods in many clinics. We evaluated the effect of propofol injection pain on AEP index and BIS in mildly sedated patients with midazolam who undergo general anesthesia.

**Methods:** 38 patients (18 to 65 age, ASA I or II grade) were separated in two groups randomly (group AEP and group BIS). Atropine 0.5 mg and midazolam 0.05 mg/kg were intramuscular injected as a premedication before going to operating room. Anesthesia was induced with propofol by target-controlled infusion. We had checked AEP index and BIS every 10 s till 90 s after propofol injection began.

**Results:** With propofol injection pain, BIS was not increased, but decreased at 70, 80 and 90 s. Whereas AEP index was increased significantly at 30, 40 and 50 s, and decreased significantly after that.

**Conclusions:** AEP index is more sensitive and reliable method to monitor depth of awareness during anesthesia induction phase in real time.

**Keywords:** Anesthesia; Propofol injection pain; Consciousness monitors; Auditory evoked potential; Bispectral index monitor

## Introduction

Recently, devices such as bispectral index (BIS), auditory evoked potential index (AEP), and EEG-entropy are utilized in clinic for evaluate depth of anesthesia and sedation. Among them, BIS, was known as useful brain function monitor device for evaluate patients' awareness, depth of anesthesia and sedation by digital numerical value that converted from analyzed some analog electroencephalogram (EEG) by databases [1].

AEP, a relatively modern approach, is capable of measuring auditory evoked potential EEG, especially middle latency auditory evoked potential (MLAEP). Moreover, there have been reports that AEP monitoring seems to be more efficient by using autoregressive model (ARX model) while BIS needs the information from the database, which results in less time delay [2].

BIS and AEP scores are decreased when patient's anxiety is alleviated by minimal sedation using midazolam as a premedication. Hence, in this study, we wanted to find out whether the change of level of consciousness triggered by pain from propofol injection has an effect on BIS and AEP scores in patients who undergo general anesthesia with midazolam premedication.

## Methods

Before conducting this survey, we had obtained approval from IRB. We registered 38 patients who were planned to have surgery under general anesthesia, at age 18 to 65 and classified as ASA 1 or 2 with informed consents. Patients had been excluded by following criteria in this study: history of cardiovascular disease such as hypertension; taking medicine that affect cardiovascular system; heart rate in the operating room was lower than 45 beats per minute or higher than 100 beats per minute; history of hearing disease or auditory disorder. The demographic factors such as age, sex, weight and height showed statistically no significant difference between each group (Table 1).

| | Group BIS (n = 19) | Group AEP (n = 19) |
|---|---|---|
| Age (years) | 35.6 (12.2) | 33.5 ± 11.8 |
| Sex (M/F) | 10/9 | 12/7 |
| Weight (kg) | 64.3 ± 12.4 | 67.4 ± 11.8 |
| Height (cm) | 163.3 ± 9.5 | 166.1 ± 8.5 |

Values are mean (SD). There were no significant differences between the groups. Group BIS: Bispectral Index Group; Group AEP: Auditory Evoked Potential index group.

**Table 1:** Patient characteristics.

All patients were received pre-medication with atropine 0.5 mg and midazolam 0.05 mg/kg at the bedside, before moved to operating room. Noninvasive blood pressure monitor, electrocardiogram, and pulse oximetry were used for monitoring the vital signs. In the group monitored by BIS (group BIS), BIS sensor was attached on patient's forehead and connected to BIS monitoring (A-2000®, software version 3.3, Aspect Medical Systems, USA). In the group monitored by AEP (group AEP), positive pole sensor was attached at forehead center and reference sensor was attached to the 1 cm right side from positive pole sensor, and negative pole sensor was placed on the right mastoid process eminence. Then, the sound of 70 decibel intensity and 7 hertz frequency was conducted to both ears by earphones. AEP sensors and earphones were connected to AEP monitoring (aepEX Plus®, software version 4.6, Medical Device Management, UK).

To measure the pain equally, all patients had 18 gauge intravenous catheters on the dorsum of the left hand. We recorded baseline values of BIS, AEP, mean arterial pressure and heart rate, in each group after patients had taken a rest closing eyes in quiet operating room. Infusion of propofol (Fresofol 2%®, Fresenius Kabi, Austria) was started as 6 /ml target concentration with using Schneider pharmacokinetics model [3,4] by target controlled infuser(Orchestra®, Fresenius Vial, France). In group BIS, BIS scoring were recorded every 10 s during 90 s of

propofol injection. Likewise, in group AEP, AEP scoring was recorded every 10 s Heart rate, mean arterial pressure and total volume of propofol infusion were recorded in the same manner.

We had calculated sample size as 19 patients to obtain more than 20% mean difference between BIS and AEP in 10 standard deviation or less, 90% statistical power and 0.05 value α (type 1 error), by conducting pilot study on 10 patients.

Statistical test was performed by SigmaStat® (version 3.5, Systat Software Inc., USA). All measurements were expressed by mean ± standard deviation. 'Unpaired t-test' and 'chi-square test' were used to compare ages, weight, height and sex. 'Paired t-test' was done to compare mean arterial pressure and heart rate in each group, and 'repeated measured ANOVA' was performed to compare BIS and AEP in each group. Turkey test for post hoc analysis was performed, and it was considered statistically significant when p-value is lesser than 0.05.

## Results

Total propofol infusion volume was 1.6 ± 0.4 mg/kg. Mean arterial pressure was increased significantly, 90 s after propofol infusion, compared to the baseline while no significant change was observed in heart rate (Table 2).

| | | Group BIS | Group AEP |
|---|---|---|---|
| Preinduction | MAP | 91.4 (9.2) | 83.2 ± 8.6 |
| | HR | 69.7 ± 11.2 | 67.6 ± 11.5 |
| 90 s after propofol injection | MAP | 90.9 ± 8.9* | 84.4 ± 9.0* |
| | HR | 70.2 ± 10.3 | 67.4 ± 12.4 |
| Values are mean ± SD; MAP: Mean Arterial Pressure; HR: Heart Rate; *: P<0.05 compared with preinduction values. | | | |

**Table 2:** The changes of mean arterial pressure (mmHg) and heart rate (beats per minute).

BIS scoring was not increased significantly and only decreased to 53.8 ± 19.5 in 70 s and 43.4 ± 11.2 in 80 s after propofol infusion compared to 87.0 ± 7.2 as the baseline score.

On the other hand, AEP scoring showed significant increment to 62.9 ± 9.4 in 20 seconds, 64.2 ± 8.3 in 30 s and 64.4 ± 8.4 in 40 s after propofol infusion when compared with the baseline AEP score of 55.2 ± 9.1. Then, AEP score was declined to 48.1 ± 10.1 in 60 s, 46.9 ± 7.9 in 70 s, 44.2 ± 6.8 in 80 s and 41.5 ± 6.1 in 90 s after propofol infusion.

## Discussion

Recently, monitoring devices such as BIS, AEP, Entropy have been developed and widely used as being raised issues on the reliability of traditional method to evaluate the proper depth of sedation and anesthesia by measuring clinical signs such as pupil size, arterial blood pressure, heart rate or patient's motion. Furthermore, advancement of neuromuscular blocking agent made it more important [5]. Ideas that the electrical activity derived from central nervous system is not influenced by neuromuscular blocking agent and even shows proportional correlation to the amount of anesthetic agent and concept considering non-invasive, more time-efficient method as an ideal monitoring device led to investigation of this monitoring tools [6].

BIS and AEP is useful devices for distinguish awareness and anesthetic state. AEP is more sensitive to distinguish awakening from unconsciousness. On the other hand, BIS score is increased progressively after the finish of anesthesia, but rather useful to monitor sedation state, and to predict the recovery from anesthetized status after operation [7].

BIS, widely used in clinic, has get as numbers between 0 to 100 per minute by calculating mean of past 60 to 15 s with measuring 2 s earlier EEG of frontal lobe per 0.5 s using 4 sensors [8].

AEP is a relatively up-to-date method of monitoring, which consists of 3 evoked potentials, brain stem auditory evoked potential (BAEP), middle latency auditory evoked potential (MLAEP) and long latency auditory evoked potential (LLAEP), produced by auditory stimuli transferred from cochlea to cerebral cortex. Middle latency auditory evoked potential (MLAEP), which is the most closely related with the degree of hypnosis during anesthesia and associated with first response of cerebral cortex, is analyzed [6,8].

There are two ways to calculate AEP. MTA (moving time average) is a classic method to transfer changes of each signal every 3 min requires 36.9 s for response time delay to calculate mean of 256 currents during 0.144 s. The method above was too slow to sense fast transforming AEP. Therefore, ARX model (autoregressive model with exogenous input) have been developed for faster extraction of AEP with the fewer currents [6,9]. The device which was designed by this manner was called 'A-line ARX index' and the AEP displayed was called A-line® monitor (Danmeter A/S, Odense, Denmark), and the MLAEP which was aroused by auditory stimulation of 65~70 dB intensity and 9 Hz frequency from earphones in both ear, is analyzed by total three sensors including forehead center, left forehead and mastoid process. Like BIS, AEP was expressed as value from 0 to 100. And the value means arousal state at 100 ~ 60, drowsy state at 59 ~ 40, light anesthesia state at 39 ~30, and adequate anesthesia state for surgery below 29 [7]. The advantage of this method is that it is able to monitor closely in real time at operating room by shortening response latency as 2 to 6 s with using just 15 currents [2,10].

Lee et al. [2] evaluated clinical efficacy by comparing latency of both monitoring devices when strong stimuli such as endotracheal intubation was delivered. So they verified that, ARX index is more sensitive than BIS. Also, Nishiyama et al. [11] revealed that ARX index is more sensitive to measure depth of anesthesia than BIS, in state of inhalation anesthesia with sevoflurane/nitrous oxide. Urhoren et al. [6] identified ARX index is significantly increased by intubation rather MTA method by comparing the latency of response time.

## Conclusion

In this study, we had observed, effects of propofol injection pain on the change of awareness, closely, in the patients who were mildly sedated with midazolam premedication. And, we divided patients into BIS monitoring group (group BIS) and AEP monitoring group (group AEP), on the basis of report by nishiyama et al. [12] suggested that, auditory stimulations by AEP monitoring device could temporarily raise 'BIS'. Then, we evaluated significance of aepEX Plus®, one of ARX model, which was recently developed, and BIS in viewpoint of response latency.

As a result, BIS did not increase significantly with response to propofol infusion pain, but just decreased significantly due to loss of conscious, in 70 s after propofol infusion. However, in case of ARX

index, it had been increased significantly in 20 s, 30 s, and 40 s, after propofol infusion, and decreased significantly in 60 s, 70 s, 80 s, and 90 s, after propofol infusion. Therefore, in this study, sensitivity for conversion of conscious in 'AEP' was better than in BIS.

In conclusion, minor alteration of mental status by mild stimuli such as propofol infusion pain in light sedated patient can be detected more sensitively and more efficiently by ARX index than BIS and AEP showed superiority to BIS in the aspect of monitoring the depth of anesthesia in real time.

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