Rev Bras Anestesiol
2011; 61: 3: 304-310

Effects of Sedation Produced by the Association of Midazolam and Ketamine S(+) on Encephalographic Variables

Rogean Rodrigues Nunes, TSA [1], Sara Lúcia Cavalcante, TSA [2], Suyane Benevides Franco [3]

Summary: Nunes RR, Cavalcante SL, Franco SB – Effects of Sedation Produced by the Association of Midazolam and Ketamine S(+) on Encephalographic Variables.

Background and objectives: Ketamine S(+) is important in pain modulation in surgical patients. The objective of the present study was to evaluate the relationship between the levels of sedation produced by low doses of ketamine S(+), as well as encephalographic variables: BIS, SEF 95%, pEMG, suppression rate, and presence of burst-suppression.

Methods: Thirty patients of both sexes, aged 25-50 years, were randomized into three groups. Group G1 (10) received intravenous ketamine S(+) 0.050 mg,kg^{-1}; group G2 (10) intravenous ketamine S(+) 0.125 mg.kg^{-1}; and group G3 (10) intravenous ketamine S(+) 0.250 mg.kg^{-1}. All patients received 0.08 mg.kg^{-1} of intravenous midazolam 10 minutes before administration of ketamine S(+). In each group, two moments were evaluated: M1, before ketamine S(+) administration; and M2, after ketamine S(+) administration. Sedation levels and encephalographic variables: BIS, SEF 95%, pEMG, suppression rate, and the presence of burst-suppression were evaluated in all patients before and after ketamine S(+) administration. ANOVA was used for repeated measurements and the p-value was adjusted for multiple comparisons by Tukey's test.

Results: A decrease in alertness-sedation scale scores was observed in all three groups in moment M2. Electroencephalographic variables showed significant variation in all three groups when moments M1 and M2 were compared, both in pEMG and BIS ($p < 0.05$).

Conclusions: Sedation levels showed significant correlation with the increase in ketamine S(+) dosage. However, increased BIS levels may have reflected increased pEMG induced by ketamine S(+).

Keywords: Ketamine; Deep Sedation; Conscious Sedation; Electroencephalography.

INTRODUCTION

The bispectral index (BIS) is a processed signal derived from multiple bispectral analysis of the electroencephalogram, which is validated for use with most inhalational and intravenous agents [1]. This technique decomposes the electroencephalogram (EEG) and quantifies the level of synchronization signal involving two parameters (amplitude and frequency), resulting in a more complete description of the EEG complex. Although it has an important role in intraoperative and postoperative pain modulation, as well as in treatment of chronic nociceptive phenomena, an important aspect in current management of surgical and oncologic patients [2], ketamine S(+) has no validated correlation with BIS variations.

The anesthetic agents, barbiturates, propofol, etomidate, and benzodiazepines produce a dose-dependent decrease in cerebral blood flow and cerebral metabolic rate – effects well-correlated with BIS [3]. The objective of the present study was to evaluate the relationship between the sedation produced by the association of midazolam and low doses of ketamine S(+), as well as electroencephalographic variables: BIS, electromyographic potency (pEMG), spectral analysis (SEF 95%), suppression rate, and presence of burst-suppression.

METHODS

After approval by the Institutional Ethics Committee and signing of the informed consent, 30 adult patients of both sexes, ages ranging from 25 to 50 years, physical status ASA I, body mass index between 21 and 26 kg.m^{-2}, scheduled for elective surgeries regardless of the size of surgery, undergoing unilateral upper limb block from July to August 2009 were included in this study. Patients on drugs that affect electroencephalographic activity were excluded. Patients were electronically randomly and non-blindly allocated into three groups. Group G1 (10 patients) received 0.050 mg.kg^{-1} of ketamine S(+); group G2 (10 patients) received 0.125 mg.kg^{-1} of ketamine S(+); and group G3 (10 patients) received 0.250 mg.kg^{-1} of ketamine S(+). In all groups ketamine S(+) was administered intravenously over 20 seconds in the operating room before brachial plexus blockade. All patients received 0.08 mg.kg^{-1}

Received from Hospital São Lucas, Fortaleza, Ceará, Brazil.

1. MSc; MD; Post-Graduation in Clinical Engineering; Clinical Director of Hospital São Lucas, Fortaleza, CE
2. PhD; Professor at Faculdade de Medicina da Universidade Federal do Ceará (UFC)
3. Medical Student (UFC)

Submitted on August 9, 2010.
Approved on December 7, 2010.

Correspondence to:
Dr. Rogean Rodrigues Nunes
Avenida Comendador Francisco de Francesco di Ângelo, 1185-casa Dunas
60181500 – Fortaleza, CE, Brazil
E-mail: rogean@fortalnet.com.br

of intravenous midazolam 10 minutes before ketamine S(+) administration. The level of sedation was evaluated before ketamine S(+) administration (M1) and two minutes after ketamine S(+) administration (M2), using the following alertness-sedation scale (Figure 1) [4]:

5 – Immediate response when called by his/her name. Normal speech, normal facial expression, and eyes opened without drooping eyelids;
4 – Lethargic response when called by his/her name, slow speech, relaxed facial expression, and cloudy eyes or with discrete facial expression;
3 – Respond only when called loudly or repeated times by his/her name. Speech with indistinct pronunciation, unintelligible, relaxed facial expression, and cloudy eyes with ptosis;
2 – Respond only to tactile stimuli, speech with few comprehensible words;
1 – No response to tactile stimuli.

Oxygen, 1 L.min^{-1}, was administered to all patients via nasal catheter. Processed electroencephalogram (EEG) was used to continuously monitor nervous system electric activity, using a BIS A-2000 monitor, version XP®, with electrodes placed in a unilateral bipolar montage: FPz (reference electrode 1), FP1 (virtual earth electrode 2), AF7 (electromyographic component for generation of BIS signal – electrode 4), and FT9 (non-EMG component for generation of BIS signal – electrode 3) [5]; an automated impedance test was performed and the function was considered adequate after each electrode tested presented impedance below 7.5 k .

The following electroencephalographic parameters were recorded: BIS (bispectral index), spectral wedge frequency 95% (SEF 95%), electromyographic potency (pEMG), and burst-suppression ratio. Variables such as non-invasive blood pressure, heart rate, and peripheral O_2 saturation of all patients at moments M1 and M2 were recorded. Electroencephalographic data were analyzed using ANOVA for repeated measurements and the value of p was adjusted for multiple comparisons by Tukey's test, considering p-values below 5% significant. Spearman's rank coefficient correlation (r_s) was used to determine the correction between pEMG and levels of alertness-sedation.

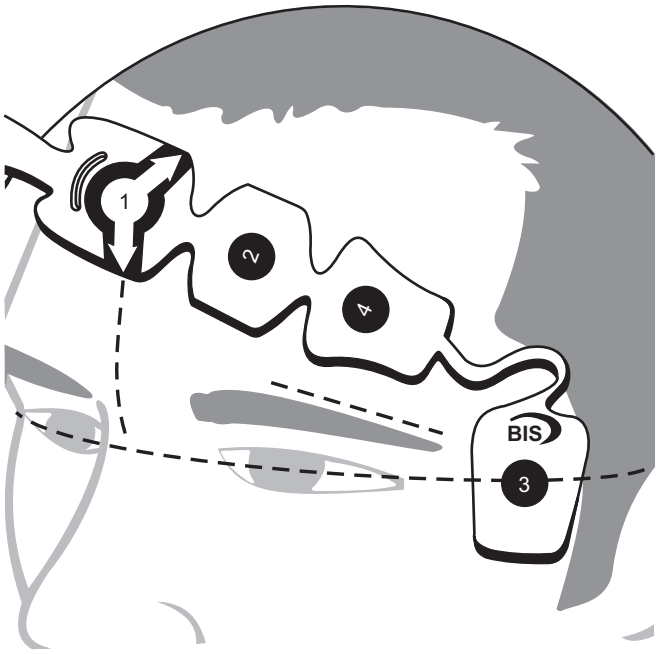

Figure 1 – Sensor with Four Electrodes.

RESULTS

Sedation levels (alertness-sedation scale), (median) and electroencephalographic variables (mean and standard deviation) before and after ketamine S(+) administration are shown in Table I.

Table I – Sedation Levels and Electroencephalographic Variables (mean ± SD) before and after Injection of Ketamine S(+)

	G1 (n = 10)	G2 (n = 10)	G3 (n = 10)
OAA/S			
M1	4	4	4
M2	3	2	1
BIS			
M1	88.3 ± 1.42	87.2 ± 1.81	86.8 ± 2.53
M2	95.2 ± 1.99*	94.7 ± 2.31*	94.3 ± 1.34*
SEF 95%			
M1	25.8 ± 2.20	25.3 ± 2.50	24.6 ± 2.27
M2	26.1 ± 2.13	25.2 ± 2.39	25.8 ± 2.20
pEMG			
M1	35.3 ± 2.36	35.1 ± 2.13	34.9 ± 1.10
M2	41.3 ± 1.06*,**	46.2 ± 1.14*,**	52.5 ± 1.84*,**

OAA/S: sedation levels; G1: 0.050 mg.kg^{-1}; G2: 0.125 mg.kg^{-1}; G3: 0.250 mg.kg^{-1}; *p < 0.05, comparing with values before ketamine S(+) administration – BIS and intragroup p EMG analysis; **p < 0.05, comparing values in different moments; M2 – intergroup pEMG analysis.

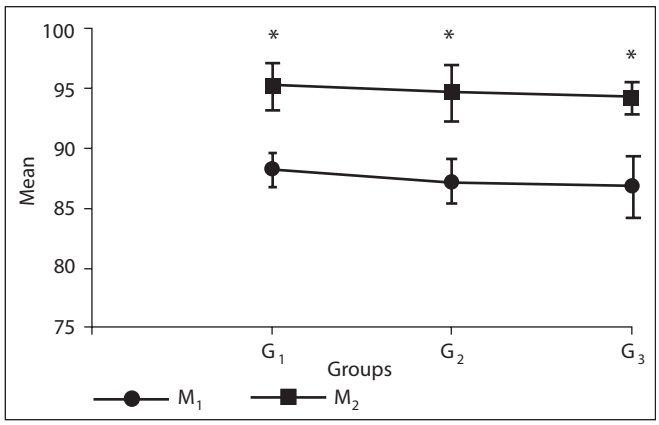

Figure 2 –Mean BIS per Group.
* p < 0.05 in G1, G2, and G3, comparing M1 and M2 in intragroup analysis.

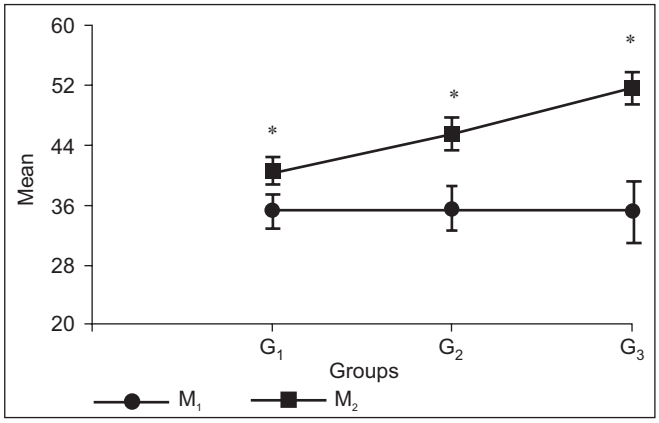

Figure 3 – Mean pEMG (dB) per Group.
***p < 0.05** 05 in G1, G2, and G3 comparing M1 and M2 in intragroup analysis.

Results demonstrated a dose-dependent reduction in alertness-sedation scores in all groups after ketamine S(+) administration – $p < 0.005$, when compared to intragroup moments (G1, G2, and G3) – before and after ketamine S(+). In the intergroup assessment, statistically significant differences were observed only in moment M2 in all groups. However, BIS values, which remained below 90 (mean) before ketamine S(+) administration increased above 90 (mean) in each group in M2, but statistically significant intergroup differences were not observed.

There were no variations in amplitude representing a suppression ratio different from zero or presence of any burst-suppression episodes. Analysis of electromyographic potency demonstrated negative correlation in all groups when compared with variations in level of alertness-sedation ($r_s < 0$). Significant increases in electromyographic frequency were seen with increasing doses of ketamine S(+) in all groups ($p < 0.05$).

The values of systolic and diastolic blood pressure, heart rate, and peripheral O_2 saturation showed no clinically significant variations.

DISCUSSION

Processed electroencephalographic analysis is a useful method to identify abnormal cerebral function, consciousness, unconscious, sleep, and coma, which can be readily identified by the EEG. The Bispectral Index (BIS), which results from digital processing of the electroencephalogram, has been used to monitor appropriate anesthesia of anesthetic agents that activate or increase the activity of gamma-aminobutyric acid type A receptors (GABA-A). However, prior reports have suggested that ketamine has negligible effects on these receptors, emphasizing its action on n-methyl-d-aspartate receptors (NMDA). Activation of NMDA receptors increases norepinephrine release more than acetylcholine, while in GABA-A receptors there is a predominance of acetylcholine, but both neurotransmitters are known as substances that promote alertness. There is also the hypothesis that anesthetics act on these wake-promoting neurons and that general anesthesia results not only from the inhibition but also the over-excitation of neurons. Therefore, there is the hypothesis that ketamine, a NMDA-type anesthetic agent, may induce anesthesia by central over-excitation [1,6]. Ketamine alone does not reduce BIS values even when patients are unconscious. Hirota et al. [7] demonstrated that additional administration of ketamine (0.4 $mg.kg^{-1}$ per hour for 20 minutes) increases BIS from 44.1 ± 0.7 to 58.6 ± 1.4 during total intravenous anesthesia with propofol and fentanyl. However, there are no studies correlating the electromyographic potency and BIS values after the use of ketamine. In the present study, a negative linear correlation between the alertness-sedation scale and ketamine S(+) administration was observed. There was no correlation between BIS values and sedation after ketamine S(+) administration (Table I). There was no significant difference in the intragroup analysis of variables SEF 95%. Ketamine induces a cataleptic state that is accompanied by nistagmus, pupillary dilation, salivation, tearing, spontaneous movements of the limbs, and increased in global muscular tonus [8], which could increase facial electromyographic activity resulting in an increase in BIS since facial electromyography is incorporated to the algorithm of this index by using a specific electrode in the AF7 position. To conclude, this study demonstrated that the levels of sedation after the administration of low doses of ketamine S(+) correlate with variations in potency of electromyographic activity (elevations), therefore elevating the BIS values, as it incorporates such activity in its algorithm. This study may represent a new perspective in the analysis of electroencephalographic activity with the use of ketamine to maintain control of electromyographic bursts of facial musculature.

REFERÊNCIAS / REFERENCES

01. Hiroka K – Special cases: ketamine, nitrous oxide and xenon. Best Pract Res Clin Anaesthesiol, 2006;20:69-79.
02. De Koch M, Lavand'Homme P, Waterloos H – "Balanced analgesia" in the perioperative period: is there a place for ketamine? Pain, 2001;92:373-380.
03. Patel PM, Drummond JC – Cerebral Physiology and the Effects of Anesthetics and Techniques, em: Miller RD - Miller's Anesthesia, 6th Ed, New York, Elsevier/Churchill-Livingstone, 2005;813-857.
04. Cavalcante SL, Nunes RR – Avaliação dos parâmetros derivados do eletroencefalograma durante administração de diferentes concentrações de óxido nitroso. Rev Bras Anestesiol, 2003;53:1-8.
05. Johansen JW – Update on bispectral index monitoring. Best Pract Res Clin Anaesthesiol, 2006;20:81-99.
06. Kubota T, Hirota K, Yoshida H et al. – Effects of sedatives on noradrenaline release from the medial prefrontal cortex in rats. Psycopharmacology (Berl), 1999;146:335-338.
07. Hirota K, Kubota T, Ishihara H et al. – The effects of nitrous oxide and ketamine on the bispectral index and 95% spectral edge frequency during propofol-fentanyl anaesthesia. Eur J Anaesthesiol, 1999;16:779-783.
08. Brunton LL, Parker KL – Goodman & Gilman´s: Manual of Pharmacology and Therapeutics, 11th Ed, New York, McGraw-Hill, 2008;231-232.

Resumen: Nunes RR, Cavalcante SL, Franco SB – Efectos de la Sedación Producida por la Asociación del Midazolam y la Cetamina S(+) sobre las Variables Electroencefalográficas.

Justificativa y objetivos: La cetamina S(+) es importante en la modulación del dolor en pacientes quirúrgicos. Este trabajo tuvo el objetivo de evaluar la relación entre los niveles de sedación producidos por la bajas dosis de cetamina S(+), como también las variables del EEG: BIS, SEF 95%, pEMG, tasa de supresión y presencia de brote-supresión.

Método: Treinta pacientes de los dos sexos, con una franja etaria entre los 25 y los 50 años, que fueron distribuidos aleatoriamente en tres grupos. El grupo G1 (10) recibió cetamina S(+) - 0,050 $mg.kg^{-1}$; el grupo G2 (10), cetamina S(+) – 0,125 $mg.kg^{-1}$ y el grupo G3(10), cetamina S(+) – 0,250 $mg.kg^{-1}$. En todos los grupos, la cetamina S(+) fue administrada por vía venosa. Todos los pacientes recibieron 0,08 $mg.kg^{-1}$ de midazolam por vía venosa 10 minutos antes de la administración de cetamina S(+). En cada grupo fueron evaluados dos momentos: M1: antes de la administración de la cetamina S(+); y M2: después de la administración de la cetamina S(+). En los tres grupos, se evaluaron los niveles de sedación y las variables del EEG: BIS, SEF 95%, pEMG, la tasa de supresión y la presencia de brote-supresión, antes y después de la inyección de cetamina S(+). Se utilizó ANOVA para medidas repetidas y valor de p ajustado para comparaciones múltiples por el test de Tukey.

Resultados: Se registró una disminución en las puntuaciones de la escala de alerta sedación en los tres grupos en los momentos M2. Las variables del EEG arrojaron una variación significativa en los tres grupos al comparar los momentos M1 y M2 tanto en la pEMG como en el BIS ($p < 0,05$).

Conclusiones: Los niveles de sedación se correlacionan de manera significativa con el aumento de la dosis de cetamina S(+). Sin embargo, los valores elevados del BIS pueden haberse reflejado en el aumento de la pEMG inducida por la cetamina S(+).

Descriptores: ANALGÉSICOS: Cetamina; MONITORIZACIÓN: índice bispectral; SEDACIÓN: profunda; TÉCNICAS DE MEDICIÓN, eletroencefalografia.