ORIGINAL ARTICLE

Effect of neuromuscular blockade on the bispectral index in critically ill patients

Eva Sanavia\textsuperscript{a}, Mirian García\textsuperscript{b.c.d,*,} Jimena del Castillo\textsuperscript{b.c,d}, Rafael González\textsuperscript{b.c.d}, Jesús López-Herce\textsuperscript{b.c.d}, Santiago Mencía\textsuperscript{b.c.d}

\textsuperscript{a} Servicio de Pediatría, Hospital Infantil Leonor, Madrid, Spain
\textsuperscript{b} Unidad de Cuidados Intensivos Pediátricos, Hospital General Universitario Gregorio Marañón, Madrid, Spain
\textsuperscript{c} Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain
\textsuperscript{d} Instituto de Investigación Sanitaria Gregorio Marañón, Red de Salud Materno Infantil y del Desarrollo (RedSAMID), Madrid, Spain

Received 13 March 2019; accepted 16 July 2019

KEYWORDS
Consciousness monitors; Child; Muscle relaxation; Neuromuscular blockade

Abstract

Introduction: It has been suggested that neuromuscular blockade (NMB) affects the capacity of bispectral index (BIS) monitoring to measure consciousness in sedated children. Our aim was to analyse the impact of NMB on BIS values in critically ill children.

Methods: We conducted a prospective observational study of children monitored with a BIS system that received a continuous infusion of vecuronium. We analysed data on clinical, diagnostic and haemodynamic variables, sedatives, analgesics, muscle relaxants, and BIS parameters. We compared BIS parameters before the use of a muscle relaxant, during its administration, before its discontinuation and for the 24 h following the end of the infusion.

Results: The analysis included 35 patients (median age, 30 months). The most common diagnosis was heart disease (85%). The most frequent indication for initiation of NMB was low cardiac output (45%), followed by adaptation to mechanical ventilation (20%). Neuromuscular blockade did not produce a significant change in BIS values. We found a decrease was observed in electromyography (EMG) values at 6 h (34.9 ± 9.4 vs 31.2 ± 7; \(P = .008\)) and 12 h after initiation of NMB (34.9 ± 9.4 vs 28.6 ± 4.8; \(P = .006\)). We observed a small significant increase in BIS after discontinuation of NMB (from 42.7 ± 11 to 48.4 ± 14.5, \(P = .001\)), and 6 and 12 h later (51.3 ± 16.6; \(P = .015\)). There were no differences in the doses of sedatives or analgesics except for fentanyl, of which the dose was lowered after discontinuation of vecuronium.

Conclusion: Continuous NMB produces small changes on BIS values that are not clinically significant and therefore does not interfere with BIS consciousness monitoring in critically ill children.

© 2020 Published by Elsevier España, S.L.U. on behalf of Asociación Española de Pediatría. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

\* Corresponding author.
E-mail address: miriamgsp@hotmail.com (M. García).
PALABRAS CLAVE
Monitorización de la conciencia; Niño; Relajantes musculares; Bloqueo neuromuscular

Efecto del bloqueo neuromuscular sobre la monitorización biespectral en los niños críticamente enfermos

Resumen
Introducción: Estudios previos sugieren que el bloqueo neuromuscular (BNM) altera la monitorización del índice biespectral (BIS) en los niños sedados. El objetivo fue analizar la repercusión del uso y suspensión del BNM en la monitorización BIS en niños críticamente enfermos.
Métodos: Estudio observacional prospectivo. Se incluyeron los niños que recibían perfusiones intravenosas de vecuronio con monitorización BIS. Se analizaron variables clínicas, diagnósticas, hemodinámicas, sedoanalgesia y relajantes musculares y parámetros del BIS. Se compararon los valores del BIS antes del uso de relajantes neuromusculares (RNM), durante su administración, antes de su retirada y durante las 24 h siguientes a su suspensión.
Resultados: Treinta y cinco pacientes (edad mediana 30 meses). El diagnóstico más frecuente fue cardiopatía (85%). Las indicaciones más frecuentes para iniciar RNM fueron bajo gasto cardiaco (45%) y adaptación a ventilación mecánica (20%). El BNM no produjo cambios significativos en los valores del BIS. Se observó una disminución de los valores del electromiograma a las 6 h (34.9 ± 9.4 vs 31.2 ± 7; p = 0.008) y a las 12 h del inicio de la perfusión de vecuronio (34.9 ± 9.4 vs 28.6 ± 4.8; p = 0.006). Tras retirar el vecuronio hubo un ligero aumento significativo del BIS (de 42.7 ± 11 a 48.4 ± 14.5, p = 0.001), así como en las siguientes 6 y 12 h (51.3 ± 16.6; p = 0.015). No hubo diferencias en las dosis de sedantes o analgésicos, excepto del fentanilo, que fue disminuido tras retirar el vecuronio.
Conclusion: El BNM continua produce cambios pequeños en los valores del BIS sin relevancia clínica, y no altera la monitorización del nivel de conciencia del BIS en los niños críticamente enfermos.

© 2020 Publicado por Elsevier España, S.L.U. en nombre de Asociación Española de Pediatría. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

The bispectral index (BIS) estimates the level of brain activity through a mathematical analysis of the frequencies of waves in electroencephalography (EEG) signals and it also obtains information from electromyography (EMG) data.

The BIS index was first introduced in 1992 by Aspect Medical Systems. The main component of the BIS monitor is the bispectral analysis, which evaluates the phase relations from a single channel EEG signal measured from the patient’s forehead. The BIS index is a dimensionless number from 0 to 100. Firstly, the EEG signal is digitized and pre-processed. BIS includes two types of burst suppression (BS) detection: the burst-suppression ratio (BSR) and the QUASI-Suppression. The pre-processed data is used to calculate the $\beta$-ratio parameter (a ratio of empirically measured frequency bands, 30–47 Hz and 11–20 Hz). Simultaneously, the second parameter, synch-fast-slow, is calculated from bispectral analysis. Finally, all parameters are then fed to the weighting algorithm, which produces the BIS index. Electromyographic data corresponds to the 30–50 Hz range, which can overlap with BIS.

BIS was initially used for the objective assessment of sedation depth in patients undergoing general anaesthesia, but it has subsequently proved to be useful in monitoring the level of sedation in patients admitted to the ICU, especially those under deep sedation. International guidelines recommend its use for monitoring patients treated with muscle relaxants in who it is not possible to use clinical scores.

Neuromuscular blockade (NMB) decreases electromyographic activity. Some authors have suggested that the administration of these drugs may also decrease BIS values and overestimate the degree of patient sedation. Several studies, most of them conducted in adult patients, have analysed the impact of NMB on BIS, with contradictory results. Many have found that neuromuscular blocking agents (NMBAs) decrease the EMG component of BIS, thus reducing the value of the latter. However, some authors attribute the impact of NMB on BIS to a coincidental deeper level of sedation in those cases. Our hypothesis was that NMB does not alter the ability of BIS to monitor consciousness in sedated children in paediatric intensive care units (PICUs).

The aim of our study was to analyse the impact of the use or discontinuation of NMB on BIS values in critically ill children.

Patients and methods

We conducted a prospective observational study in a tertiary referral hospital in Madrid, Spain, between 2011 and 2012. We included all patients aged 1 month to 16 years admitted to PICU during the period under study that were monitored with BIS and required infusion of NMBAs. We excluded patients with a duration of NMB of less than 6 h and those with seizures or encephalopathy that could affect BIS values. The study was approved by the local ethics committee.
Effect of neuromuscular blockade on BIS monitoring

We collected data on demographic (age, sex) and clinical characteristics (reason for admission, underlying disease), haemodynamic parameters (blood pressure, heart rate, central venous pressure and urine output), inotropic therapy, mechanical ventilation and reason for using NMB. Sedatives and analgesics drugs were administered per the PICU protocol, which adheres to the guidelines of the Sociedad Española de Cuidados Intensivos Pediatrícos (Spanish Society of Paediatric Intensive Care). The protocol includes the rotation of different sedative and analgesic drugs with the aim of minimising withdrawal symptoms on discontinuation of opioids and benzodiazepines. We recorded the administered sedatives and analgesics and their dosage. The NMBA used in every case was vecuronium, always given at a rate of 0.1 mg kg⁻¹ h⁻¹.

Bispectral index monitoring was performed with a BIS XP Aspect Medical Systems® monitor and paediatric BIS sensors. Bispectral index values were recorded continuously, as were values of electromyographic (EMG) parameters, the signal quality index (SQI), the total power (TP) and the spectral edge frequency (SEF). We measured and recorded BIS parameters, the blood pressure (BP) and the heart rate (HR) 30 min before initiation of NMB and 6, 12 and 24 h thereafter. We also measured and documented the same variables were also before discontinuing NMBA, and 6, 12 and 24 h after discontinuation. At the same time, we monitored the level of pain and of sedation using internationally validated scales such as the COMFORT behaviour scale and the pain ladder, and adjusted the infusion of sedatives and analgesics based on the resulting scores.

We defined moderate sedation as a BIS value of 40–60 and deep sedation as a BIS value of less than 40. We discarded BIS values when the signal quality index was less than 60% or the impede level was greater than 10 kΩ.

Statistical analysis

We analysed the data using the software SPSS Statistics version 19. We used the Fisher exact test to compare frequencies and the Mann-Whitney U test to compare quantitative variables. Also, we used the Wilcoxon test to compare BIS, EMG, SQI, BP and HR values before and after NMB. We analysed the correlation between nonparametric variables by means of the Spearman rank correlation coefficient. We defined statistical significance as a p-value of less than 0.05.

Results

The analysis included 35 patients with a mean age of 30 months (range, 2-288 months), 52.9% male. The primary diagnosis in 85% of cases was postoperative care after cardiac surgery, followed by head injury (9%) and bronchiolitis (6%). The most frequent reasons for use of NMB administration were haemodynamic instability (low cardiac output, ECMO, junctional ectopic tachycardia; 49%), improvement of patient-ventilator synchrony (23%), pulmonary hypertension (14%) and increased intracranial pressure (6%).

Fig. 1 presents the BIS, EMG and SQI values. The SQI was above 80% at all times. Before administration of NMBAs, patients were under moderate-to-deep sedation (mean BIS,
12 significant did we find. However , we observed a small but significant increase in BIS values 6 h ($P = .001$) and 12 h after discontinuing the NMBA ($P = .015$).

We observed a decrease in electromyogram (EMG) values at 6 h (34.9 ± 9.4 vs 31.2 ± 7; $P = .008$) and 12 h after initiation of NMBA (34.9 ± 9.4 vs 28.6 ± 4.8; $P = .006$). There was a small significant increase in BIS on discontinuation of NMBA (from 42.7 ± 11 to 48.4 ± 14.5; $P = .001$), as well as 6 and 12 h after discontinuation (51.3 ± 16.6; $P = .015$). Furthermore, EMG values increased significantly after discontinuation of NMBA at 6 h ($P = .08$) and 12 h ($P = .012$). We did not find any other statistically significant changes in BIS parameters.

We did not find a significant correlation between BIS and EMG values before and after NMBA. We also found no significant changes in haemodynamic parameters during the infusion or after discontinuation of NMBA (Fig. 2).

There were no differences in the sedatives and analgesics used during these periods or their doses, save for the dose of fentanyl, which was significantly reduced after discontinuation of NMBA (at 6 h, 2.2 ± 1.6 vs 1.9 ± 1.6; $P = .011$ and at 12 h, 2.2 ± 1.6 vs 1.7 ± 1.6; $P = .01$) (Fig. 3).

**Discussion**

Our study shows that the administration of NMBA in children does not alter BIS significantly, so the latter is a useful method for monitoring sedation in patients under NMBA.

Bruhn observed that, after administering NMBA to a volunteer, electromyographic activity could distort BIS measurements, and other research groups have since confirmed these findings. However, other studies, most of them conducted in adults, have not found significant changes in those measurements.

Weber et al. compared the effect on BIS values of a dose of muscle relaxant versus placebo after anaesthetic induction in 40 children that were undergoing surgery. They found no differences between the treatment and the placebo groups.

We conducted our study in critically ill children. Rather than analysing the effect on BIS values of a single dose of NMBA, we studied the effect of continuous infusion of NMBA and its discontinuation. Our results showed no relevant changes in BIS values with administration of NMBA, although we did find a small but significant increase in BIS values after discontinuation of vecuronium. However, although there was a statistically significant change in BIS values, they remained within the 40 to 60 range (moderate sedation).

Previous studies that showed that BIS was affected by NMBA were mostly performed in patients under moderate sedation or in conscious volunteers. However, studies conducted in patients under deep sedation have not found significant changes in BIS values.

This could explain the discrepancies between the findings of different studies, as EMG activity probably affects BIS values in conscious patients. When NMBA is used, EMG activity decreases and causes a secondary drop in BIS values. In contrast, our patients were already under moderate or deep sedation with low EMG activity before the initiation of NMBA. This probably explains why the infusion of the NMBA was associated with a decrease in EMG values and NMBA dis-
continuation with minor increase in EMG values, which did not have a significant effect on the BIS.

In agreement with the findings of other authors, we observed statically significant changes on BIS and EMG values 6 and 12 h after discontinuing the NMB infusion. These changes may be explained in part by muscular contraction, but they are so small that we think they do not have any clinical significance in the assessment of the level of sedation.

In addition, we found no correlation between BIS values and haemodynamic parameters (blood pressure and heart rate), which was consistent with previous studies. A probable explanation is that these parameters are influenced by many different factors, and not only the degree of sedation or relaxation of the patient.

There are several limitations to our study. The sample size was relatively small, which could reduce the statistical validity of comparisons. In addition, all of the participants were under deep sedation because, for ethical reasons, we do not use muscle relaxation in patients with mild sedation. Furthermore, our study did not measure the degree of muscle relaxation.

**Conclusion**

Continuous infusion of NMB produces small changes on BIS values in critically ill children under moderate-to-deep sedation that are not clinically relevant, and therefore it does not compromise BIS monitoring of the level of consciousness in critically ill children.

**Acknowledgements**

We thank our colleagues at the PICU of the Hospital Gregorio Marañón, who volunteered to participate in our study and contributed expertise and insights that were very helpful in the research project.

**References**

7. Tobias JD, Grindstaff R. Bispectral index monitoring during the administration of neuromuscular blocking agents in the...
15. 13.
11. 10.
6
9.
steady
rapidly
propofol
controlled
induced
of
Lim
phenomenon?