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# Ketamine has no effect on bispectral index during stable propofol–remifentanil anaesthesia

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**Background.** Ketamine 0.15–1 mg $kg^{-1}$ decreases postoperative morphine consumption, but 0.5 mg $kg^{-1}$ is associated with an increase in the bispectral index (BIS) values that can lead to an overdose of hypnotic agents. The purpose of our investigation was to study the effect of ketamine 0.2 mg $kg^{-1}$ administered over a 5 min period on the BIS during stable target-controlled infusion (TCI) propofol–remifentanil general anaesthesia.

**Methods.** Thirty ASA I or II patients undergoing abdominal laparoscopic surgery were included in this double-blind, randomized study. Anaesthesia was induced and maintained with a TCI of propofol and remifentanil. After 5 min of steady-state anaesthesia (BIS at 40) without surgical stimulation, patients received either an infusion of ketamine 0.2 mg $kg^{-1}$ or normal saline. The test drug was infused over 5 min. Standard parameters and BIS values were recorded every minute until 15 min post-infusion.

**Results.** The baseline mean (SD) value for the BIS was 37 (6.5) for the ketamine group and 39 (8.2) for the placebo group. The highest mean BIS value during the recording period was 41.5 (8.7) for the ketamine group and 40.1 (8.9) for the placebo group. BIS values were not statistically different between the groups ($P$=0.62); there was no significant change over time ($P$=0.65) with no group–time interaction ($P$=0.55).

**Conclusions.** Under stable propofol and remifentanil TCI anaesthesia, a slow bolus infusion of ketamine 0.2 mg $kg^{-1}$ administered over a 5 min period did not increase the BIS value over the next 15 min.

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Ketamine is a non-competitive antagonist of the ionotrophic *N*-methyl-D-aspartic acid (NMDA) receptor that participates in excitatory neurotransmission in the central nervous system.[1 2] Two recent systematic review articles on the perioperative use of ketamine for acute postoperative pain showed a wide range of ketamine doses used i.v. (between 0.15 and 1 mg $kg^{-1}$).[3–5] Bell and colleagues, in a Cochrane review, concluded that ketamine reduces morphine requirements in the first 24 h after surgery and also reduces postoperative nausea and vomiting (PONV); the authors reported that adverse effects were mild or absent.

The bispectral index (BIS) is a processed electroencephalography (EEG) variable widely used to guide the administration of hypnotic drugs.[6] Several studies have reported an increase in BIS values, despite a deepening level of hypnosis when ketamine 0.5 mg $kg^{-1}$ is administered as a rapid bolus during general anaesthesia.[7 8]

The aim of this study was to analyse the effect of low-dose (0.2 mg $kg^{-1}$) ketamine administered over a 5 min period on BIS values during stable target-controlled infusion (TCI) propofol–remifentanil anaesthesia before any surgical stimulation.

## Methods

After approval from the local ethics committee and obtaining written informed consent, 30 patients, ASA I or II, aged 18–65 yr, undergoing gynaecological or digestive laparoscopic surgery were included. Exclusion criteria were BMI under 18 kg $m^{-2}$ or more than 35 kg $m^{-2}$,

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neurological disorder, recent use of psychotropic drugs, and chronic alcohol consumption. Premedication consisted of alprazolam 0.5 mg given orally 30 min before surgery. In the operating theatre, all patients were connected to non-invasive arterial pressure monitoring and pulse oximetry. The BIS was monitored using an XP monitor (Monitor BIS Module A-2000 Revision 3.12) with an electrode BIS Quatro TM (Aspect Medical Systems, Newton, MA, USA and Leiden, The Netherlands) on the forehead of the patient.

For induction of anaesthesia, the effect-site remifentanil[9] TCI was started at 2 ng $ml^{-1}$ followed by a progressive stepwise increase in TCI of the effect-site propofol[10] until loss of consciousness was obtained using a software system called TOOLBOX, designed in the Department of Computer Sciences of our faculty.[11] The drugs were administered using two Fresenius Orchestra® Module DPS infusion pump (Fresenius Vial Infusion Systems, Brezins, France). All patients received a loading dose of rocuronium 0.6 mg $kg^{-1}$ before tracheal intubation, and remifentanil TCI was increased to 5 ng $ml^{-1}$ to prevent the haemodynamic response. Thereafter, remifentanil TCI was titrated down to 2 ng $ml^{-1}$ and the propofol TCI was continuously titrated (between 2.0 and 4.0 μg $ml^{-1}$) to maintain a stable BIS value of ~40. After 5 min of BIS and propofol TCI steady state and in the absence of any surgical or noxious stimulus, patients received randomly in a double-blind fashion either an infusion of ketamine 0.2 mg $kg^{-1}$ ($n$=14) or the same volume of normal saline ($n$=16). The solution was prepared in a 50 cc syringe by an independent anaesthetist and administered using a Fresenius Orchestra® Module DPS infusion pump at the rate of 600 ml $h^{-1}$ over a 5 min period. Non-invasive arterial pressure, heart rate, pulse oximetry, and BIS values were recorded automatically, using the TOOLBOX software system, before the start of the drug administration until the end of the study period of 15 min in the absence of any surgical stimulation.

The BIS values are given as mean (SD). Statistical analysis was performed by two-way analysis of variance for repeated measures, testing for a difference between the groups, a difference between values at various times, and for a time×group interaction. $P<0.05$ was considered as statistically significant. For each time, the 95% confidence interval for the difference was calculated. The propofol values are given as mean (SD) effect-site concentration values. The same statistical analysis was performed for the propofol results.

## Results

The patient characteristics are shown in Table 1. The baseline mean value for the BIS was 37 (6.5) for the ketamine group and 39 (8.2) for the placebo group. The highest mean BIS value during the 15 min of recording period was 41.5 (8.7) for the ketamine group and 40.1 (8.9) for the placebo group (Table 2). BIS values were not statistically different between the groups ($P$=0.62); there was no significant change over time ($P$=0.65) with no group× time interaction ($P$=0.55) (Fig. 1). Figure 2 shows the mean (SD) values of the effect-site concentration of propofol in each group over a 5 min period after start of ketamine injection. There was no significant difference between the groups ($P$=0.69) with no group×time interaction ($P$=0.24) during the recording period.

**Table 1** Patient characteristics

| | Ketamine | Placebo |
|---|---|---|
| Number of patient | 14 | 16 |
| Age (yr) [mean (range)] | 50.3 (24–76) | 56.4 (33–75) |
| Male (no.) (%) | 7 (50) | 10 (62.5) |
| ASA I (no.) (%) | 7 (50) | 4 (25) |
| ASA II (no.) (%) | 7 (50) | 12 (75) |
| BMI (kg $m^{-2}$) (SD) | 27.2 (5.6) | 27.1 (3.9) |

**Table 2** Mean (SD) BIS values during time period after start of infusion

| Time (min) | Ketamine | Placebo | 95% CI for the difference |
|---|---|---|---|
| 0 | 37.38 (6.5) | 39.06 (8.17) | −7.26 to +3.90 |
| 1 | 37.77 (4.9) | 37.5 (8.6) | −5.07 to +5.61 |
| 2 | 35.62 (4.8) | 36.32 (8.3) | −5.87 to +4.47 |
| 3 | 36.69 (6.7) | 38.48 (9.3) | −7.93 to +4.35 |
| 4 | 35.02 (6.4) | 37.65 (9.9) | −8.97 to +3.71 |
| 5 | 39.17 (7.5) | 40.06 (13.1) | −9.03 to +7.25 |
| 6 | 36.95 (8.3) | 38.34 (11.5) | −8.99 to +6.21 |
| 7 | 38.41 (9.2) | 38.47 (9.9) | −7.24 to +7.12 |
| 8 | 39.31 (7.6) | 39.66 (11.2) | −7.63 to +6.91 |
| 9 | 40.71 (9.7) | 39.76 (10.4) | −6.62 to +8.50 |
| 10 | 38.24 (9.1) | 38.94 (10.6) | −8.14 to +6.74 |
| 11 | 38.68 (9.6) | 38.88 (8.3) | −6.89 to +6.49 |
| 12 | 38.71 (6.5) | 39.02 (10.6) | −7.00 to +6.39 |
| 13 | 39.64 (7.7) | 39.48 (8.1) | −5.77 to +6.09 |
| 14 | 41.57 (8.7) | 40.1 (8.9) | −5.13 to +8.07 |
| 15 | 39.4 (8.0) | 38.85 (9.4) | −6.03 to +7.13 |

## Discussion

In the literature, doses of ketamine administered perioperatively varied almost seven-fold, from 0.15 to 1 mg $kg^{-1}$ i.v. Consequently, there is no consensus on a specific and systematic administration regimen of ketamine in the context of the pre-emptive anti-hyperalgesic effects of ketamine or the decrease in postoperative morphine consumption.[5]

In 1969, Corssen and colleagues[12] reported that ketamine 1 mg $kg^{-1}$ 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.[13–15] The precise mechanism of ketamine effects on EEG findings is not well understood, but likely involves the NMDA and gamma-aminobutyric $acid_A$ receptors. These effects explain the modifications observed on the BIS, which

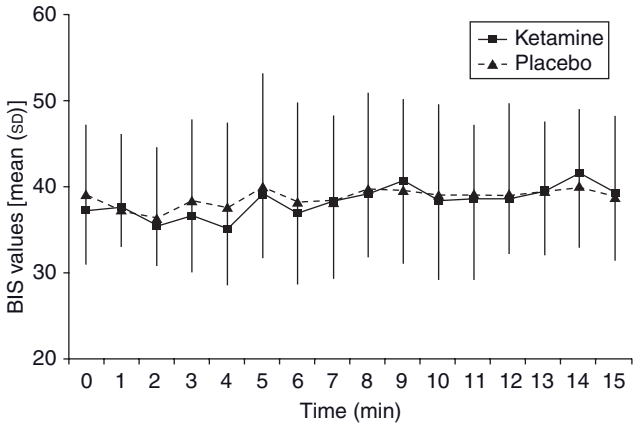


**Fig 1** Mean (SD) of BIS values in the two groups.

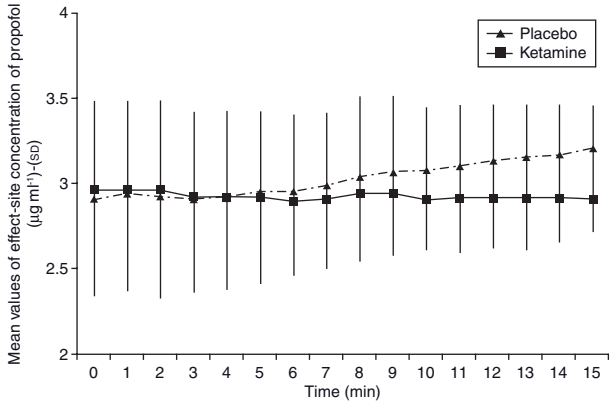


**Fig 2** Mean (SD) values of the effect-site concentration of propofol in each group over a 5 min period after start of ketamine injection.

takes into account the beta power and slow synchronized activity of the EEG and the amount of suppression of activity.

In clinical practice, Hirota and colleagues[16] showed that a bolus of ketamine 0.4 mg $kg^{-1}$ significantly increases the BIS values during propofol–fentanyl anaesthesia. Vereecke and colleagues[8] showed the same effects on the BIS after a bolus injection of ketamine 0.4 mg $kg^{-1}$ followed by a continuous infusion of 1 mg $kg^{-1}$ $h^{-1}$. During sevoflurane anaesthesia, Hans and colleagues[7] showed that a bolus of 0.5 mg $kg^{-1}$ ketamine also significantly increases the BIS values.

As Lauretti and Azevedo[17] have demonstrated the efficacy of 0.2 mg $kg^{-1}$ of ketamine on the decrease of rescue analgesic drug requirement for postoperative pain therapy after vaginoplasty, we decided to evaluate the effect of that dose on BIS values in the context of patients undergoing minor abdominal surgery. The results of our study show that a low dose of ketamine 0.2 mg $kg^{-1}$ administered over a 5 min period does not increase the BIS values when stable propofol and remifentanil effect-site concentrations are maintained and in the absence of any noxious surgical stimulus.

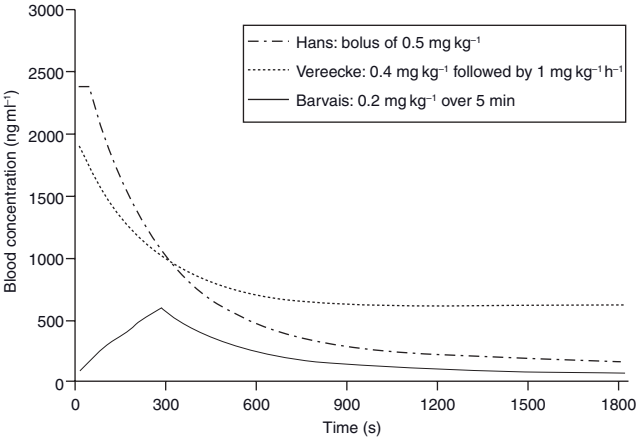


**Fig 3** Pharmacokinetic simulation (simulation parameters: a man, 40 yr old, ASA I, 70 kg, and 1.70 m) of plasma ketamine concentration (TIVAtrainer 8, Frank Engbers)[18] after either the slow administration of 0.2 mg $kg^{-1}$ over 5 min or the rapid bolus administration of a dose of 0.5 mg $kg^{-1}$, or 0.4 mg $kg^{-1}$ followed by 1 mg $kg^{-1}$ $h^{-1}$, using a solution of ketamine 10 mg $ml^{-1}$ and the phamacokinetic model of Ihmsen and colleagues.[19]

The differences in dose and regimen of ketamine administration between our study protocol and previous studies are most likely the reason for the different outcomes found with the ketamine administration. Figure 3 shows the pharmacokinetic simulation (simulation parameters: a man, 40 yr old, ASA I, 70 kg, and 1.70 m) of plasma ketamine concentration evolution (TIVAtrainer 8, Frank Engbers)[18] after either the slow administration of 0.2 mg $kg^{-1}$ over 5 min or the rapid bolus administration of a dose of 0.5 mg $kg^{-1}$, using a solution of ketamine 10 mg $ml^{-1}$ and the phamacokinetic model of Ihmsen and colleagues.[19] The slow infusion of 0.2 mg $kg^{-1}$ generates a peak plasma concentration of 597 ng $ml^{-1}$ after a 5 min infusion. The peak plasma ketamine concentrations calculated after the rapid bolus of 0.5 or 0.4 mg $kg^{-1}$ are 2421 and 1900 ng $ml^{-1}$, respectively.

We have performed a statistical analysis for the mean values of the effect-site concentration of propofol and we have compared the two groups during the recording period. There is no difference between the groups.

Our study was performed before surgery, in order to avoid the influence of surgical stimulation on the EEG cortical measurements, whereas the previous studies[7 8] were performed during surgery. This may account for the different findings. Indeed, in a recent study, Sandin and colleagues[20] have shown that there was variation in BIS during pain stimulation in patients under sevoflurane anaesthesia, with increases in BIS values.

We did not evaluate the effects of ketamine on postoperative analgesia, 24 h morphine consumption, or on incidence of PONV in our study because the selected surgeries were of short duration and usually not very painful. Thus, we could not reinforce the data of Lauretti and colleagues for the effect of a low dose of ketamine 0.2 mg $kg^{-1}$ in the same postoperative context.

In conclusion, in ASA I and II patients under stable propofol and remifentanil TCI anaesthesia and in the absence of surgical stimulation, a slow administration of ketamine 0.2 mg $kg^{-1}$ over 5 min did not increase the BIS values during the next 15 min. The relationship between peak plasma ketamine and BIS values has to be evaluated.

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