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

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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.
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 kΩ.

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 O₂ 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 (rₛ) was used to determine the correction between pEMG and levels of alertness-sedation.

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>
<thead>
<tr>
<th>Table I – Sedation Levels and Electroencephalographic Variables (mean ± SD) before and after Injection of Ketamine S(+)</th>
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<tbody>
<tr>
<td>G1 (n = 10)</td>
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<td>OAA/S</td>
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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 1 – Sensor with Four Electrodes.

Figure 2 – Mean BIS per Group. * p < 0.05 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 nystagmus, 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


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 brotesupresión.

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 los 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 brotesupresión, 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; TECNICAS DE MEDICION, eletroencefalografia.