EFFECT OF KETAMINE ON BISPECTRAL INDEX DURING PROPOFOL - FENTANYL ANESTHESIA: A RANDOMIZED CONTROLLED STUDY*

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Abstract

Background: The Bispectral Index (BIS) helps in the assessment of the depth of hypnosis. N-methyl-D-aspartic acid antagonist, ketamine, has been used in various doses to decrease postoperative morphine consumption. The purpose of our study was to compare the effects of two different doses (0.5 mg/kg and 0.2 mg/kg) of ketamine on BIS values.

Methods: Forty-five ASA I or II patients undergoing general anesthesia were included in this double-blind, prospective, control trial and randomly allocated into three groups. After induction of anesthesia and tracheal intubation, a propofol infusion was started and titrated to attain BIS values of around 40. After five minutes of stable BIS values and in the absence of any surgical stimulus, patients received either 0.5 mg/kg of ketamine (Group K1) or 0.2 mg/kg of ketamine (Group K2) or normal saline (Group N) as bolus intravenously. BIS values were recorded for the next 15 minutes, at five-minutes interval.

Results: Mean BIS values were significantly increased in Group K1 (63.5) while Group K2 (42.0) failed to show any significant rise. BIS values in Group K2 were comparable to those in Group N.

Conclusion: Thus, under stable propofol anesthesia, a bolus of ketamine 0.5 mg/kg increases BIS values while ketamine 0.2 mg/kg does not.

Introduction

Ketamine is an intravenous anesthetic with analgesic properties in subanesthetic doses. It is a non-competitive antagonist of the N-methyl - D - aspartic acid (NMDA) receptor that participates in excitatory neurotransmission in the central nervous system. Although analgesia produced by ketamine alone does not seem to be equivalent to that produced by opioid analgesics[1-4], ketamine can prevent the development of opioid tolerance via NMDA receptors[5-8] (Fig. 1). Opioid tolerance is a major concern when postoperative pain requires large doses of opioids, such as in major abdominal and thoracic surgeries and in cancer patients with chronic opioid intake. In such patients, Ketamine has proved to be a useful adjuvant for the management of pain[9-11].

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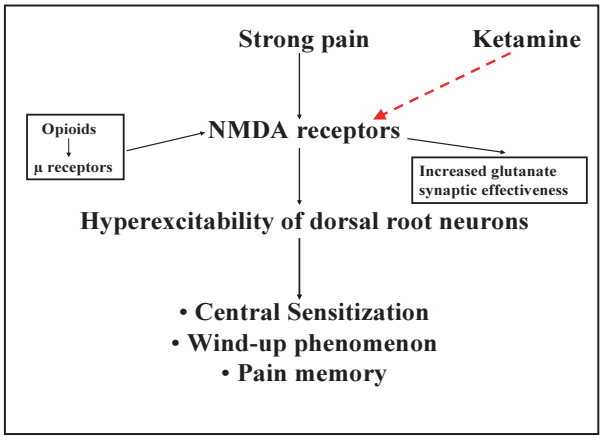
Fig. 1
Pain pathway and action of Ketamine



Among the three components of the triad of anesthesia (hypnosis, areflexia, analgesia) hypnosis is perhaps the most difficult to measure and monitor. The importance of measuring hypnosis or depth of anesthesia lies in the prevention of awareness, which can be a very unpleasant experience and result in tragic consequences for both the patient and the anesthesiologist. Several non-continuous clinical scales for describing sedation levels in adults have been devised, such as the Observer's Assessment of Alertness and Sedation (OAAS) and the Ramsay Scales. However, these have proved inadequate in measuring the depth of anesthesia and have paved the way for processed EEG monitors. ECG monitors provide a continuous measure that encompasses the full range of sedation levels measured by the discontinuous scales. In October 1996, the Food and Drug Administration (Rockville, MD) approved the Bispectral Index (BIS) monitor (Aspect Medical Systems, Newton, MA) as an accepted measure of the hypnotic effect of anesthetics and sedative drugs[12]. BIS was derived by empirically estimating the EEG parameters that best predicted OAAS measurements and may be described as a "probability of state" measure, reflecting the complex nature of consciousness[13]. Today, BIS is widely used to monitor the hypnotic component of anesthesia and guide the administration of volatile and intravenous anesthetics.

Several studies have reported an increase in BIS values, despite a deepening level of hypnosis when ketamine 0.5 mg/Kg is administered as a rapid bolus during general anesthesia[14-15]. Perioperative use of ketamine for acute postoperative pain involves a wide range of ketamine doses (between 0.15 and 1 mg/Kg) used intravenously[16-18]. We undertook this study to determine the dose of ketamine which would provide analgesia but be devoid of its paradoxical effects on BIS. Specifically, the study aims to compare the effect of ketamine on BIS when given at two different doses as i.v. bolus: 0.2 mg/Kg and 0.5mg/Kg.

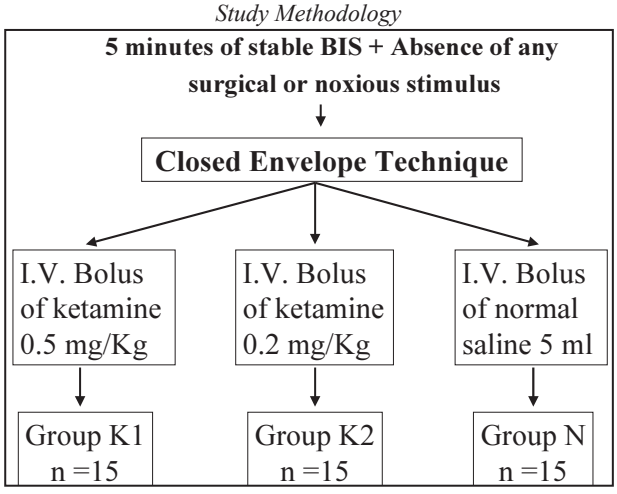
Methods

After approval from the Institutional Review Board, and obtaining written informed consent, 45 patients, ASA I or II, aged 18-65 years, posted for surgeries under general anesthesia were enrolled in this prospective, double-blind, randomized control trial. Selection criteria included the absence of any neurological or psychiatric disease, obesity and arterial hypertension, as well as complete abstinence from illicit drugs and alcohol.

Upon arrival in the operating theatre, non-invasive blood pressure monitoring, continuous electrocardiography and pulse oximetry were instituted in all patients. BIS was monitored using a Quatro TM sensor applied appropriately to the patient's forehead.

Premedication consisted of midazolam 0.02 mg/Kg and glycopyrrolate 0.04 mg/Kg. General anesthesia was induced with propofol titrated to attain a BIS value just below 40 and fentanyl 2 μg/Kg. Tracheal intubation was facilitated with rocuronium 0.6 mg/Kg and maintenance of anesthesia was achieved with propofol infusion titrated to attain BIS values below 40 and air in oxygen (50% inspired fraction). The propofol infusion was continuously titrated to maintain stable BIS of ~ 40. After 5 minutes of stable BIS and in the absence of any surgical or noxious stimulus, patients received randomly (using closed enveloped technique), in double-blind fashion either a bolus of ketamine 0.5 mg/Kg diluted to 5 ml (Group K1; n = 15) or ketamine 0.2 mg/Kg diluted to 5 ml (Group K2; n = 15) or normal saline 5 ml (Group N; n = 15) (Fig. 2). The solution was prepared by an independent anesthesiologist unaware of the study protocol. Non-invasive arterial pressure, heart rate, pulse oximetry, end tidal CO_2 and BIS values were recorded automatically, before the start of the drug administration until the end of the study period of 15 minutes in the absence of any surgical stimulation.

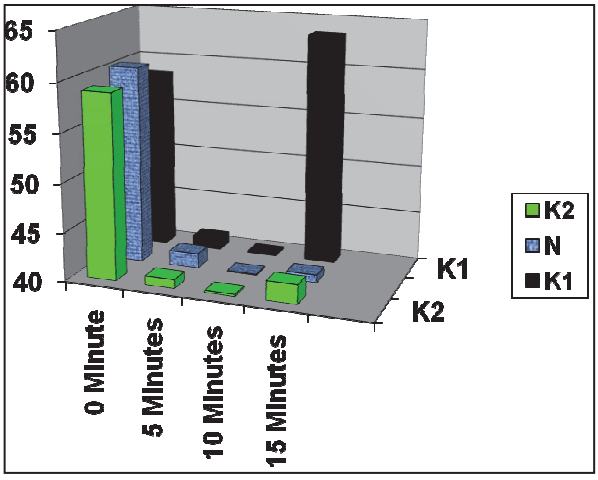
Fig. 2
Study Methodology



Results

SPSS software version 11.5 was used for statistical analysis. Power analysis yielded a sample size of 43 when the confidence level was fixed as 95% to achieve an α error of 0.05 and a β error of 0.2. On analysis of demographic data using Chi-square test, no statistically significant differences were noted among the 3 study groups (Table 1). BIS values were expressed as mean (SD) and analyzed using two-way analysis of variance (ANOVA). Compared to the control group (normal saline 5 ml), statistically significant increase in BIS values was noted in Group K1 (ketamine 0.5 mg/Kg) although Group K2 (ketamine 0.2 mg/Kg) showed no such increase (Table 2) (Fig. 4). Vital parameters, however, did not vary significantly among the groups.

Fig. 4
Graphical Representation of study results



Discussion

Review of relevant literature showed that doses of ketamine administered perioperatively varied almost seven-fold, from 0.15 to 1 mg/Kg i.v. No consensus seems to be present on a specific and systematic administration regimen of ketamine in the context of its preemptive anti-hyperalgesic effects.

Table 1
Demographic Characteristics of Study Sample

	K1	K2	N
	0.5 mg/kg	0.2 mg/kg	Normal saline
No. of Patients	15	15	15
Age (Yrs.)	45 ± 2*	44 ± 2#	43 ± 4
Males (Nos.) (%)	8 (53.3)*	7 (46.7)#	8 (53.3)

* P value > 0.05 compared to N.
\# P value > 0.05 compared to N.

Table 2
BIS Values as Mean (SD)

	K1	K2	N
	0.5 mg/kg	0.2 mg/kg	Normal saline
0 Min (Baseline)	58.4 (3.5)	59.0 (1.69)	60.3 (1.49)
5 Mins (After Induction)	41.2 (3.99)	40.9 (1.66)	41.5 (1.60)
10 Mins (After Stabilization of BIS)	40.2 (0.77)	40.2 (0.77)	40.1 (0.80)
15 Mins (5 Mins after Bolus)	63.5 (2.03)*	42.0 (0.75)#	40.8 (1.01)

** P value < 0.05 compared to N.*
\# P value > 0.05 compared to N.

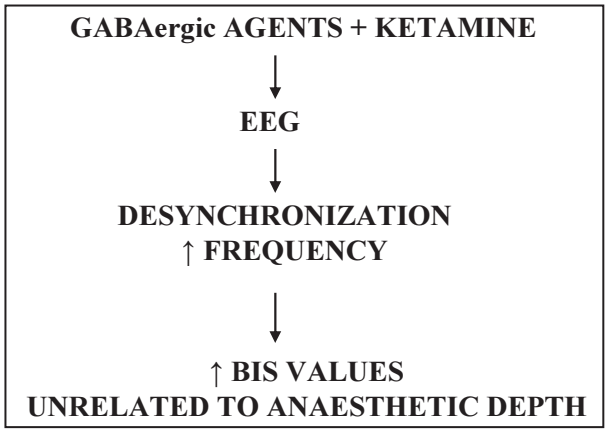
In 1969, Corssen et al[19] reported that ketamine 1 mg/Kg increases the activity of the EEG spectrum. In more recent studies, ketamine shifted the alpha peak of bicoherence induced by propofol to higher frequencies, but did not block their formation[20-22]. Hirota et al[23] showed that a bolus of ketamine 0.4 mg/Kg significantly increases the BIS values during propofol-fentanyl anesthesia. Vereecke et al[15] showed the same effects on the BIS after a bolus injection of ketamine 0.4 mg/Kg followed by a continuous infusion of 1 mg/Kg/h. During sevoflurane anesthesia, Hans et al[14] showed that a bolus of 0.5 mg/Kg ketamine also significantly increases the BIS values. Lauretti and Azevedo[24] have demonstrated the efficacy of 0.2 mg/Kg of ketamine on the decrease of rescue analgesic drug requirement for postoperative pain therapy after vaginoplasty. Faraoni et al[25] showed that under stable propofol and remifentanil TCI anesthesia, a slow bolus infusion of ketamine 0.2 mg/Kg administered over a 5 min period did not increase the BIS value over the next 15 min.

With such a wide spectrum of used doses, we decided to evaluate the effect of two different doses of ketamine on BIS values – 0.5 mg/Kg and 0.2 mg/Kg. Although 0.5mg/Kg of ketamine has been proved to increase BIS values when given as an i.v bolus under sevoflurane anesthesia[14], 0.2 mg/Kg of ketamine has been shown to have no effects on BIS when given as an infusion over 5 minutes[25]. Does this hold true when 0.2 mg/Kg ketamine is administered as a bolus? Can the use of a propofol infusion for maintenance of anesthesia alter the effects of 0.5mg/Kg of ketamine on BIS? We sought the answers to these questions through our study. The results of our study corroborate the findings of Hans et al[14] as well as Faraoni et al[25] in that a bolus of 0.5 mg/Kg of ketamine significantly increases BIS values but 0.2 mg/Kg does not, inspite of differences in the study protocol. Faraoni et al[25] have used propofol and remifentanil TCI anesthesia while we have used propofol infusion titrated according to BIS alongwith fentanyl. Ketamine was administered as a bolus in our study but Faraoni et al[25] administered a slow bolus infusion over a 5 min period.

The hypnotic effect of ketamine is characterized by a dissociative mechanism and an increase in Θ activity of EEG. The increase in BIS in response to ketamine is paradoxical in that the level of anesthesia is deepened by the administration of an additional anesthetic agent. Thus, BIS must be considered to reflect cortical activity rather than the level of consciousness[26].

Ketamine administered in patients anaesthetized with GABAergic agents that depress cortical activity, induces a change in the EEG pattern towards higher frequencies and desynchronisation (Fig. 3). This modification is reflected in an increase in BIS and has no relationship with the depth of anesthesia. Anesthesiologists unaware of this paradox will inadvertently administer additional hypnotic agents in order to decrease BIS values, ultimately landing the patient in an over dose of hypnotic agents which may have profound effects on the perioperative outcome. Once aware, the anesthesiologist will use his clinical skills to determine the depth of anesthesia and thus refrain from chasing the BIS values and causing an over dose of hypnotic agents and better perioperative outcomes.

Fig. 3
Ketamine and its effect on BIS



The reason of increase in BIS values with a low dose of ketamine remains unclear. We also did not evaluate the effects of ketamine on postoperative analgesia, 24 hour morphine consumption or on the incidence of PONV.

In conclusion, a bolus dose of ketamine 0.2 mg/Kg does not affect BIS values during propofol anesthesia whereas higher doses of 0.5 mg/kg increase BIS values despite a deepening level of anesthesia. This increase modifies the relationship between BIS and the hypnotic component of anesthesia. Ignoring this effect could lead to inadvertent over dose of hypnotic agents and thus calls for increased awareness

among anesthesiologists.

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