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The Effect of a Dissociative Dose of Ketamine on the Bispectral Index (BIS) During Propofol Hypnosis

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Study Objective: *To compare the effect of a standardized stimulus during propofol-only hypnosis on the bispectral index (BIS) value with the effect of the injection of local anesthesia for surgery during ketamine plus propofol hypnosis (dissociative monitored anesthesia care). To determine whether ketamine increases the level of propofol hypnosis when used in dissociative doses.*
Design: *Descriptive case study.*
Setting: *Private practice office plastic surgery suites.*
Patients: *30 nonpremedicated ASA physical status I and II adult female (23) and male (7) patients scheduled for elective cosmetic surgery.*
Interventions: *Hypnosis was induced via slow (60 to 80 drops [gtts]/min), dilute (5 mg/ml) propofol solution. Hypnosis was induced using the BIS monitor as an adjunct to traditional vital signs and verbal contact. Patients were engaged in conversation and note was taken of the BIS value when verbal contact was lost and when BIS appeared to stabilize (BIS_1). A standardized stimulus (0.3 ml 1% lidocaine plain via 30-gauge needle) was applied to the area of the supraorbital nerve. Note was taken of the highest BIS value (BIS_2) in the patient response. The BIS returned to baseline hypnosis (BIS_1) and a 50-mg dissociative dose (independent of body weight) of ketamine was administered. Two minutes were allowed to elapse and then the surgeon was allowed to inject the local anesthesia for the proposed surgery. Note was taken of the BIS value (BIS_3) in response to the surgeon's injection.*
Measurements and Main Results: *The average delta ($BIS_2 - BIS_1$) was 9.5 ± 6.9. Patients did not move in response to the surgeon's injection: $BIS_3 = BIS_1$. When movement occurred, the injection was terminated and additional ketamine was given before resuming the injection. Sixteen patients received ketamine 50 mg, 12 received ketamine 100 mg, one received ketamine 150 mg, and one received ketamine 200 mg. Men required an average 19% less propofol than women in this group.*
Conclusion: *This study demonstrated a positive BIS response to a standardized local anesthetic stimulus during propofol-only hypnosis and a zero response during ketamine plus propofol hypnosis (dissociative anesthesia). Ketamine administered in dissociative doses does not deepen the level of propofol hypnosis. Hypnosis alone does not imply general anesthesia. Patients move in response to inadequate local anesthesia. Because the ketamine analgesia is only transitory and the primary analgesia is not given intravenously, propofol-ketamine technique is not a total intravenous anesthetic technique (TIVA). Instead, propofol-ketamine technique may be classified as a form of monitored anesthesia care (MAC).* © 1999 by Elsevier Science Inc.

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Introduction

The bispectral index (BIS) monitor (Aspect Medical Systems, Natick, MA) has been shown to improve propofol (Diprivan) titration.[1] Aramov *et al.*[2] found no impact on BIS when administering propofol and ketamine (Ketalar) concomitantly. Although Morioka *et al.*[3] reported a paradoxical increase in BIS with ketamine, the hallucinogenic potential of ketamine makes it impractical to study its effect when administered alone in office plastic surgery patients. Hypnotic levels of propofol have been reported to prevent ketamine-induced hallucinations.[4] Propofol-ketamine technique[5] requires hypnosis from propofol prior to administering the dissociative dose of ketamine. Before incorporating the BIS monitor into the author's practice, hypnosis was determined by both the loss of eyelid reflex and the loss of verbal contact with the patient.

This study was undertaken to attempt to separate the effect of a standardized local anesthetic stimulus on BIS of a propofol-only hypnosis anesthetic with the effect of the surgeon's injection of local anesthetic to the surgical field during a dissociative anesthetic (ketamine plus propofol hypnosis). This study may clarify the classification of the propofol-ketamine technique.

Materials and Methods

Thirty ASA physical status I or II patients scheduled for elective, office-based plastic surgery were interviewed by the author prior to surgery. History of medications taken, allergy to medications, smoking history, alcohol tolerance, history of asthma or hepatitis, history of prior surgery, and anesthesia experiences (i.e., nausea, emesis, and hangover), susceptibility to motion sickness, and morning caffeine usage were recorded. Patients taking antidepressants, beta blockers, asthma, and antihypertensive medications were maintained on their usual morning dose, with the exception of diuretics. Regular caffeine users were allowed their morning dose, with the exception of dairy products. Patients who were very hungry on the morning of surgery were allowed toast and jam as a light breakfast no sooner than 2 hours prior to surgery. No patients were taking phentermine (Adipex) or fenfluramine (Pondimin) within 2 weeks of surgery. Patients' age, gender, and weight were recorded. All anesthetics were administered by the author.

Prior to anesthetizing the patient, the upper airway was examined and the heart and lungs were auscultated. Laboratory results as well as chest radiograph and electrocardiogram (ECG), when appropriate, were reviewed as well. ECG, noninvasive automated blood pressure (NIABP), pulse oximetry (SpO_2), and BIS monitoring were explained to the patients. The agents for the anesthetic technique were discussed with all patients, with particular attention given to the expected postoperative dry mouth from the glycopyrrolate (Robinul) and the history and hallucinogenic potential of ketamine. All patients signed informed consent for anesthesia in addition to a separate consent for participation in the BIS Propofol Ketamine Study.

All operating rooms had oxygen, Ambu bags, and suction apparatus in good working order, in addition to "crash" carts with functioning defibrillators. An anesthesia machine was not required. Before induction of anesthesia, a 20- or 22-gauge intravenous (IV) access line catheter established in the left lower arm and connected to a 15 drop/ml IV set connected to a 500-ml bag of lactated Ringer's solution. The NIABP, ECG, SpO_2, and BIS sensor strip were applied to the patient to obtain baseline values before any medications were given. The NIABP was applied to the right upper arm, limb lead II for ECG, left index finger for SpO_2, and forehead for BIS sensor strip.

Hypnosis was induced by means of a slow (60 to 80 drops [gtts]/min) IV infusion of a dilute propofol (5 mg/ml) solution via a 60 gtts/ml IV infusion set piggybacked into the most distal port of the main IV set. One milliliter of deadspace existed between the distal port and the IV access site. A second milliliter of deadspace existed between the most distal injection port of the piggyback set and the main IV set.

No bolus or loading doses of propofol were used to hasten the induction. The patient was engaged in conversation. Other than glycopyrrolate 0.2 mg, no other medications (i.e., metoclopramide, opioids, H_2 antagonists, tranquilizers, or antiemetics) were administered. Patients breathed room air spontaneously. Note was taken of the BIS when loss of verbal contact occurred. When the patient's BIS appeared to stabilize, note was taken of that value (BIS_1). The goal was to achieve a BIS value between 50 and 70 with a loss of verbal contact. The propofol infusion was titrated to achieve this goal. The infusion was varied according to patient requirement rather than a fixed rate. Once a stable level of hypnosis was achieved, the author administered a standardized stimulus (0.3 ml 1% lidocaine via a 30-gauge needle without epinephrine or bicarbonate in a 1-ml syringe) in the area of the supraorbital nerve. The highest BIS value obtained after the stimulus was recorded (BIS_2).

Several patients moved their extremities in response to the stimulus without a change in the muscle activity scale (EMG). The EMG is more responsive to the activity of the facial muscles than that of the extremities. The BIS was allowed to return to the prior baseline hypnotic value (BIS_1). Independent of body weight, a 50-mg bolus IV dose of ketamine then was administered via push through the most distal IV piggyback port (containing a total 2-ml propofol solution or 10-mg propofol), followed by a 2-minute wait. Note was taken of any changes in heart rate or blood pressure (BP) during this interval. After the 2 minutes had elapsed, the surgeon injected the local anesthesia for the surgical procedure. Blocking of the supraorbital nerve was done last in any sequences requiring that block. Any changes in the BIS value (BIS_3) during the surgeon's injection were recorded.

Total anesthesia time, and propofol and ketamine dosages were tallied at the conclusion of the surgery. On

Table 1. Average Patient Data

Gender	N	Propofol (mg)	Ketamine (mg)	Time (min)	Propofol Dosages (mg/min)	Propofol Dosages (μg/kg/min)	BIS_2	BIS_1	Delta
F	23	2356	76*	175	13.5	219	61	51	10
M	7	1899	86†	168	11.5	150	55	47	8

BIS_2 = highest value recorded on the bispectral index; BIS_1 = BIS value that represented stability; Delta = $BIS_2 - BIS_1$.

*Of the female patients, 14 were dissociated with a single dose of ketamine 50 mg, seven patients with ketamine 100 mg, one patient with 150 mg, and one patient with ketamine 200 mg.

†Of the male patients, two were dissociated with a single dose of ketamine 50 mg, and five patients with ketamine 100 mg.

both emergence and discharge from the office, patients were asked about recall of the standardized stimulus, local anesthesia injection, operation, or occurrence of dreams. If patients responded yes to dreaming, they were asked if the dreams were pleasant or unpleasant.

Results

A total of 23 female and 7 male patients participated in this descriptive case study. The females were an average 43 years old (range 23 to 76 years) and weighed an average 61 kg (range 45 to 79.5 kg). The males were an average 41 years old (range 19 to 63 years) and weighed an average 80 kg (range 63 to 96 kg).

Table 1 shows similar lengths of procedures between the female and male groups, as well as similar rates of propofol consumption in milligrams per minute. The average BIS_1 values reflect the average values with propofol-only hypnosis. No patient in this study had surgery performed with propofol-only anesthesia. The average BIS_2 values reflect the average rise in response to the standardized local anesthetic stimulus administered by the author. The average delta ($BIS_2 - BIS_1$) was 9.5 ± 6.9. When BIS was allowed to return to BIS_1 before injection of ketamine, no change in BIS ($BIS_3 = BIS_1$) was observed after the surgeon injected local anesthesia into the surgical field. Sixteen patients were dissociated with a single 50-mg dose of ketamine. Twelve patients required a second 50-mg dose, one patient required a third 50-mg dose, and one patient required a fourth 50-mg dose of ketamine so as to remain still for the local anesthetic injection. Twelve patients (43%) admitted to pleasant dreaming. No hallucinations were reported on emergence from anesthesia or on subsequent office visits for surgical follow-up.

Discussion

Propofol-ketamine technique is a room air, spontaneous ventilation (RASV), IV dissociative anesthetic technique that simulates the conditions of general anesthesia (a relaxed surgical field in a quiet, immobile patient) without the requirement of an anesthesia machine. Despite a recent suggestion by White and SaRego[6] that there is something inherently unsafe about the absence of an anesthesia machine when propofol-ketamine technique is used for office-based anesthesia, in none of the 1,264 cases did any airway management problem arise that was not easily managed by the availability of suction, oxygen, and Ambu bag.[7]

The BIS monitor does not eliminate the need for the traditional monitors of vital signs or judgment on the part of the anesthesia provider. The BIS is a far more complex number than the SpO_2 value. Proper use of the BIS monitor includes qualifying the number with the ancillary information (EMG and signal-to-noise ratio) on the screen before altering clinical care based on changes in the index. The computer program cannot distinguish between facial muscle and central nervous system activity.[8] It is important to note both patient activity as well as the EMG display bar before altering anesthesia management. The monitor is also disturbed by electrocautery devices. A low signal-to-noise ratio is indicative of poor quality input into the computer.[8] "Garbage in, garbage out" is as true for BIS as any other computing system.

The addition of the BIS monitor has increased the ability to provide hypnosis without administering more propofol than necessary to achieve hypnosis. During induction, observing the slope of the BIS values allowed a more precise titration rate for hypnosis. Once the monitor showed evidence of a decreasing slope, it usually became necessary to decrease the drip rate of the propofol to avoid dropping the BIS to unnecessarily low values such as 20 to 40. Less overshoot was observed as fewer patients experienced episodes of desaturation with the induction of hypnosis compared with the pre-BIS experience.[7] Enormous individual variation in propofol requirements occurs,[7] making the qualitative approach simpler than a statistically derived infusion rate.

Hypnosis is essential to prevent ketamine-induced hallucinations.[4] This principle was confirmed by both later publications[5,7] prior to undertaking this study. Most patients in this study lost eyelid reflex and verbal contact with a BIS value in the low 70s. There were three patients who maintained verbal contact with BIS values in the low 40s. That none of these three patients had any recall of the conversations confirms previously published data that the probability of recall is virtually nil when the BIS value is below 60.[1] Although there was a 43% incidence of dreaming, there were no patient complaints about pleasant

[1] Kearse LA Jr, Rosow CE, Sebel PS, et al: The bispectral index correlates with sedation/hypnosis and recall: comparisons using multiple agents [Abstract]. *Anesthesiology* 1995;83:A507.

dreams. This incidence is a sharp contrast to a previously reported rate of less than 1%,[7] but is suggestive that more propofol than necessary was being administered prior to the use of the BIS monitor. Because all patients were alerted to the possibility of dreaming, some patients who did not experience dreaming felt "shortchanged."

Men required an average 19% less propofol than women in this study group. This finding was similar to the 5-year review of 1,264 cases.[7] In that series, men required an average 28% less propofol or an average of 118 μg/kg/min compared with women at 165 μg/kg/min. Individual propofol-sparing effects may have been obscured by averaging or by small sample size. Only one patient in this study had been anesthetized with propofol-ketamine technique for surgery prior to the current study. This patient required 15% less propofol during this study anesthetic than on the prior anesthetic without the BIS monitor.

In response to the standardized local anesthetic stimulus, similar average magnitudes of change in BIS were experienced in both women and men in the propofol-only hypnotic state (i.e., delta 10 vs. 8, respectively). Patients are known to move in response to local anesthetic injection during midazolam-fentanyl monitored anesthesia care. Because propofol has no analgesic properties, it was not surprising that patients moved in response to the standardized local anesthetic stimulus. None of the transitory changes in BIS in this phase of the study was of a duration or magnitude that caused concern for patient awareness. As there was no increase in the EMG display bar with patient movement, one cannot attribute the upward changes to muscle artifact.

Although patients moved in response to the standardized stimulus during propofol-only hypnosis, there was no recall of the stimulus. After 2 minutes was allowed to elapse following administration of the dissociative dose of ketamine, patients did not move in response to the stimulus of the surgeon's local anesthetic injection. Lack of movement in response to local anesthetic injection defines one goal of dissociative anesthesia. In addition to the lack of movement, no changes (either up or down) in BIS ($BIS_3 = BIS_1$) occurred when the surgeon injected local anesthesia during the dissociative (ketamine plus propofol hypnosis) state. An increase in BIS during the dissociative state would likely have been due to inadequate hypnosis. Conversely, a decrease in BIS during the dissociative state would likely have been due to an increasing level of hypnosis. The lack of a downward change in BIS may support the assertion that a dissociative dose of ketamine, when added to a stable level of propofol hypnosis, acts as only an analgesic. Hypnosis from propofol alone does not constitute general anesthesia. The analgesia provided by the dissociative dose of ketamine is ephemeral, lasting only between 10 and 20 minutes (Vinnik, CA, personal communication, March 1992). Patients moved when stimulated in areas of inadequate local anesthesia. Patients remained motionless for the surgery because of the analgesia from the local anesthetic, which is traditionally administered by the surgeon. In the absence of operative pain, adequate muscle relaxation existed to safely perform even classical abdominoplasties in an office setting with RASV.[7]

Properly used, BIS may be a reliable monitor of hypnosis level but not patient movement. Although several patients moved during surgery without changes in any of the usual clinical signs or any changes in either the EMG display bar or BIS or any recall, it was reassuring both to the author and to the surgeons that patient movement was not a sign of patient awareness. The opportunity to titrate hypnotic medication to BIS adds a new and valuable dimension to propofol-ketamine technique. Patient movement in the absence of an increasing BIS may not signify awareness. Conversely, increases in BP without patient movement, and in the absence of increasing BIS, should prompt treatment of BP changes, not the level of hypnosis.

This study demonstrated a positive BIS response to a standardized local anesthetic stimulus during propofol-only hypnosis and no response after a dissociative dose of ketamine plus propofol hypnosis. In addition, this study confirms the earlier cited study by Aramov *et al.*[2] Ketamine in a dissociative dose tends to acts as an analgesic. Because the ketamine analgesia is only transitory and the primary analgesia is not given intravenously, propofol-ketamine technique may not be properly classified as a total IV anesthetic technique (TIVA). Instead, propofol-ketamine technique may be classified as a form of monitored anesthesia care (MAC).

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