ORIGINAL ARTICLE

Is there an appropriate bispectral index for upper gastrointestinal endoscopy in spontaneous breathing in the pediatric patient?

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KEYWORDS
Bispectral index; Propofol; Upper gastrointestinal endoscopy; Spontaneous breathing; Pediatric anaesthesia; Patient safety

Abstract
Objective: The bispectral index (BIS) values that predict appropriate anaesthetic level to perform an upper gastrointestinal endoscopy in spontaneous breathing are not well established in Pediatrics. The objective of this study is to determine whether it is possible to find an appropriate, less profound, BIS level in the pediatric patient that would enable an upper gastrointestinal endoscopy (UGE) to be performed in spontaneous breathing without causing gag reflex or motor response.

Materials and methods: A prospective study was designed and included 61 patients from 12 to 167 months old, and an ASA I–II who needed a diagnostic UGE. The study was conducted from October 2011 to March 2013.

Intervention: UGE performed with an anaesthetic protocol using propofol. The vital signs measured were heart and respiratory rate, pulse oximetry, non-invasive blood pressure. The sedation level score (Ramsay scale) and BIS values were also measured. The first attempt was performed at BIS level 60–69, and this was not feasible, then the anaesthetic was deepened and a second attempt made at BIS level 50–59. If this was still not possible a deeper anaesthetic level was then achieved and a third attempt made at BIS level 45–49. Variables of interest were: effective BIS level (eBIS), BIS level at which UGE was performed without gag reflex or motor response; propofol total dose (mg·kg⁻¹), induction time (time from onset of sedation to effective start of UGE). A logistic regression analysis was performed to obtain an equation to estimate the possibility of UGE success.

Results: The distribution of the patient was: male 40%, female 60%, with 11 (18%) patients under 36 months. The statistical values are expressed as mean and standard deviation, with following results; age (months): 95.9 ± 45.86; weight (kg): 30.5 ± 14.68; effective BIS: 56.41 ± 4.63;


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¿Existe un valor de índice biespectral adecuado para endoscopias digestivas altas en respiración espontánea en el paciente pediátrico?

Resumen

Objetivo: Las cifras del índice biespectral (BIS) en las que un paciente está adecuadamente anestesiado para la realización de endoscopias digestivas altas (EDA) en respiración espontánea están por definir. Por ello se decide realizar este estudio, para determinar un nivel de BIS adecuado, lo menos profundo posible en el paciente pediátrico anestesiado, para la realización de EDA en respiración espontánea sin aparición de reflejo nauseoso y/o respuesta motora. Material y método: Se realizó un estudio prospectivo. La población de estudio fueron niños entre 12 y 167 meses, ASA-I-II, que precisaban EDA diagnóstica; se estudiaron un total de 61 pacientes. El periodo analizado fue de octubre de 2011 a marzo de 2013. Intervenciones: Realización de EDA aplicando protocolo de anestesia con propofol. La monitorización realizada fue: constantes vitales (frecuencia cardiaca, frecuencia respiratoria, saturación por pulsoximetría y presión arterial no invasiva), puntuación de la escala de Ramsay y valor del BIS. El primer intento de EDA se realizó con BIS 60-69; si no era posible, se procedía a profundización anestésica, realizando el segundo intento con valores del BIS 50-59; si tampoco era posible la realización de la EDA, se procedía de nuevo a profundización anestésica, realizando el tercer intento con BIS 45-49. Las variables de interés fueron: dosis total de propofol (mg kg⁻¹), tiempo de inducción (tiempo necesario desde el inicio de la administración de la anestesia hasta inicio de la EDA sin rechazo por parte del paciente), valor del BIS efectivo (BIsE) al inicio de la EDA. Se realizó una regresión logística para estimar la posibilidad de realización de EDA según el valor del BIS.

Resultados: Sesenta y un pacientes con la siguiente distribución: sexo masculino 40%, femenino 60%. Pacientes menores de 36 meses, 11 (18%); mayores, 50 (82%). Datos expresados como media y desviación típica. Edad (meses): 95,9 ± 45,86; peso (kg): 30,5 ± 14,68. BIS efectivo: 56,41 ± 4,63. Tiempo de inducción (min): 11,07 ± 2,69. Dosis de propofol total (por kg): 4,86 ± 1,21. Necesitaron bolo adicional de propofol 38 pacientes (62%); 7/38 (18%) por presencia de movimientos y 31/38 (82%) por aumento del BIS. No hubo diferencias significativas entre valor del BIsE por edades.

Conclusiones: En base a estos resultados se puede concluir que en la población pediátrica estudiada niveles de BIS menores de 59 predicen que sí es posible realizar la EDA con una sensibilidad del 72,13% y una especificidad del 88,06%.

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(0 indicating absence of brain activity, and 100 indicating that the patient is fully awake). This non-invasive method of measuring the level of activity in the cerebral cortex is now widely used. According to a Cochrane review from 2007, BIS reduced both incidence of intraoperative awareness and anaesthesia recovery time.

"Ideal" BIS values for general anaesthesia range from 45 to 55; however, few studies have been carried out in procedures performed under spontaneous breathing. This has prompted us to conduct a study to attempt to predict the lowest possible BIS index for the performance of this invasive technique.

Diagnostic pediatric esophagogastroduodenoscopy (EGD) must be performed on a collaborating patient; deep sedation is often needed to minimise discomfort, and the procedure can be performed under spontaneous breathing. Due to the nature of the surgery, the most critical time occurs during introduction of the endoscope, which may trigger a gag or cough reflex or cause the patient to move. These reflexes can be abolished with the use of anesthetic drugs. Intravenous delivery is best during EGD under spontaneous breathing.

Working hypothesis: There is a specific BIS value in an anaesthetised patient that can guarantee successful pediatric EGD under spontaneous breathing.

Primary objective: To study which BIS values in an anaesthetised patient allow EGD to be performed under spontaneous breathing.

Secondary objective: To estimate the propofol dose required to perform pediatric EGD under spontaneous breathing.

Patients and methods

This is a prospective study carried out in the Pediatric ICU unit of a hospital in Jaen, Spain. The study was approved by the hospital's Independent Ethics Committee, and conducted in accordance with the principals of the Helsinki Declaration. Authorisation was obtained from the parents of all study patients. The study was conducted from October 2011 to March 2013, and patients were included consecutively.

The reference population was the pediatric population (12–167 months) of the province of Jaen, Spain. Study patients were included and excluded on the basis of the following criteria: (1) inclusion criteria: aged over 12 months and under 168 months; scheduled for EGD; pathologies included were suspicion of celiac disease and dyspepsia. (2) Exclusion criteria: known neurologic deficit, kidney failure and/or liver disease; receiving anticonvulsant therapy; grade III or IV on the ASA anaesthesia risk scale; EGD to extract a foreign body; caustic ingestion; parents refuse to sign informed consent form.

Method

The following procedure was used for patients meeting the inclusion criteria: (1) pre-surgery laboratory studies were ordered to rule out impaired kidney or liver function and coagulopathy. If the results were normal, we proceeded to the next step. (2) The invasive procedure and the scientific study undertaken were explained to the child's parents/legal representatives, who were asked to sign an informed consent form. (3) The fasting patient was admitted to the Pediatric ICU. (4) Non-invasive monitoring (Siemens SC 7000, Draeger Medical Systems, USA) of heart rate, breathing rate, blood pressure and pulse oximetry was started. (5) The BIS sensor (BIS Vista monitor, BIS × 4 processing unit, BIS pediatric sensors, Aspect Medical Systems, USA) was placed in position and continuous monitoring started. (6) Initial and 3–5 min sedation level was measured on the Ramsay scale; the pain stimulus used was pressure on the nail bed. (7) Oxygen therapy (1–21/min) was delivered using nasal prongs. (8) Anaesthetics were delivered according to the following general anaesthesia protocol: fentanyl 1 µg/kg bolus, and propofol 2 mg/kg bolus in 2–3 min, followed by continuous perfusion of 4–5 mg/kg/h propofol; if deeper sedation was required, additional bolus of 0.5–1 mg/kg propofol was administered and/or perfusion rate was increased to 6–7 mg/kg/h, depending on the patient's response, until the correct BIS was reached. The first attempt at EGD was made at a BIS level of between 60 and 69. If the attempt was unsuccessful, anaesthesia was deepened to BIS level 50–59 and a second attempt was made. If this was also unsuccessful, anaesthesia was deepened further to BIS level 45–49 and a third attempt was made. The BIS level at which introduction of the endoscope was not rejected by the patient was called effective BIS (eBIS). After successful introduction of the endoscope, we attempted to maintain BIS at a stable level in all patients (±5 units with respect to eBIS). Drugs were administered as indicated. Dosing was calculated using the specifications of the Perfusor compact delivery system (Braun, Germany). During the procedure, the patient was monitored for adverse effects and complications such as hypotension (defined as arterial pressure below the 10th percentile for the child's age or weight), pulse oximetry saturation of less than 85%, allergic reaction to any of the anaesthesia drugs, gag reflex and emesis.

Study variables were grouped under two categories:

Dependent variables. Total dose of propofol delivered, indexed by patient weight (in mg kg⁻¹); time to awakening (time from conclusion of the invasive procedure to a Ramsay value of 2 or less) measured in minutes; BIS level (ranging from 0 to 100) at each attempted endoscopy: eBIS–level at which introduction of the endoscope was not rejected by the patient—and BIS level measured during the procedure; time of the different attempts to introduce the endoscope (measured in minutes from the start of anaesthesia induction), duration of anaesthesia induction (from the start of anaesthesia induction until effective start of the EGD procedure, in minutes).

Independent variables. Age, sex and weight of the patient, time (duration) of the invasive procedure, in minutes; level of sedation measured on the Ramsay scale: (1–6).

Statistical analysis consisted of a bivariate analysis to compare eBIS with the other variables using Pearson's correlation coefficient test. Logistic regression was used to determine the correlation between eBIS levels. Before performing regression, the bivariate correlation between EGD and the other variables was studied using Student's t and Fisher's tests, showing statistically significant differences in only two variables: BIS and EGD. Performance of the equation

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obtained from logistic regression was analysed using the ROC curve analysis.

Results

A total of 61 patients were included. All data, unless otherwise indicated, are expressed as mean ± standard deviation. Of the total cohort, 40% were boys and 60% girls. Ages ranged from 16 to 168 months, with a median of 105 months and a mean of 95.90. Eleven of the total (61) were aged under 36 months. Weight range was 9–67 kg, with a mean weight of 30.52 kg (±14.68). The first EGD was attempted at a BIS level of 63.46 ± 2.45; EGD was successful at the first attempt in only 2/61 patients. The second EGD was attempted at a BIS level of 54.88 ± 1.55; this was successful in 51/59 of patients. The second EGD was attempted at a BIS level of 49.5 ± 0.567, and was successful in 8/8 remaining patients (Fig. 1).

Analysing all data gave an effective BIS level of 56.41 ± 4.63, with an interquartile range of 52.5–60. The BIS value did not differ in the population aged over and under 36 months (p = 0.696); under 36 months: mean 56.91 ± 6.64, total range from 46 to 65; over 36 months: mean 56.30 ± 4.18, total range from 49 to 67). There were no differences between sexes (p = 0.153) (Figs. 2 and 3).

Time (minutes) from the start of delivery of anaesthesia drugs to the first and successive attempts was: 7.97 ± 1.86 at the first attempt; 10.5 ± 1.77 at the second attempt, and 13.37 ± 2.29 at the third attempt. Analysing all 61 patients, time to induction was 11.07 ± 2.69 min. Total propofol dose was 4.86 (±1.21) mg kg⁻¹, with an interquartile range of 4.14–5.14 mg kg⁻¹; including propofol boluses and infusion rate, total dose in milligrams per kilogram of weight and minute was 0.24. Time to awakening was 12.46 ± 4.18 min. Duration of EGD was 9.34 ± 4.08 min, with an interquartile range of 6–12 min.

After start of EGD, 62% of patients (38/61) required administration of additional propofol bolus. Of these 38 patients, only seven (18%) required additional propofol due to movement or gagging reflex. In 31/38 patients, the additional bolus was administered to increase the level of BIS over eBIS, although the patients showed no signs of movement or gagging; BIS was increased over eBIS by 7.89 ± 2.46, with an interquartile range of 6–10. In patients in whom bolus increase was due to some kind of movement, BIS had been increased over eBIS by 6.71 ± 3.58, with an interquartile range of 5–6.

Logistic regression was used to determine the correlation between eBIS levels. Before performing regression, the bivariate correlation between EGD and the other variables was studied, showing statistically significant differences in only two variables (BIS and EGD).

In view of the results, BIS was the only variable worth including in the regression. The regression was performed, and the following model obtained:

\[
\ln \left( \frac{\text{prob}(\text{EGD} = \text{Yes})}{\text{prob}(\text{EGD} = \text{No})} \right) = -0.355 \times \text{BIS} + 21.14
\]

Therefore, according to the second equation, patients with a probability greater than 0.5 will have an EGD = Yes response, i.e., the procedure can be performed. However, a probability of less than 0.5 would give an EGD = No response, i.e., the procedure cannot be performed. Since performance of EGD depended solely on the BIS value, we can conclude that, based on the results of the equation, EGD cannot be performed with a BIS level of over 59, whereas values of 59 and below are suitable for the procedure.

Fig. 4 shows a Kaplan–Meier survival curve that more clearly illustrates how likelihood of success increase in parallel with increased dosage.

The ROC curve (Fig. 5) shows that the equation obtained is in fact discriminatory, since the area below the curve is 0.80, which yields statistically significant differences of 0.5,
representing the randomly chosen EGD Yes or No classification.

However, the equation is not 100% accurate in classifying procedure attempts: only 80.5% of cases were classified correctly.

Sensitivity is the probability that the model will predict EGD = Yes in a patient in whom EGD = Yes is indeed true. The equation has a sensitivity of 72.13%. Specificity is the probability that the model will predict EGD = No in a patient in whom EGD = No is indeed true. The equation has a specificity of 83.06%. Positive predictive value (PPV) is 84.62% and negative predictive value (NPV) is 77.63%.

Negative and positive likelihood ratios (LR) were also estimated: LR+ was 6.04 and LR− was 0.32.

We also performed statistical analysis on data from the over-36 month patient group. In this partial analysis, the discriminatory BIS value was also 59; equation sensitivity was 74.00%; specificity was 87.50%; PPV was 84.09%; NPV was 79.03%; LR+, was 5.9222, and LR− was 0.30.

**Discussion**

BIS monitoring improved patient safety. Although the system is costly, its use is recommended in clinical anaesthetic practice because it reduces both the risk of intraoperative awareness and anaesthetic dosage. In this study, we excluded the under-12-month population because the BIS index has not been fully validated in infants. Propofol was chosen for this protocol because it is widely used in invasive pediatric procedures; when administered correctly during induction, it prevents apnoea.

The hypnotic state is known to abolish all motor response to stimuli, and frequently affects airway permeability. A lighter level of anaesthesia can reduce the risk of airway compromise, but might not prevent motor response. Motor response in pain stimulus and the reflexes elicited during manipulation of the mouth, larynx and oesophagus do not originate in the cerebral cortex but in the subcortical region (brain stem, spinal cord). Although anaesthetic drugs are known to affect both the cortex and the subcortex, currently their effect can only be monitored in the cortex. We know that even at "deep" BIS levels some patients can display motor reflexes, and this can reduce the effectiveness of BIS in predicting whether a patient will react during performance of EGD. Some studies have gone as far as to say that neither BIS nor entropy monitoring are able to clearly differentiate consciousness from unconsciousness. While using BIS monitoring during anaesthetic induction, authors such as Golparvar et al. have found the same percentage of somatic movement on airway manipulation at BIS levels 60, 50 or 40.

Despite these limitations, however, BIS level is a good indicator of depth of anaesthesia.

The aim of this study was to estimate the highest BIS value at which EGD can be performed. On this basis, the first attempt was made with BIS levels indicating a light level of anaesthesia. At this level EGD was only successful in two of the 61 patients. BIS values on the second and third attempts were set empirically. The use of progressively deeper BIS levels in the same patient until the goal is achieved (EGD without rejection/movement) is interesting, since it allowed us to estimate the highest BIS values for successful EGD. Moreover, we found that eBIS values did not vary significantly from patient to patient (interquartile range 52.5–60).

The use of fentanyl in our protocol, which, unlike plasma concentration takes several minutes to reach peak biophase concentration, could be a confounding factor because we could not rule out that in patients requiring additional propofol the diminishing movement response to endoscopy stimulus was not in fact due to the progressive effect of fentanyl.

As shown in this study, the probability of successful EGD at BIS levels below 59 has a positive predictive value of close
to 85%. Test specificity, moreover, is close to 90%. Estimates suggest that a solid test should have an LR− of around 0 and a high LR+ (there is no upper limit of LR+). In this study, LR− is 0.32, with a CI of 95%, range 0.21–0.48.

The analysis has shown no significant difference between the smaller under-36-month (but above 12 months) subpopulation and the over-36 month population, and that inclusion of the former population does not significantly affect the sensitivity, specificity, PPV and NPV of the logistic regression.

We also analysed the signal quality index (SQI) of the BIS, which was 94.54 (±2.22); it should be noted that some studies in BIS consider SQI values over 50 to be adequate.

With regard to the need to deepen the level of anaesthesia during EGD, it would seem more advisable to maintain BIS levels below eBIS + 5; however, since this variable was not included in our statistical analysis, this recommendation cannot be validated.

In our study, we used BIS levels as low as 46 without signs of desaturation. On this point, the work of Benini et al.13 in healthy pediatric patients is interesting. This group studied BIS values during different stages of physiological (non-drug-induced) sleep, finding no evidence of desaturation when BIS values of between 20 and 30 were recorded during the stages of deepest sleep.

Most similar studies focussing exclusively on BIS levels in pediatric EGD under spontaneous breathing15,16 include few EGD patients because they analyse BIS in a wide range of invasive procedures (Sadhasivam et al.17 only include 40 EGD patients in their series). Although more studies have been carried out in adults,15,16,20,21 BIS levels at which EGD can be performed under spontaneous breathing with no patient discomfort are higher: only 7% of the patients studied by Lera dos Santos et al.18 needed BIS levels below 65, while the average BIS level reported by Jang et al.20 for endoscopic retrograde cholangiopancreatography (ERCP) was 76.5.

Our study is innovative in that it focuses on determining the highest possible BIS level in order to reduce time to awakening and anaesthetic dosage. In other studies, such as that of Powers et al.,17 the objective BIS value for starting the invasive procedure was 50, and mean time to awakening was 14.9 min (range 4–27 min) with a total propofol dose of 0.50 mg kg−1 min−1.

Limitations of the study

We did not calculate the size of the sample, which prevented us from estimating the statistical power of the study. Another possible limitation lies in the fact that the anaesthesia protocol was limited to fentanyl and propofol, preventing us from extrapolating valid conclusions for other anaesthesia methods. The effect of opioid derivatives on BIS levels remains controversial. Ferreira et al.21 found that in patients given intravenous propofol plus remifentanil, additional remifentanil bolus reduces BIS values.

Conclusions

In the pediatric population studied, EGD can be performed under spontaneous breathing using BIS values of 59 or less, with a positive predictive value of over 80%.

Conflict of interests

The authors have no conflicts of interest.

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