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Cerebral and Cardiovascular Effects of Analgesic Doses of Ketamine During a Target Controlled General Anesthesia-a Prospective Randomized Study

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Abstract

Introduction: Ketamine is increasingly being used in various pain settings. The purpose of this study was to assess the effect of an analgesic dose of ketamine in the bispectral index (BIS), spectral edge frequency (SEF-95), density spectral array (DSA), cerebral oximetry (rSO_2) and mean arterial pressure (MAP) during general anaesthesia with a target controlled infusion.

Methods: A prospective, single-blinded and randomized study on adult patients scheduled for elective spine surgery was carried out. After anaesthesia induction with propofol, remifentanil and rocuronium, when a stable BIS value (45-55) was achieved, an automatic recording of BIS, SEF-95, rSO_2 and MAP values during 9 min was performed to establish patients baseline values. Subsequently, patients were randomly assigned to receive a ketamine bolus dose of 0.2 mg/kg, 0.5 mg/kg or 1 mg/kg; all variables were recorded for additional 9 min after the ketamine bolus, in the absence of any surgical stimulus. A p-value <0.05 was considered significant in the statistical analysis.

Results and discussion: Thirty-nine patients were enrolled in the study. Our results show a dose-related increase of SEF-95 and BIS values. DSA demonstrate a shift in the frequency range and power distribution towards higher frequencies. Our results do not show significant differences in MAP and rSO_2 values.

Conclusion: When ketamine is used intraoperatively in analgesic doses, the anaesthetist should anticipate an increase in SEF-95 and BIS values which will not be associated with the level of anaesthesia.

Keywords: Ketamine; Bispectral index (BIS); Spectral edge frequencies (SEF-95); Regional cerebral oxygen saturation (rSO_2); Near-infrared spectroscopy (NIRS); Mean arterial pressure

Introduction

Ketamine was first used simply as an anaesthetic, although it is increasingly used at sub-anaesthetic doses as an analgesic in a wide range of pain settings, including the treatment of acute post-operative pain [1-3]. The anti-nociceptive effect of ketamine is primarily associated with the antagonism of the N-methyl-D-aspartate (NMDA) receptor [2,4-6].

Published literature shows that ketamine is used in abdominal, orthopaedic, spine and gynaecological surgery. Ketamine has demonstrated an increase in time to first analgesic request and a decrease in overall opioid requirement [3]. However, the use of ketamine as an adjuvant analgesic involves different practice regarding doses (0.15-1 mg/kg), route and time of administration [1].

Regardless of the benefits and the increasing use of ketamine, there are some adverse effects, namely visual hallucinations, vivid dreams, hypertension, increased cardiac output, tachycardia and tonic-clonic movements. Ketamine produces the so-called "dissociative" anaesthetic state and it increases cerebral metabolism, cerebral blood flow and intracranial pressure. Moreover, it does not follow the basic anaesthesia related electroencephalogram (EEG) pattern. Anaesthesia with ketamine is characterized by frontally dominant theta activity with abolition of alpha rhythms. EEG activity may be very disorganized and variable at all doses and electrocortical silence cannot be produced. Ketamine alone has been shown to reduce the spectral edge frequencies (SEF-95), an effect that is driven predominantly by increases in absolute theta band power at the expense of alpha band power [5,7,8].

The Bispectral index (BIS), a processed index derived from raw EEG data, is commonly used to monitor the hypnotic component of anaesthesia. Consequently, several authors have assessed the effect of different analgesic doses of ketamine in BIS values [9-14].

Additionally, effects of analgesic doses of ketamine on regional cerebral blood flow, oxygen consumption and regional cerebral blood volume have also been evaluated. The most recent studies showed that analgesic doses of ketamine induce a global increase in cerebral blood flow but no changes on metabolic rate of oxygen [15,16]. However, Engelhard et al. [17] concluded that ketamine in combination with low dose propofol did not alter the dynamic cerebrovascular response. The effects of analgesic doses on cerebral oxygenation using near-infrared spectroscopy (NIRS) have not been studied yet. NIRS is a non-invasive optical technique and current commercially available NIRS devices are used to evaluate regional cerebral oxygen saturation (rSO_2). It is not possible to detect changes in areas located distant from the monitored site, although global cerebral oxygen sufficiency can also be assessed [18].

Concerning cardiovascular effects of ketamine, published data points to its sympathomimetic effects. Nonetheless, certain pharmacologic methods have been used to block these effects, namely benzodiazepines and propofol [5]. Even so hemodynamic effects of analgesic doses of ketamine have not been estimated until now in clinical studies.

The purpose of the present study was to assess the effect of an analgesic dose of ketamine in BIS and SEF-95 values, density spectral array (DSA) of the EEG, rSO_2 and mean arterial pressure (MAP) during a stable target controlled infusion general anaesthesia.

Methods

The study was performed at Centro Hospitalar do Porto (CHP), Porto, Portugal after Hospital Review Board and Ethical Committee approvals (IRB: N/REF.ª249/13(159-DEFI/200-CES)). Written, informed consent was obtained from all study patients.

Participants

Adult patients, ASA physical status I and II, with more than 18 years, scheduled for elective spine surgery were included.

Exclusion criteria included severe uncontrolled high blood pressure; heart failure; cardiac ischemic disease; increased intracranial pressure; increased intraocular pressure; hyperthyroidism or use of anti-thyroid medications; presence of any neurological or psychiatric disease; consumption of illicit drugs and chronic alcohol abuse; liver disease; hypersensitivity to ketamine.

Blinding and randomization

This is a prospective, single-blind and randomized study. A random number generator was used to randomly assign the patients into three groups accordingly to the bolus ketamine dose (0.2, 0.5 or 1 mg/kg). Each patient serves as his or her own control. The patients were blinded to group assignments.

Standard anaesthetic protocol and study design

In the operating room, continuous pulse oximetry, electrocardiography, temperature, invasive blood pressure and neuromuscular blockade monitoring were instituted in all patients. The BIS was monitored using a BIS VISTA^{TM} Bilateral Monitoring System (Covidien, Colorado, US) with a bilateral sensor on the forehead of the patient. The cerebral oximetry was monitored with INVOS^{TM} 5100C Cerebral/Somatic Oximeter (Covidien, Colorado, US) with two sensors placed bilaterally on forehead. Central temperature was likewise monitored by an oesophageal thermometer placed after orotracheal intubation.

General anaesthesia with propofol and remifentanil was achieved using the Orchestra^{TM} Mobile stand (Fresenius Vial, Brézins, France) and a rocuronium (0.6 mg/kg) initial bolus was used for neuromuscular blockade. A continuous infusion of propofol was started at 2000 mg/h until loss of consciousness (LOC), defined by the clinical signs of "loss of eyelash reflex" and "loss of response to name calling". At LOC, the calculated effect site concentration was recorded and the propofol infusion system was adjusted to an effect compartment controlled infusion based on Schnider pharmacokinetic model, according to the BIS values [19]. The infusion profile was continued during the study period. Remifentanil infusion was adjusted accordingly to pharmacokinetic model of Minto [20]; a 3 ng/mL effect site concentration was established initially. After orotracheal intubation the effect site concentration was adjusted to 1 ng/mL.

The study period started when BIS values are steady between 45 and 55, pCO_2 between 34 and 42 mmHg and when mean arterial pressure values were between a 30% interval from baseline value. BIS, SEF, rSO_2 and MAP values were subsequently automatically recorded during 9 min without any surgical or noxious stimuli. During this time the drug infusions were not changed.

Lastly, patients randomly received a bolus of ketamine 0.2 mg/Kg (Group 1), 0.5 mg/Kg (Group 2) or 1 mg/Kg (Group 3). BIS, SEF-95, rSO_2 and MAP values were automatically recorded during further 9 min without any surgical or noxious stimuli.

All BIS and SEF-95 values, cerebral oximetry and hemodynamic data were recorded automatically every 1, 35 and 30 s, respectively, for 18 min.

Sample size

Literature shows that mean BIS value is higher when increasing sub-anaesthetic doses of ketamine are applied [11]. Sample size calculation with a power of 0.80 (β of 0.2) and an α of 0.05 was performed, considering the primary hypothesis of an increase in the BIS after the ketamine bolus of 0.2 mg/Kg. Considering our protocol, we assumed an average BIS value of 50 ± 3 during the 9 min before the administration of ketamine and an increase of 6 (12%) values as clinical significant. This resulted in a sample size of 12 patients per group. Considering the above results and the possibility of patient exclusion due to external complications, a total of 13 patients per group were included in the study.

Statistical methodology

Statistical analysis was performed using IBM SPSS statistics version 22. Categorical variables are presented as frequency and percentage and continuous variables are presented as mean ± standard deviation (SD). The Shapiro-Wilk test was used to test for the normality of data. ANOVA and Kruskal Wallis test were used for continuous variables; Chi-Square test was used for categorical variables, on comparisons between groups. Paired t-test and Wilcoxon two-sample paired signed rank test were used for comparisons within groups. 95% confidence intervals were estimated using bootstrapping (1000 replicates). A p-value <0.05 was considered to be statistically significant.

Results

Sixty-six patients were eligible for participation in the study from December 2013 to June 2015. Twenty-seven patients were excluded, and thirty-nine patients were recruited and assigned to a ketamine group (Figure 1).

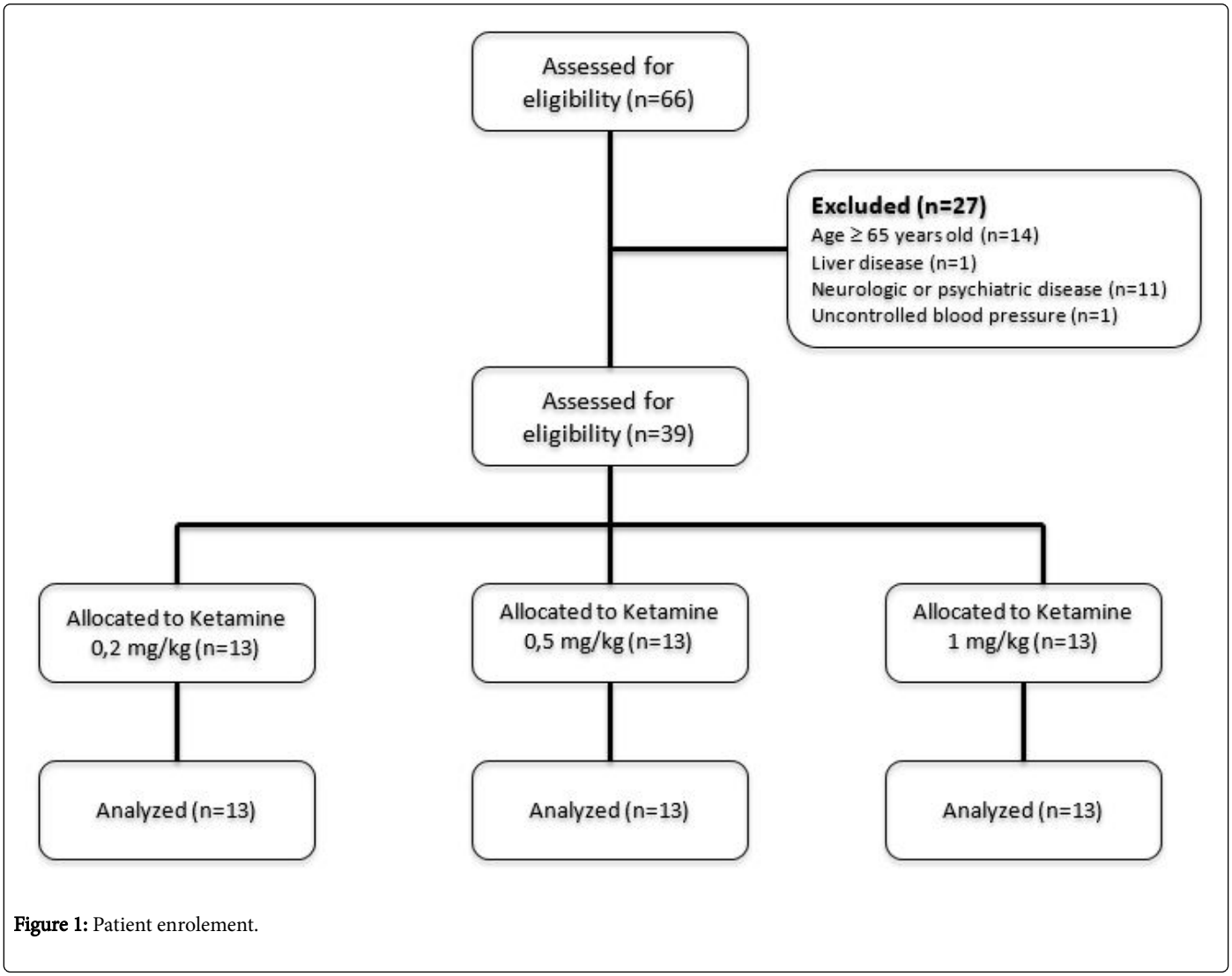

Figure 1: Patient enrolement.

Patient´s demographics and perioperative data are presented in Table 1. There were no statistical significant differences between groups except for age.

Variables	Group 1	Group 2	Group 3
Age	53.77 ± 10.47	49.85 ± 12.56	43.46 ± 8.09
Gender			
Female	6	7	5
Male	7	6	8
ASA			
I	3	5	7
II	10	8	6
BMI	27.89 ± 4.59	27.08 ± 3.18	26.22 ± 3.60
$PaCO_2$	37.32 ± 2.79	37.57 ± 3.89	37.95 ± 3.21
Temperature	36.22 ± 0.53	36.30 ± 0.51	36.09 ± 0.56

Data are presented as frequency or mean ± SD; ASA: American Society of Anaesthesiology; BMI: Body Mass Index (kg/m^2); $PaCO_2$: Partial Pressure of CO_2 in the Arterial Blood (mmHg); Oesophageal Temperature (°C)

Table 1: Patient demographic characteristics and perioperative data.

Outcome variables are illustrated in tables 2-4, respectively for group 1, 2 and 3. Only rSO_2 values proved not to be normally distributed. These tables also show BIS VISTA^{TM} monitor signal quality indicators, namely electromyography indicator (EMG) and signal quality indicator (SQI), which were not different among the groups (p=0.326 and p=0.834, respectively for EMG and SQI).

Group 1 (n=13)				
	Before ketamine		After ketamine	
Variables	Mean ± SD	(95% CI)	Mean ± SD	(95% CI)
EMG	26.09 ± 1.14	(25.50; 26.69)	26.37 ± 1.19	(25.76; 27.01)
SQI	95.62 ± 1.93	(94.60; 96.62)	93.31 ± 5.74	(89.81; 95.76)
SEF-L	16.94 ± 1.23	(16.26; 17.55)	18.27 ± 1.44*	(17.47; 19.03)
SEF-R	17.01 ± 1.19	(16.33; 17.61)	18.32 ± 1.36*	(17.55; 19.03)
BIS-L	49.82 ± 4.45	(47.65; 52.41)	51.97 ± 6.97	(47.93; 55.51)
BIS-R	50.18 ± 4.30	(48.17; 52.65)	52.32 ± 7.43	(48.05; 56.07)
MAP (mmHg)	71.53 ± 7.48	(67.32; 75.45)	70.91 ± 8.32	(66.51; 75.08)
CI: Confidence Interval for the Mean; EMG: Electromyography Indicator; L: left; MAP: Mean Arterial Pressure; R: right; SD: Standard Deviation; SQI: Signal Quality Indicator				

Table 2: SEF, BIS and MAP results before and after Ketamine administration for the patients in Group 1 (Ketamine 0.2 mg/kg) (*p<0.05).

Group 2 (n=13)				
Variables	Before ketamine		After ketamine	
	Mean ± SD	(95% CI)	Mean ± SD	(95% CI)
EMG	25.84 ± 0.95	(25.27; 26.06)	26.28 ± 1.01	(25.62; 26.61)
SQI	94.51 ± 3.98	(91.70; 96.32)	92.27 ± 6.92	(87.38; 94.80)
SEF-L	16.86 ± 0.78	(16.48; 17.31)	19.88 ± 2.08*	(18.85; 21.06)
SEF-R	16.91 ± 0.81	(16.49; 17.37)	19.97 ± 2.14*	(18.88; 21.18)
BIS-L	50.27 ± 3.81	(47.69; 51.87)	56.74 ± 5.99*	(54.21; 60.42)
BIS-R	51.07 ± 3.86	(48.69; 52.82)	57.46 ± 7.74*	(53.98; 62.19)
MAP (mmHg)	74.84 ± 10.95	(68.71; 81.54)	74.97 ± 15.71	(66.15; 84.66)
CI: confidence Interval for the Mean; EMG: Electromyography Indicator; L: Left; MAP: Mean Arterial Pressure; R: Right; SD: Standard Deviation; SQI: Signal Quality Indicator				

Table 3: SEF. BIS and MAP results before and after Ketamine administration for the patients in Group 2 (Ketamine 0.5 mg/kg) (*p<0.05).

Our results do not show statistically significant differences between right and left side for SEF-95 and BIS values in the three groups. Consequently, we have considered the left side values on our analysis. With respect to group 1 (Table 2), our results show an increase of SEF-95 value by 1.34 ± 0.99 after ketamine bolus (p<0.001). Regarding group 2 (Table 3), our results establish an increase of SEF-95 value by 3.03 ± 2.04 (p<0.01) and an increase of BIS value by 6.65 ± 7.40 (p=0.008). The 95% CI for BIS in group 2 shows that the mean BIS after ketamine could be 60. In group 3 (Table 4), we also find an increase of SEF-95 and BIS values, respectively, by 3.30 ± 2.77 (p=0.01) and 6.85 ± 10.35 (p=0.034). The 95% CI for BIS in group 3 shows that the mean BIS after ketamine could increase to 63. DSA, in accordance to SEF-95 and BIS values, demonstrate a shift in the frequency range and power distribution towards higher frequencies in the three groups (Figure 2).

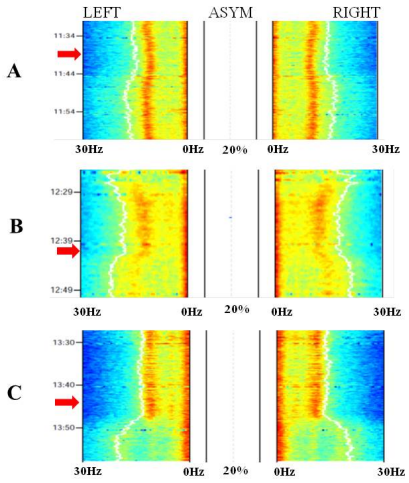

Figure 2: Density Spectral Array in patient groups.

Regarding the differences between SEF-95 and BIS values in the three groups after ketamine bolus (Table 5), our results only show a statistically significant difference between mean SEF-95 values of groups 1 and 2. Furthermore, attending that in clinical practice a BIS value between 40 and 60 indicates an appropriate level for general anaesthesia, our results shows that in group 1, there is no any patient with a mean BIS value higher than 60. In groups 2 and 3, our results show at least 25% and 45% patients with a mean BIS value higher than 60, respectively.

Group 3 (n=13)				
	Before ketamine		After ketamine	
Variables	Mean ± SD	(95% CI)	Mean ± SD	(95% CI)
EMG	26.15 ± 0.77	(25.75; 26.52)	26.87 ± 0.99	(26.37; 27.42)
SQI	94.14 ± 2.43	(92.84; 95.30)	91.89 ± 6.02	(88.35; 94.74)
SEF-L	17.21 ± 1.49	(16.40; 17.91)	20.51 ± 2.46*	(19.32; 21.93)
SEF-R	17.30 ± 1.46	(16.51; 18.04)	20.59 ± 2.39*	(19.43; 21.96)
BIS-L	51.44 ± 4.13	(49.28; 53.60)	58.29 ± 10.34*	(52.73; 63.31)
BIS-R	51.44 ± 4.52	(48.92; 53.84)	58.03 ± 11.34*	(51.53; 63.39)
MAP (mmHg)	77.74 ± 12.73	(71.28; 84.59)	78.23 ± 12.25	(72.11; 84.58)
CI: Confidence Interval for the Mean; EMG: Electromyography Indicator; L: Left; MAP-Mean Arterial Pressure; R: Right; SD: Standard Deviation; SQI: Signal Quality Indicator				

Table 4: SEF. BIS and MAP results before and after Ketamine administration for the patients in Group 1 (Ketamine 1 mg/kg) (*p<0.05).

Difference=value before ketamine–value after ketamine		
Ketamine group	SEF-Difference	BIS-Difference
Group 1 (ketamine 0.2 mg/kg)	-1.34 ± 0.99	-2.15 ± 7.81
Group 2 (ketamine 0.5 mg/kg)	-3.03 ± 2.04	-6.46 ± 7.40
Group 3 (ketamine 1 mg/kg)	-3.30 ± 2.77	-6.85 ± 10.55
Data are presented as mean ± SD		

Table 5: Differences in SEF-95 and BIS values before and after the ketamine bolus.

Considering mean MAP values, our results do not show a statistical significant difference in all the groups before and after the ketamine bolus (Tables 2-4).

Variation=(Baseline-rSO_2 value)/Baseline		
Ketamine group	rSO_2-L	rSO_2-R
Group 1 (ketamine 0.2 mg/kg)	2.08	1.19
Group 2 (ketamine 0.5 mg/kg)	1.72	1.69
Group 3 (ketamine 1 mg/kg)	2.55	3.18
Data are presented as %. L-Left; R-Right.		

Table 6: Variation in rSO_2 after the ketamine bolus.

Moreover, our results show a statistically significant decrease from baseline in right and left rSO_2 values after the Ketamine bolus in all the groups (Table 6). However, when looking at the decrease in rSO_2 values relative to the pre-ketamine bolus values, these are not significantly different between groups and they are on average 2%.

Discussion

For post-operative pain, ketamine has an opioid-sparing effect and conceivably reduce the development of chronic post-operative pain through NMDA receptor blockade and reduction of central sensitization. Ketamine administrations by boluses, infusion or both, before incision, after incision or in the post-operative period are frequent modes of usage [1].

When used in the intra-operative period, practitioners must be aware that the disorganization of the EEG with ketamine administration will possibly be responsible for the failure of BIS monitoring.

Our results show an increase in SEF-95 and BIS values related to the bolus dose. The highest increase is seen after a ketamine bolus dose of 1 mg/kg. In fact, recent studies have shown that the ketamine effect on EEG activity is qualitatively altered when administered in the presence of propofol. In the presence of steady state propofol levels, ketamine is associated with a definitive acceleration of alpha band activity, increasing its peak frequency [21,22]. Additionally, Hirota et al. [10] have previously showed that a ketamine bolus of 0.4 mg/kg significantly increases the BIS values during propofol-fentanyl anaesthesia. Vereecke et al. [9] presented the same effects on the BIS values after a ketamine bolus of 0.4 mg/kg followed by a 1 mg/kg/h continuous infusion. Hans et al. [13] concluded that a ketamine bolus of 0.5 mg/kg also significantly increases the BIS values, during a sevoflurane anaesthesia. Faraoni et al. [12] showed that a ketamine bolus of 0.2 mg/kg administered over 5 min did not increase the BIS value over the next 15 min, during a propofol and remifentanil target-controlled infusion and Sengupta et al. [11] verified, more recently, that a bolus dose of ketamine 0.2 mg/kg did not affect BIS values during propofol-fentanyl anaesthesia whereas a bolus dose of 0.5 mg/kg increased BIS values.

With respect to cardiovascular effects of ketamine, our results do not show a statistical significant difference in all the groups. Nevertheless, this can be related to the lower dose of ketamine in comparison to anaesthetic doses or to the blockade effects of propofol to the sympathomimetic effects of ketamine.

In reference to rSO_2, despite our results show a statistically significant difference between baseline and rSO_2 value after ketamine bolus, we do not consider these deviations as clinically relevant. Actually, specific considerations should be given only to rSO_2 values lower than 50 or to a large decrease (>20%) or increase (>10%) in rSO_2 from baseline. However, it has been already published that rising doses of powerful cortical suppressant anaesthetics as volatile halogenated anaesthetics, barbiturate hypnotics and propofol may rise rSO_2 as oxygen consumption is decreased [23]. Consequently, co-administration of analgesic doses of ketamine and propofol could have opposite effects on rSO_2 and because of that our results only show a small variation of rSO_2 values. Additionally, it has also been published, recently, that the increase of inspired oxygen fraction and end-tidal CO_2 resulted in a significant increase in rSO_2 in patients anesthetized in the beach chair position and that appeared to be independent of anaesthetic choice (desflurane or total intravenous anaesthesia with propofol) [24].

There are potential limitations associated to our study. Firstly, the duration of effects of ketamine on study variables after a single bolus was not quantified. In order to avoid the influence of surgical stimulation on the EEG cortical measurements, we conducted our study before the surgery start, resulting in a rather limited time to collect data. Additionally, an awareness specific questionnaire at the end of surgery was not carried out. Nonetheless, regarding this final limitation, as the propofol and remifentanil doses before the ketamine bolus were maintained after testing bolus dose administration and also, considering that no external stimuli was done to the patient, the level of anaesthesia after ketamine bolus was possibly the same in comparison to the level of anaesthesia before ketamine bolus.

Conclusion

This study shows that when ketamine is used intraoperatively in analgesic doses, during an intravenous target controlled-infusion of propofol and remifentanil, the anaesthetist should anticipate a dose-related increase in SEF-95 and BIS values higher than 60 in some patients, depending on the dose administered, which will not be associated with the level of hypnosis. Furthermore, changes in the power distribution pattern in the spectral matrix of the EEG should also be expected. With respect to cerebral perfusion/oxygenation and cardiovascular effects of ketamine, our results do not show significant differences in all the groups, supporting the idea of mantained metabolic and cerebral blood flow coupling in this ketamine dose setting.

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