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Comparative effects of ketamine on Bispectral Index and spectral entropy of the electroencephalogram under sevoflurane anaesthesia

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Background. The Bispectral Index (BIS) and spectral entropy of the electroencephalogram can be used to assess the depth of hypnosis. Ketamine is known to increase BIS in anaesthetized patients and may confound that index as a guide to steer administration of hypnotics. We compared the effects of ketamine on BIS, response entropy (RE) and state entropy (SE) during surgery under sevoflurane anaesthesia.

Methods. Twenty-two women undergoing gynaecological surgery were enrolled in this double-blind, randomized study. Anaesthesia was induced i.v. and maintained with sevoflurane. Under stable surgical and anaesthetic conditions, patients were assigned to receive either a bolus of ketamine 0.5 mg kg^{-1} or the same volume of saline. Blood pressure, heart rate, BIS, RE and SE were measured every 2.5 min from 10 min before (baseline) until 15 min after ketamine or saline administration. The maximum relative increase in BIS, RE and SE compared with baseline was calculated for each patient. Values are mean (SD).

Results. Baseline values were BIS 33 (4), RE 31 (5), SE 30 (5) for the ketamine patients and BIS 35 (3), RE 33 (5) and SE 32 (6) for the patients receiving saline. BIS, RE and SE increased significantly from 5 min (BIS) and 2.5 min (RE and SE) after ketamine administration, peaking at 46 (8) (BIS), 52 (12) (RE) and 50 (12) (SE) respectively. The maximum relative increase in RE [42.2 (10.4%)] and SE [41.6 (10.9)%] was higher than that of BIS [29.4 (10.4%)]. Blood pressure, heart rate and RE–SE gradient did not change in either group.

Conclusions. Ketamine administered under sevoflurane anaesthesia causes a significant increase in BIS, RE and SE without modification of the RE–SE gradient. This increase is paradoxical in that it is associated with a deepening level of hypnosis.

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The Bispectral Index (BIS) is a processed electroencephalogram (EEG) variable used to monitor the hypnotic component of anaesthesia and guide the administration of volatile and intravenous anaesthetics.[1–3] Entropy is a concept that addresses system randomness and predictability[4] and characterizes chaotic behaviour.[5] This concept applied to the EEG quantifies the degree of complexity and irregularity of the EEG signal. It has also been proposed for assessing depth of hypnosis, the underlying hypothesis being that EEG activity would show more regularity in sedated than in awake patients. Several entropy algorithms have been developed and applied to the EEG signal. Approximate entropy and Shannon entropy have been shown to correlate with end-tidal desflurane concentrations in surgical patients.[5,6] The new Datex-Ohmeda™ S/5™ Entropy Module (M-Entropy™) provides two values of entropy, namely the state entropy (SE) and the response entropy (RE), calculated from specific ranges of frequencies and displayed on the monitor screen as numbers varying between 0 and 100. SE is computed over the frequency range from 0.8 to 32 Hz, which includes the EEG-dominant part of the spectrum and mainly reflects the cortical state. RE is computed over a frequency range from 0.8 to 47 Hz and includes both the EEG-dominant and the electromyographic (EMG)-dominant part of the spectrum. RE and SE have been demonstrated to be useful measures of anaesthetic drug effect.[7,8]

Ketamine is an old drug from the anaesthetist's armamentarium and is currently used at low doses as an adjunct

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to improve perioperative analgesia by preventing acute opioid tolerance and postoperative hyperalgesia in surgical patients.[9–11] When administered during propofol anaesthesia, it has been reported to increase BIS significantly despite a deepening level of hypnosis.[12 13] In these conditions the relationship between BIS and hypnotic depth is modified, which could bias BIS-guided administration of hypnotic agents. Because spectral entropy, such as BIS, is an electroencephalographic measure of the hypnotic effect of anaesthetic drugs, we were interested in comparing the effect of ketamine on BIS, RE and SE during surgery under sevoflurane anaesthesia.

Patients and methods

After approval from the regional hospital ethics committee and informed consent, 22 women, ASA I or II (age 20–63 years, weight 48–78 kg, height 153–170 cm) undergoing routine gynaecological surgery, were enrolled in this double-blind, randomized study. Selection criteria for eligibility included the absence of any neurological or psychiatric disease, obesity and arterial hypertension, and complete abstinence from illicit drugs and alcohol. Surgery consisted in laparoscopic hysterectomies, laparoscopy-prepared vaginal hysterectomies or conventional hysterectomies through laparotomy.

Premedication consisted in alprazolam 0.5 mg and atropine 0.5 mg given orally 1 h before surgery. Upon arrival in the operating theatre, non-invasive blood pressure monitoring, electrocardiography and pulse oximetry were instituted in all patients (Datex-Ohmeda^{TM} S/5^{TM}, Helsinki, Finland). BIS was monitored using the XP device (version 4.0) and a specific quatro sensor (Aspect Medical Systems, Newton, MA, USA and Leiden, The Netherlands). RE and SE were monitored with the Datex-Ohmeda S/5 Entropy Module (M-Entropy^{TM}), using a specific entropy sensor (Datex-Ohmeda Division, Instrumentarium Corporation, Helsinki, Finland). Both sensors were applied appropriately to the patient's forehead, one on each side.

In all patients, general anaesthesia was induced with propofol 1.5 mg kg^{-1} and sufentanil 0.15 μg kg^{-1}, tracheal intubation was facilitated with rocuronium 0.5 mg kg^{-1} and maintenance of anaesthesia was achieved with sevoflurane 2% end-tidal concentration vaporized in air–oxygen (50% inspired fraction). Throughout the procedure, end-tidal P_{CO_2} was monitored and maintained in the 35–40 mm Hg range. No supplementary dose of muscle relaxant was administered before the end of the study period. Under steady-state anaesthetic and surgical conditions, patients received either a bolus of ketamine 0.5 mg kg^{-1} (group K; n=12) or the same volume of normal saline (group S; n=10). According to the randomization process, under the responsibility of a first certified anaesthetist, patients who were operated on on even days received ketamine and those operated on on odd days received saline. A second anaesthetist was in charge of conducting the anaesthetic procedure and was blinded to the randomization and to the syringe containing ketamine or saline. Mean arterial blood pressure (MAP), heart rate (HR), RE and SE were recorded automatically every 2.5 min from 10 min before (baseline conditions) until 15 min after ketamine or saline administration by the Datex-Ohmeda S/5 monitor. A numerical report was printed from the monitor at the end of the procedure. The anaesthetist in charge of the procedure collected BIS data manually each time the automatic non-invasive blood pressure measuring device started measurement (automatic interval time of 2.5 min). The first five values recorded in each patient were averaged to obtain baseline values. The baseline period of recording started 30 min after induction of anaesthesia on average, when all the following criteria were met: stable 2% end-tidal sevoflurane concentration for at least 10 min; stable haemodynamic parameters; full pneumoperitoneum installed in case of laparoscopic surgery; surgical retractors in place in case of laparotomy; and first stages of surgical dissection started in all cases. The difference between RE and SE (RE–SE gradient) was calculated at each time point.

Data were expressed as mean (SD) and analysed using two-way mixed-designed analysis of variance (ANOVA) and Tukey's honestly significant difference (HSD) test for *post hoc* comparisons. Normality of distribution was checked when appropriate. Maximum relative increases in BIS, RE and SE, expressed as a percentage of baseline, were calculated using the formula 100×[(maximum observed increase–baseline)/maximum increase] and compared using Bonferroni-corrected Wilcoxon tests. P<0.05 was considered statistically significant. Power calculation was performed using G-Power software (version 2.0; Franz Faul & Edgar Erdfelder, Trier, Germany).[14] For the RE–SE gradient, a clinically relevant difference of 10, a standard deviation of 2 and a Bonferroni-corrected α value of 0.001 were chosen. Regarding MAP and HR, the clinically relevant difference was set at 30 mm Hg and 30 beats min^{-1}, respectively, the standard deviation at 15, and the same α value was used.

Results

Mean age, weight and height were 46 (12) and 37 (8) yr, 54 (4) and 63 (11) kg and 163 (6) and 164 (5) cm in groups K and S respectively. The repartition of surgeries in groups K and S respectively was 7 and 9 for laparoscopic hysterectomies, 2 and 1 for laparoscopy-prepared vaginal hysterectomies and 3 and 0 for conventional hysterectomies through laparotomy. Baseline values were BIS 33 (4), RE 31 (5), SE 30 (5) for the ketamine patients, and BIS 35 (3), RE 33 (5) and SE 32 (6) for the saline patients, respectively. BIS, RE and SE increased significantly from 5 min (BIS, corresponding Tukey's HSD *post hoc* test: $q_{(120)}$=9.03, P<0.01) and 2.5 min (RE and SE, $q_{(120)}$=4.88, P<0.05 and $q_{(120)}$=5.08, P<0.01, respectively) after ketamine administration, peaking at 46 (8) (BIS), 52 (12) (RE) and 50 (12) (SE) (Fig. 1). The increase of BIS, RE and SE remained

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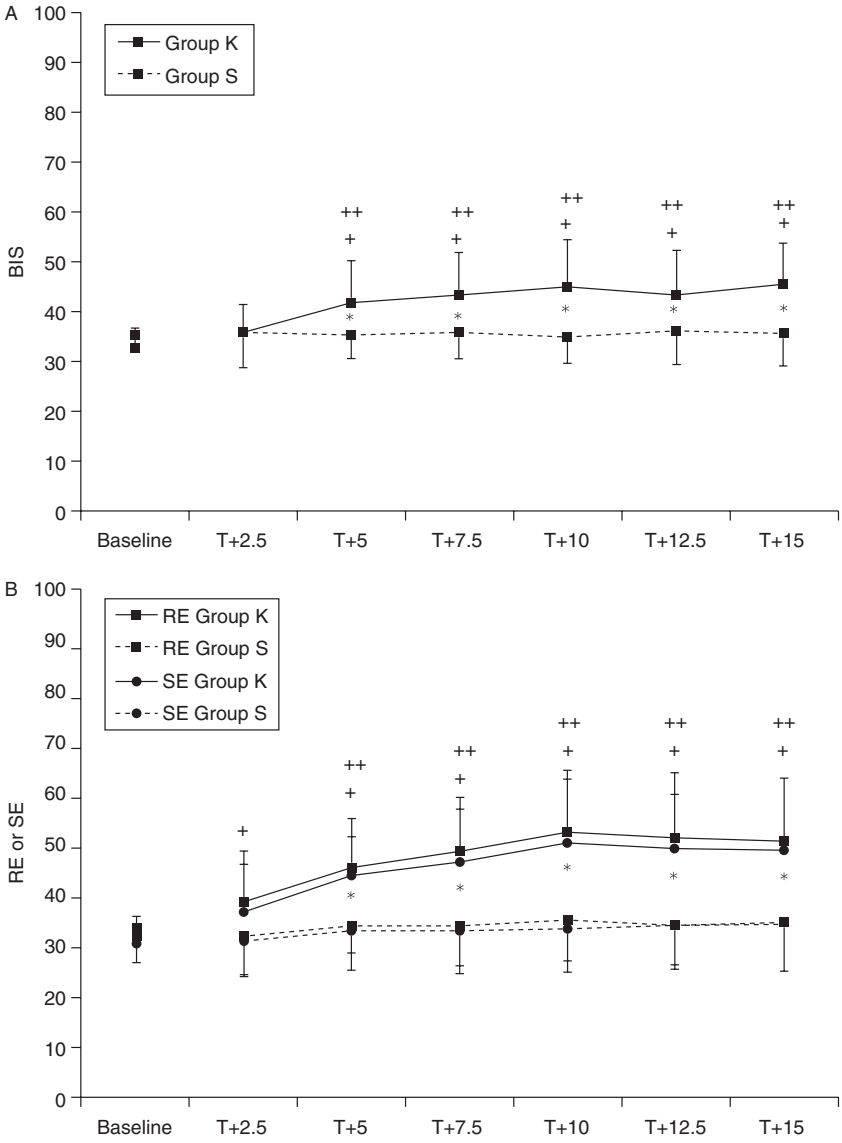

Fig 1 BIS (A), RE and SE (B) recordings in group K and group S during baseline (first five recorded values averaged for each patient) and 2.5 (T+2.5), 5 (T+5), ... and 15 (T+15) min after injection of ketamine or saline. Values are mean (SD). $^{+}$significantly higher than baseline (BIS, RE or SE); $^{++}$significantly higher than T+2.5 (BIS, RE or SE); *significantly higher in group K than in group S. Two-way mixed-design ANOVA and Tukey's HSD.

statistically significant for 10 min after ketamine administration. The maximum relative increase of RE [42.2 (10.4%)] and SE [41.6 (10.9%)] was higher than that of BIS [29.4 (10.4%)] (Bonferroni-corrected Wilcoxon signed rank test: W–=2 when comparing BIS and RE and W–=3 when comparing BIS and SE; critical $W_{(12,\,P<0.01)}$=7). The RE–SE gradient did not change within or between groups [overall mean 1.4 (2.3), range 0–14]. The power of detecting a significant difference in RE–SE gradient greater than 10 with a type 1 error risk of 0.001 was greater than 0.9. MAP and HR did not change and remained similar in both groups [overall mean (SD) for the whole study period: 83 (16) and 89 (17) mm Hg for MAP, and 78 (15) and 78 (13) beats min^{-1} for HR in groups K and S respectively]. The power of detecting a significant difference in MAP or HR greater than 30 with a type 1 error risk of 0.001 approached 0.8.

Discussion

The main finding of this study is that ketamine, administered as a bolus of 0.5 mg kg^{-1} during surgery under sevoflurane anaesthesia, provoked a significant increase in BIS and spectral entropy of the EEG without affecting the gradient between RE and SE. This increase is clinically relevant in so far as some recorded values could exceed the upper threshold recommended for surgical anaesthesia.

The increase in BIS induced by ketamine has already been described in patients under propofol anaesthesia.[12 13] In the study by Vereecke and colleagues, BIS increased a few minutes after the administration of ketamine 0.4 mg kg^{-1} and then decreased progressively in spite of ketamine being continuously infused at 1 mg kg^{-1} h^{-1}.[13] In the present study, the increase in BIS was noted 5 min after ketamine

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0.5 mg kg^{-1} and remained statistically significant up to 15 min after ketamine administration in the absence of a continuous infusion. The fact that BIS remained elevated for a longer time in our study may be related to methodological differences in ketamine administration or to the presence of surgical stimulation during our period of recording. The magnitude of BIS increase in our study is comparable to that observed by Hirota and colleagues[12] after a bolus of ketamine 0.4 mg kg^{-1} [from 44 (1) to 59 (1)]. Baseline BIS values, which were considerably lower in our patients under sevoflurane anaesthesia than in the patients studied by Hirota and Vereecke, who received a propofol infusion, reflect a deeper level of hypnosis. Under the above-defined stable surgical and anaesthetic conditions, the increase in BIS after ketamine is probably related to the effect of this drug on the EEG. The BIS algorithm was elaborated from the statistical analysis of an EEG data bank, allowing identification of parameters significantly correlated to anaesthetic agent concentration and patient reactivity. Those parameters take into account the amount of suppression of activity, β power and slow synchronized activity of the EEG. Each parameter is given weighted coefficients to obtain a linear relationship between BIS on the one hand and plasma concentration of the anaesthetic agent and clinical response of patients on the other hand.[15] The hypnotic effect of ketamine is characterized by a dissociative mechanism, and this drug has been shown to increase θ activity of the EEG.[16] The BIS increase in response to ketamine is paradoxical in so far as the anaesthesia level is deepened by the administration of an additional anaesthetic agent. However, as discussed by Sleigh and Barnard,[17] BIS must be considered to reflect cortical activity rather than the level of consciousness.[14] Ketamine administered in patients anaesthetized with GABAergic agents that depress cortical activity, such as propofol or sevoflurane, induces a change in the EEG pattern towards higher frequencies and desynchronization. This modification is reflected in a BIS increase and has no relationship with anaesthetic depth.

The increase in entropy observed after ketamine is not surprising since entropy, like BIS, quantifies the degree of regularity or synchronization of EEG frequency signals. This increase reflects some desynchronization of the EEG signal resulting from the dissociative action of ketamine rather than any lightening of the anaesthetic depth. As noted for BIS, baseline entropy values in our patients were lower than those usually considered to reflect appropriate depth of anaesthesia (below 60). Those low values reflect the deep level of anaesthesia provided by 2% end-tidal sevoflurane in the absence of major surgical stimulation. Ketamine administration did not change the gradient between RE and SE, which remained very low during the study period [overall mean 1.4 (2.3), range 0–14]. This absence of modification of the RE–SE gradient by ketamine under sevoflurane anaesthesia can be accepted with a reasonably low risk of type 2 error (power >0.9).

Regarding the maximum relative increase of the recorded variables after ketamine, those of RE and SE were significantly higher than that observed for BIS. The reason for this difference probably relies on the calculation algorithm of these variables, but a clear understanding would also require further investigation with simultaneous EEG recording and analysis to determine what EEG component is affected by ketamine administration.

A potential limitation of this study is that the results might have been affected by surgical stimulation. This cannot be considered a major concern. Indeed, baseline parameters were recorded for 10 min during surgery before patient randomization, and therefore constitute a valid control for statistical comparisons. Stability of recorded parameters was checked before ketamine or saline administration, during the baseline period of recording. In addition, patients underwent a moderately painful procedure and no difference was observed in blood pressure and heart rate between the two groups at any time throughout the study. Finally, the time points of recording were similar in the two groups. Vanluchene *et al*. have demonstrated that BIS, RE and SE are fairly good measures of anaesthetic drug effect during propofol-alone anaesthesia.[7] The same has been demonstrated when using sevoflurane alone.[18 19] However, the relationship between depth of anaesthesia and EEG-derived indices is less clear during surgery and during concomitant use of more than one anaesthetic agent.[20] In these circumstances, correct interpretation of the indices must take into account the effect-site concentration of anaesthetic agents, their interactions and the intensity of painful stimulation.[21] In the present study, the recording period can be assumed to reflect a stable balance between anaesthetic regimen and surgical stimulation, as indicated by low baseline values of BIS, RE and SE with small standard deviations. The administration of ketamine introduces an additional potentially confounding factor for correct interpretation of the recorded indices, as it not only modifies the balance between anaesthetic regimen and surgical stimulation towards a deeper anaesthetic level, but also increases the recorded EEG-derived indices.

The choice of the ketamine dose was guided by the studies investigating the effect of ketamine on BIS that have already been cited.[12 13] Furthermore, as ketamine is recommended to prevent opioid tolerance and improve postoperative analgesia,[9–11] our study was designed to mimic a clinically relevant situation. In such circumstances, practitioners must be aware that ketamine administration impairs the interpretation of BIS and entropy monitoring.

Another limitation could be related to a difference in the degree of muscle relaxation between groups. Although this cannot be definitely ruled out in the absence of neuromuscular monitoring, such an eventuality is not likely. Data were recorded after a similar delay from the muscle relaxant induction dose in all patients and no additional dose of muscle relaxant was administered thereafter. We can therefore assume a similar degree of recovery of neuromuscular

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function in both groups on average. The XP version of BIS has been improved from previous BIS versions for optimal EMG activity rejection. BIS has been shown to vary according to muscle relaxation in awake and sedated patients,[22 23] but Greif and colleagues have demonstrated that non-depolarizing muscle relaxation does not affect BIS in deeply unconscious patients.[8] Calculation of state entropy is based on a frequency range that does not include the frequency band of EMG activity and response entropy does take into account facial EMG activity. A between-groups difference in EMG activity would have affected RE–SE gradient rather than state entropy. The mechanism of the increase in BIS and entropy after ketamine administration was not the primary goal of the present study. However, these arguments suggest that this increase cannot be reasonably explained by the ability of ketamine to increase muscle tone.[24] Even if this were the case, it remains that BIS and entropy increase in response to ketamine administration, and this must be taken into account when assessing hypnotic depth with those parameters.

We conclude that, during surgery, ketamine administered as a bolus in patients under sevoflurane anaesthesia increases BIS and entropy of the EEG used to monitor hypnotic depth, despite a deepening level of anaesthesia. Regardless of the mechanism, this increase modifies the relationship between these parameters and the hypnotic component of anaesthesia. Ignoring this effect could lead to inappropriately deepening anaesthesia and overdosing of hypnotic agents. Further studies are needed to determine if this effect of ketamine on spectral entropy is dose-dependent and if it can be observed to the same extent when varying the balance between hypnosis, analgesia and surgical stimulation.

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