Relationship between Bispectral Index, Sedation Score and Plasma Concentration, during Midazolam Sedation

Eun Jin Park, Hyun-Jeong Kim, Chang-Joo Park*, Kwang-Won Yum

Department of Dental Anesthesiology, College of Dentistry, Seoul National University
*Department of Oral and Maxillofacial Surgery, College of Dentistry, Seoul National University

Abstract

Midazolam을 이용한 진정법시 Bispectral Index, 진정점수, 그리고 midazolam의 혈중 농도 사이의 관계

박은진, 김현정, 박정주*, 염광원
서울대학교 치과대학 치과마취학교실, *서울대학교 치과대학 구강악민의과학학교실

연구배경: 임상적으로 진정법을 시행할 경우 화자의 상태에 대한 접근은 매우 중요하다. 화자의 인지에 대한 마취의 영향을 측정하기 위해 개발된 Bispectral Index (BIS)는 화자의 인지의 변화를 반영하지 않고 객관적인 진정정도를 평가할 수 있다. 그러나 이는 항상 진정 깊이의 임상적인 측도와는 일직하지 않는다. 이로 인해 연구에서는 진정법 시행 시 화자의 진정 정도를 측정하기 위한 BIS의 유용성을 검증하기 위하여 BIS, 진정점수, 그리고 midazolam의 혈중 농도와의 관계를 연구하였다.

방법: 25명의 건강한 성인 자원자들을 대상으로 무의식적 유도하기 위하여 midazolam 0.08 mg/kg을 정맥으로 주입하였으며 화자의 의식 상태를 진정 중 화차시까지 관찰하였다. BIS와 진정점수는 진정 전후, midazolam 두여 후 10, 20, 30분 간격으로 측정하였다. Midazolam의 혈중 농도는 주입 후 10분 경과 후에 정맥혈체취 후 HPLC를 이용하여 측정하였다. BIS는 BISTM monitor (Aspect Medical Systems, USA)으로 측정하였으며 또한 진정 정도는 진정 점수로도 평가하였다.

결과: BIS 수치는 진정점수와 유의한 상관관계를 보였다(r = 0.676, P < 0.05). 혈중 midazolam 농도가 감소함에 따라 혈중 농도는 진정점수와 유의한 상관관계를 보였다(r = -0.656). Midazolam 두여 후 10분에서 BIS 수치와 midazolam의 혈중 농도는 유의한 상관관계를 보이지 않았지만(r = 0.467) 진정 후 수치는 진정 전 수치와 명확히 구분되었다.

결론: BIS는 화자의 수면상태의 효과적인 측도로 알려져 있으며 진정점수와도 높은 상관관계를 보였다. 그러나 항상 진정 깊이를 나타내는 임상적인 측도와는 일직하지 않았다. 그러므로 진정법 시험단계 BIS만을 사용하는 것은 더욱 많은 주의가 필요하며 예를 들어 진전 시간마다 다양한 진정점수 측정방법으로 화자의 의식을 감시하는 것이 추천된다. (JKDSA 2001; 1: 21~25)

Key Words: Bispectral index, sedation score, Plasma midazolam concentration, HPLC
INTRODUCTION

It is very important to assess of the patient's conscious levels during sedation. But up to now, there are no direct measuring methods of hypnotic state, so the indirect assessment of the hypnotic state is performed clinically by observing physiological signs and patient responsiveness to voice or touch. For example, sedation score systems, such as sedation score, sedation rating scale, and the Ramsay scale and the Modified Observer's Assessment of Alertness/Sedation Scale have been used. But it is of no use patients who are incapable of responding, and the stimulation for assessment itself may arouse the patient. Also subjective and spontaneous assessment have their own limitation.

Bispectral Index (BIS) is the EEG parameter to measure the effects of anesthetic agents on the patient's brain, which examines the relationships or "coupling" among the sine wave components. Specifically bispectral analysis quantifies the level of synchronization in the EEG, along with the traditional amplitude and frequency parameters. This provides better prediction of the awakening compared with conventional methods such as spectral edge frequency (SEF), median frequency, and auditory evoked potential index (Doi et al, 1997). Also, in the study of EEG measurement about the effect of alfentanil, propofol, and midazolam, BIS was the same or better predictor than spectral edge or delta power (Billard et al, 1997). But Stanski suggested several unsolved problems, including (1) lack of understanding of the effects of interactions of anesthetic drugs on the EEG, (2) inability to choose the most appropriate EEG parameters, and (3) lack of a gold standard of clinical drug effect for comparison (Stanski, 1990).

This study was designed to clearly define the relationship between clinical assessment of consciousness state after administration of midazolam and BIS, sedation score, and plasma drug concentration. By comparing these parameters, we verified the prediction accuracy of BBS.

PATIENTS AND METHODS

Twenty-five young, healthy, ASA PS 1 status subjects participated in this study. Informed written consent was obtained from all volunteers. All sessions were performed in a post anesthetic care unit, with airway management and cardiopulmonary resuscitation (CPR) equipment readily available.

An intravenous catheter placed in the left antecubital vein was used for midazolam administration and the other right antecubital intravenous route was used blood sampling. Heart rate, respiratory rate, automated non-invasive blood pressure, axillary skin temperature, end-tidal carbon dioxide tension (EtCO₂) and arterial oxyhemoglobin saturation (SpO₂) were monitored and oxygen, at a flow rate of 5 L/min, was supplied via face mask during study.

Ten minutes after stabilizing periods, we titrated midazolam intravenously to produce unconsciousness up to 0.08 mg/kg midazolam over two to three minutes. Blood

<table>
<thead>
<tr>
<th>Table 1. Sedation score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response</strong></td>
</tr>
<tr>
<td>Fully awake and oriented</td>
</tr>
<tr>
<td>Drowsy</td>
</tr>
<tr>
<td>Eyes closed but rousable to command</td>
</tr>
<tr>
<td>Eyes closed but rousable to mild physical stimulation</td>
</tr>
<tr>
<td>Eyes closed but unrousable to mild physical stimulation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. Demographic Data of Volunteer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sedation with midazolam</strong></td>
</tr>
<tr>
<td>Sex (M/F)</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>Dosage of midazolam (mg)</td>
</tr>
</tbody>
</table>
samples were used to collect samples for measurement of plasma midazolam concentration. The blood samples were immediately centrifuged with 2,500 rpm for 15 min and were stored at −20°C until assayed. Plasma midazolam concentrations were measured using high performance liquid chromatography (HPLC).

BIS were first measured using A-2000 BIS™ monitor (Aspect Medical Systems, USA) and then we measured sedation score (Table 1) to evaluate volunteer’s level of consciousness before and 10, 20 and 30 minutes after midazolam administration. To maintain the consistency, only one medical personnel engaged in assessment.

Each data has been analyzed statistically by multivariate ANOVA and correlation analysis (P < 0.05).

RESULTS

Table 2 shows the demographic distribution of participants. They had no known allergies to midazolam. There were no significant changes in heart rate, blood pressure, SpO₂, respiratory rate and body temperature during study. BIS and sedation score showed a significant decrease after midazolam administration are depicted in Fig. 1 and Fig. 2. The correlation between BIS and sedation score was shown in Fig. 3, which was measured before and at 10, 20, and 30 minutes after midazolam administration. They showed significant correlation between them (r = 0.676, P < 0.05).
Ten minutes after midazolam administration, plasma concentration was 0.59 ± 0.23 mg/ml, BIS and sedation score were 74.64 ± 7.41, 3.07 ± 0.62, respectively. Fig. 4 shows the relation among BIS, measured drug concentration, and sedation score at 10 minutes after midazolam administration.

With the decreased plasma concentration, the correlation was better with sedation score \( r = -0.656 \). Although BIS values did not accurately correspond to calculated plasma concentrations of midazolam \( r = 0.467, P < 0.05 \), BIS values after sedation were well distinguished from those before drug administration.

**DISCUSSION**

This study provides a quantitative comparison of the correlations among drug concentrations, BIS, and sedation score for midazolam. Results from this study show that there is significant correlation between BIS and sedation score. Even though correlation coefficient was not high \( r = 0.676, P < 0.05 \), it was statistically significant. The sedation score was expected to provide a good correlation with the critical evaluation of sedation and linear correlation between the observed clinical effect and the BIS value or drug concentration. By Smith et al, 1996, ordinal values obtained using a responsiveness rating scale may not allow a perfect linear relation between the observed effect and the measure of anesthetic depth. The good correlation between BIS and level of sedation, coupled with the excellent prediction probability values, supports the value of the BIS to monitor sedation depth and consciousness level.

Several previous reports have shown that BIS is useful predictor of patient response (Kearse et al, 1994; Vernon et al, 1995). It remains the possibility that clinician has complete dependence on BIS only. Because of individual variance and real gap between theoretical and clinical patient status, if one has excessive confidence to BIS, there may be some patient’s movement during control. Even though no specific action was needed and no patients reported awareness during the postoperative interview, there was a report about patient’s apneic state or movement (Mortier et al, 1998).

So, there is a limitation in using the BIS only, and various variables, which measure anesthetic depth, must be accompanied. Of course BIS can be used to predict recovery from anesthesia, it is possible to contribute to a faster recovery from anesthesia in outpatients (Flaishon et al, 1997; Song et al, 1997). But in case of operation that needs deep sedation, using several methods to measure the patient’s state with BIS is recommended.

Actually there are lots of study that aware of the disagreement of BIS (Sebel et al, 1995; Hall and Lockwood, 1998), BIS is less helpful when making comparison between patients or as a single value and it is dependent on the drug used in addition to depth of anesthesia. But as in our study, BIS is good predictor of movement in response to stimulation, it can be sufficiently used for checking the patient’s state more subjectively.

In the definition, the depth of anesthesia is composed of two anesthetic state (Prys-Roberts, 1987; Kissin, 1993); one is loss of consciousness and recall, implying inability to respond to a non-noxious stimulus or recall and the other is the obtundation of reflex responses to noxious stimulus. This supports the concept of the triad of anesthesia: 1) unconsciousness and lack of recall, 2) analgesia, and 3) muscle relaxation. But monitoring may only measure one of these components, clinical assessment of the state of consciousness is needed. It is very difficult and complex, so the use of several method, and comparing one with another is essential.

In conclusion, BIS is very useful predictor for recovery of consciousness, helpful for faster recovery, and decreases anesthetic dosage. But there is a limitation in using the BIS only, and various methods which measure anesthetic depth must be accompanied because of individual variety and the effect of drugs used to control the depth of anesthesia.

**REFERENCES**

Billard V, Gambus PL, Chamoun N, Stanski DR, Shafer SR: A comparison of spectral edge, delta power, and bispectral index as EEG measures of alfentanil, propofol,


