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Influence of (S)-Ketamine on the Bispectral Index and Electroencephalogram during Total Intravenous Anesthesia: A Randomized Clinical Trial

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ABSTRACT

Background: This study aims to evaluate the influence of different doses of (S)-ketamine on bispectral index (BIS) and electromyographic power (pEMG).

Method: Forty participants, submitted to controlled venous effector site anesthesia, were randomly distributed into 5 groups. In the k0 control group, participants did not receive (S)-ketamine; k1, k2, k3, and k4 received (S)-ketamine 200 $\mu g.kg^{-1}$ iv followed by a continuous infusion of 100, 200, 300, and 400 $\mu g.kg^{-1} h^{-1}$, respectively. In each group, 11 moments were evaluated: M0, before anesthetic induction, M1, 10 minutes after anesthesia stabilization with BIS between 45 and 55, and M2 to M10, 3, 6, 9, 12, 15, 18, 21, 24, and 27 minutes after (S)-ketamine. At all moments, BIS and pEMG values were recorded. An ANOVA was used for repeated measures, and the p-value was adjusted for multiple comparisons by Tukey's test, considering $p< 0.05$ as significant.

Results: No significant changes ($p> 0.05$) were observed at each moment after M0 by comparing the mean BIS and pEMG values between all groups.

Conclusion: Electroencephalographic parameters (BIS and pEMG) are not significantly influenced when this (S)-ketamine infusion model and total intravenous anesthesia are performed.

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Introduction

(S)-ketamine is a drug used as an adjuvant during general anesthesia because it has important analgesic and hypnotic properties, thus reducing the need for opioids and hypnotics [1]. However, several studies show important changes in electroencephalographic activity caused by (S)-ketamine, commonly identified through the bispectral index (BIS) [2-7].

BIS is a parameter derived from electroencephalogram (EEG) processing, resulting from the analysis of three sub-parameters: burst-suppression, fast Fourier transform, and bispectrum [8]. BIS values can be altered by several factors, including hypnotics, analgesics, pathological processes, and neuromuscular blockers [9-11].

In addition to changes in BIS values, other indices derived from the electroencephalogram can be altered by (S)-ketamine, including the spectrogram. The most important alterations observed in the spectrogram after (S)-ketamine infusion are gamma-burst pattern, theta oscillations, and reduction of alpha-beta oscillations [12-14].

Another parameter used in brain monitoring during general anesthesia is electromyographic power (pEMG). This variable analyzes subcortical activity through the facial muscles [15]. Although pEMG is also a complementary parameter to monitoring anesthetic depth, there are data in the literature about the influence of (S)-ketamine on pEMG. This study aim is to evaluate the influence of different doses of (S)-ketamine on BIS and pEMG [15,16].

Materials and Methods

Design

A triple-blind clinical trial was conducted in a large size hospital in Fortaleza, Brazil, after submission to Plataforma Brasil and approval by the Clinical Research Ethics Committee (CAAE: 61237222.9.0000.5043), and all participants provided informed consent. This study was published in the Brazilian Registry of Clinical Trials (ReBEC) under the number RBR-7qmdrhy.

Casuistic

We evaluated 40 participants of both genders, undergoing elective operations under general anesthesia, with a physical status P1 (American Society of Anesthesiologists), aged between 20 and 45 years, and with a body mass index between 21 and 26 kg/m^2.

Participants were randomly allocated into five groups of 8, by a restricted (sequential) randomization method:
Group k0: 0.9% saline bolus, followed by continuous infusion of 0.9% saline.
Group k1: (S)-ketamine 200 μg.kg^{-1} iv, followed by the infusion of 100 μg kg^{-1}.h^{-1}.
Group k2: (S)-ketamine 200 μg.kg^{-1} iv, followed by the infusion of 200 μg kg^{-1}.h^{-1}.
Group k3: (S)-ketamine 200 μg.kg^{-1} iv, followed by the infusion of 300 μg kg^{-1}.h^{-1}.
Group k4: (S)-ketamine 200 μg.kg^{-1} iv, followed by the infusion of 400 μg kg^{-1}.h^{-1}.
Syringes with 10 mL of solution were used for bolus administration and with 50 mL for continuous infusion. The diluent was 0.9% saline.

Exclusion Criteria
Participants with neurological diseases or recent use of drugs that could alter the electroencephalogram, such as antidepressants, anticonvulsants, and central nervous system stimulants were excluded.

Equipment used
1) Processed electroencephalogram with bispectral index (BIS) readings and facial electromyography, Bis Vista® version 3.5. The electrodes were adapted in the following points: FPz (referential-electrode 1), AF7 (electrode 4), FT9 (electrode 3), and Virtual Earth (electrode 2, Figure 1);
2) Electrocardiogram in two channels (DII and V5);
3) Pulse oximetry;
4) Capnography and capnometry;
5) Automatic non-invasive blood pressure;
6) Convective forced thermal air heater;
7) Effector-site (Se) infusion pumps, using the following pharmacokinetic models: Minto, for remifentanil, and Schnider, for propofol.
8) Thermometer with a nasopharyngeal sensor.

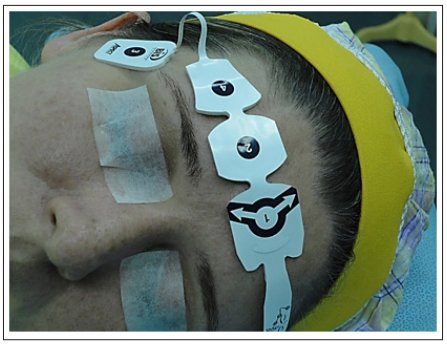

Figure 1: BIS Sensor with Two Channels

Preoperative Evaluation
All participants were previously submitted to preoperative clinical and laboratory evaluations.

Anesthetic Technique
None of the participants received pre-anesthetic medication. All participants underwent the same anesthetic technique. After venipuncture in the right upper limb with a 20G catheter, Ringer's lactate (RL) solution was installed, 2 mL.kg^{-1} to replace fasting, and 4 mL.kg^{-1} to replace intraoperative losses.

In both groups, participants breathed 100% oxygen through mask (pre-oxigenation), 5 minutes before drug infusions until immediately before orotracheal intubation (OTI). Anesthetic induction was performed with intravenous sufentanil 0.3.μg.kg^{-1} with simultaneous infusions, also intravenously, of propofol, controlled effector site (Se), with an initial target of 3.0μg.mL^{-1}, and remifentanil hydrochloride (Se), with an initial target of 3.0 ng.mL^{-1} until the BIS value reached 40. If the BIS did not reach 40, the Se concentration of remifentanil would be increased by 0.5 in 0.5 ng.mL^{-1} until a BIS of 40 was obtained. At this moment, the Se concentration of remifentanil hydrochloride was fixed, and OTI was performed.

Immediately after OTI, propofol and remifentanil infusions were adjusted to maintain a BIS in the closed range of 45 to 55, with these adjustments being made immediately before (S)-ketamine infusion. Maintenance of anesthesia was performed according to the guidelines shown in Figure 2 [17]. Modifications in propofol concentrations were performed every 0.5μg.mL^{-1}, with subsequent variations only performed after reaching the concentration at the effector site provided by the infusion pump. The same conduct was applied to remifentanil hydrochloride.

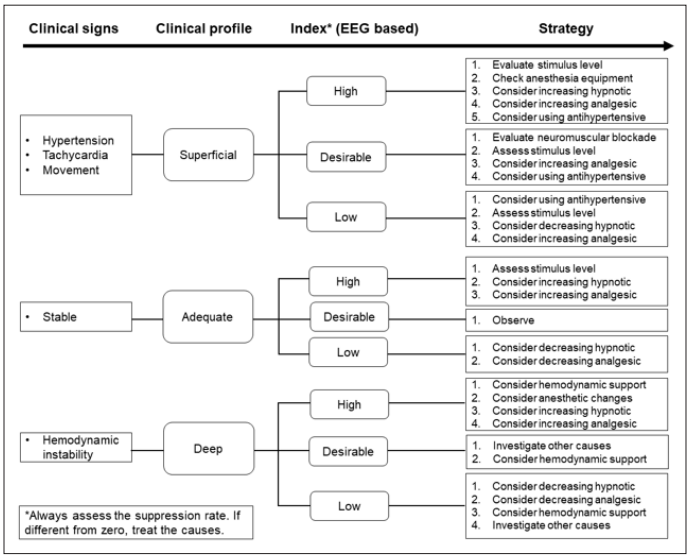

Figure 2: Strategy for anesthesia maintenance with EEG-based monitoring. Source: Nunes et al

A neuromuscular blocker was not used due to the possibility of interference in the processed values of the electroencephalogram. After OTI, the respiratory rate was adjusted to maintain $PETCO_2$ between 35 mmHg and 40 mmHg. A FiO_2 of 35% and a tidal volume of 7 mL.kg^{-1} of body weight were set. Ventilation was performed using a circular system with a CO_2 absorber.

Evaluated Moments
For the purposes of clinical studies and statistical evaluation, 11 moments were analyzed:
1) M0 – Immediately before pre-oxygenation
2) M1 – 10 minutes after anesthesia stabilization with BIS between 45 and 55 (with a target of 50)
3) M2 – 3 minutes after (S)-ketamine administration
4) M3 – 6 minutes after (S)-ketamine administration
5) M4 – 9 minutes after (S)-ketamine administration
6) M5 – 12 minutes after (S)-ketamine administration
7) M6 – 15 minutes after (S)-ketamine administration
8) M7 – 18 minutes after (S)-ketamine administration
9) M8 – 21 minutes after (S)-ketamine administration
10) M9 – 24 minutes after (S)-ketamine administration
11) M10 – 27 minutes after (S)-ketamine administration

BIS and pEMG were the main variables recorded at each moment. The protocol's hemodynamic variables considered the following lower limits: SBP=80mmHg and DBP=50mmHg. The upper limits for SBP and DBP were considered clinically significant if they exceeded 20% of the baseline (admission to the operating room). Heart rates with variations greater than ±25% of baseline (before anesthetic induction) were considered clinically significant. In all participants, the nasopharyngeal temperature was maintained between 35°C and 36°C with a thermal sheet of forced convective hot air. Participants whose hemodynamic variables exceeded pre-established values in at least one of the evaluated moments would be excluded from the study.

Evaluation Criteria

The data obtained were compared between moments in the same group and between groups at equivalent moments.

Sample Size Calculation and Statistical Analysis

The sample size calculation was performed considering an α error = 5%, β error = 5%, a difference to be detected of 8 in the main variable (BIS), a standard deviation of 4, and a two-tailed hypothesis test, which resulted in 8 participants for each group. Student's t-test was used for independent samples. Descriptive statistical analyzes with repeated measures and Tukey's test were performed. A value of $p \leq 0.05$ was considered significant. Statistical analysis was performed using SPSS version 22.0.

Results

After recruitment and randomization, no participant was excluded or lost. The five groups were considered homogeneous regarding age, weight, physical status, and height. Regarding the BIS, it was found that there was a significant difference only between M0 and the other moments ($p<0.05$), regardless of the infused dose. The Tukey's test showed no significant differences between k0, k1, k2, k3, and k4, allowing comparative measurements between the moments in each group ($p>0.05$), with the highest averages recorded in k4, after the use of (S)-ketamine, with the highest value observed in M10 (55.08±1.80), and the lowest averages in k0, with the lowest value observed in M4 (51.30±1.28) (Figure 3).

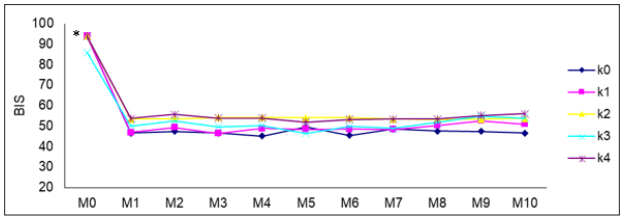

Figure 3: BIS assessment at different moments in all groups. *p<0.05 between M0 and the remaining moments. No statistical difference in intragroup analysis was observed at each moment

The electromyographic power (pEMG) remained below 30 dB in all groups and at all assessments from M1 onwards. Values between 40 and 50 were recorded at M0 in a closed interval (Figure 4).

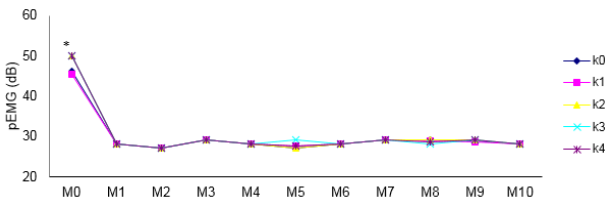

Figure 4: Evaluation of pEMG averages at different times in all groups. *p<0.05 between M0 and the remaining moments. No statistical difference in intragroup analysis was observed at each moment.

Discussion

(S)-ketamine, due to its analgesic and hypnotic properties, has been used more frequently during general anesthesia. In addition, it has several beneficial effects: neuroprotection, preemptive analgesia, preventive analgesia, reduction of opioid-induced tolerance, and hyperalgesia [18].

Low or subanesthetic dose ketamine is defined as a bolus dose of < 2 $mg.kg^{-1}$ intramuscularly and < 1 $mg.kg^{-1}$ intravenously or epidurally. In continuous intravenous administration, the definition of low-dose ketamine varies in the literature, from an infusion rate ≤ 20 $\mu g.kg^{-1}.min^{-1}$ at a rate between 0.1 and 0.3 $mg.kg^{-1}.h^{-1}$ [19,20].

In a randomized and blind study, low doses of (S)-ketamine (100 $\mu g.kg^{-1}$) in bolus were followed by the continuous infusion of 2 $\mu g.kg^{-1}$ min^{-1} during radical prostatectomy, reducing, in the first 48 hours after the operation, the consumption of morphine by 34%. There was also a decrease in pain intensity at rest when compared to the control group that did not receive (S)-ketamine [21].

In another study carried out with participants who underwent cholecystectomy, the use of (S)-ketamine 0.2 $mg.kg^{-1}$ bolus followed by 100$\mu g.kg^{-1}$ h^{-1} in continuous infusion reduced opioid consumption in the first 24 hours after the procedure [19].

The processed electroencephalographic analysis is an important method for monitoring anesthetic depth and shows a good correlation with the effect of several agents used in clinical practice, including propofol, midazolam, isoflurane, and alfentanil [22]. While unconsciousness induced by various anesthetic agents is predominantly associated with a slowing of the electroencephalogram (EEG) pattern, unconsciousness induced by ketamine is associated with active EEG patterns. Ketamine preferentially inhibits glutamatergic impulses to GABAergic interneurons, resulting in excitatory activity in the brain cortex, including the hippocampus and limbic system, resulting in unconsciousness (Figure 5) [23]. The hallucinations observed with the use of ketamine may be the result of this activation, which allows the association of information inconsistently in time and space. These hallucinations can be alleviated by drugs that act on or elevate the activity of GABA-A-mediated interneurons [23].

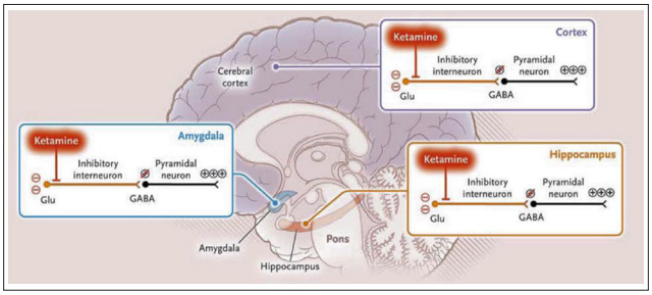

Figure 5: Activation of the electrical activity of the nervous system caused by ketamine. Ketamine blocks the glutamatergic pathway that inhibits inhibitory interneurons in the hippocampus, amygdala, and cerebral cortex diffusely. Source: Brown et al.

The bispectral index, a derivative of EEG subparameter analysis and facial electromyographic activity, did not correlate well with the depth of sedation when low doses of (S)-ketamine were used in participants sedated with pre-anesthetic doses of midazolam [24]. Ketamine, alone, at a high dose, significantly increases both

the theta relative potency and the relative gamma potency, which may be associated with paradoxically increased BIS values [25].

Hirota et al.'s study showed that administration of ketamine at a dose of 0.4 mg.kg^{-1} IV, followed by the infusion of 1 mg.kg^{-1} h^{-1}, increased BIS from 44.1±0.7 to 58.6 ±1.4 ($p<0.01$) [2]. Chaaben et al. described two cases in which there was an increase in BIS after a bolus injection of ketamine at a dose of 0.5 mg.kg^{-1} and 0.2 mg.kg^{-1} [3]. Hans et al. also showed increased BIS only with a bolus of 0.5 mg.kg^{-1} of ketamine, but anesthesia was performed with sevoflurane [4].

The study conducted by Dahaba showed that ketamine does not follow the pattern observed with other anesthetic agents during induction, with increases in potencies in lower frequency bands [5]. On the contrary, ketamine increased the BIS value, simulating awakening.

Sengupta et al. compared ketamine doses of 0.2 mg.kg^{-1} with 0.5 mg.kg^{-1}, and the results showed that only the 0.5 mg.kg^{-1} dose significantly raised BIS [6]. Kurehara et al. investigated the influence of ketamine on BIS, using a bolus dose of 1 mg.kg^{-1} and, in another group, a bolus of 0.5 mg.kg^{-1}, followed by a continuous infusion of 0.5 mg.kg^{-1} h^{-1} [7]. BIS was significantly increased after ketamine administration.

Nonaka et al. investigated the effects of ketamine on BIS during general anesthesia (BIS maintained between 35 and 45, before ketamine), with targeted controlled infusions of propofol and remifentanil, comparing two groups: the first using 0.2 mg.kg^{-1} and the second 0.5 mg.kg^{-1}, in addition to the control group (without ketamine). The authors found no significant changes when comparing the groups with low doses of ketamine and the control. However, when comparing the control groups and the group with the highest dose of ketamine, the latter showed significant increases ($p<0.05$) [26].

In the KETABIS study, the use of (S)-ketamine 0.25 mg.kg^{-1} IV bolus was compared every hour with (S)-ketamine 0.25 mg.kg^{-1} h-1 in continuous infusion (and without initial bolus) in participants under balanced general anesthesia maintained with desflurane and remifentanil. In both groups, there was an increase in BIS values; however, the increase was statistically significant only in the ketamine bolus group [27]. No studies were found in the literature evaluating different doses of continuous infusion of (S)-ketamine during total intravenous anesthesia and its influence on BIS and pEMG.

In our study, BIS values proved reliable in all groups where (S)-ketamine was used, both in continuous infusions of low or high doses, with no significant differences at the same moments between all groups, even when (S)-ketamine was administered at 0.4 mg.kg^{-1} h^{-1}. In addition, the electromyographic power did not show significant changes, remaining below 30 dB at all times after M1, thus not leading to subcortical activation. Different results were observed by Schüler et al., who observed an increase in BIS values during continuous (S)-ketamine infusion at 10 µg kg^{-1} min^{-1} (after 0.5 mg kg-1 bolus) and 5 µg.kg^{-1} min^{-1} (after a bolus of 0.25 mg kg^{-1}) in participants under manually controlled total intravenous anesthesia [28].

This study is in agreement with others that used ketamine in bolus doses below 0.5 mg.kg^{-1} associated or not with continuous infusion in which no significant BIS value alterations were observed [26,29,30]. The findings evidenced in this trial are limited to a population of young adults without comorbidities. Further studies should be carried out to evaluate the effect of (S)-ketamine in the neuromonitoring of individuals with comorbidities and of other age groups.

In conclusion, the electroencephalographic parameters, BIS and pEMG, did not show significant changes in this total intravenous anesthesia model with the intravenous (S)-ketamine doses used (bolus and infusion). The findings may be valid for the monitoring of anesthetic adequacy.

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None

Conflict of Interest
None

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