

The Effects of Small-Dose Ketamine on Propofol Sedation: Respiration, Postoperative Mood, Perception, Cognition, and Pain

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We compared the effects of coadministration of propofol and small-dose ketamine to propofol alone on respiration during monitored anesthesia care. In addition, mood, perception, and cognition in the recovery room, and pain after discharge were evaluated. In the Propofol group ($n = 20$), patients received propofol $38 \pm 24 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. The Coadministration group ($n = 19$) received propofol $33 \pm 13 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and ketamine $3.7 \pm 1.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Respiration was assessed by using end-expiratory Pco_2 measurements at nasal prongs. After surgeries, mood, perception, and thought were assessed by using visual analog scales, and cognition was assessed by Mini-Mental State Examination (MMSE). Pain after discharge was assessed

by a five-point rating scale in the evening for 5 days. End-expiratory Pco_2 was lower in the Coadministration group ($P < 0.0001$). Mood and MMSE scores were higher in the Coadministration group ($P < 0.004$ and $P = 0.001$, respectively). Pain scores and analgesic consumption after discharge were less in the Coadministration group ($P = 0.0004$ and $P < 0.0001$, respectively). We conclude that coadministration of small-dose ketamine attenuates propofol-induced hypoventilation, produces positive mood effects without perceptual changes after surgery, and may provide earlier recovery of cognition.

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Anesthetic drugs are often combined to enhance their therapeutic effect while minimizing toxicity. Propofol is an IV anesthetic that is often used as an adjuvant during monitored anesthesia care (1). It produces dose-related sedation, amnesia, and anxiety (2). However, propofol is a poor analgesic, causes respiratory depression, and produces transient cognitive impairment (2). Ketamine is an IV anesthetic that produces minimal cardiovascular or respiratory depression (3). The major problem with ketamine is that it produces psychotomimetic effects that may be associated with postoperative dysphoria (4,5). In subanesthetic doses, ketamine possesses analgesic properties (6).

Earlier studies suggested that the analgesic effects of small-dose ketamine complement the sedation provided by propofol during monitored anesthesia care (7,8). Thus, the combination of propofol and ketamine has the potential to provide better sedation with less

toxicity than either drug alone. We therefore tested the hypothesis that the combination of propofol and ketamine produces superior analgesia than propofol alone, and that the combination is associated with improved spontaneous ventilation and faster recovery of postoperative cognitive function.

Methods

Forty outpatients, ASA physical status I to III, scheduled for elective ambulatory surgery under monitored anesthesia care were recruited to participate in this randomized, double-blinded study approved by the IRB at the University of Louisville. Written informed consent was obtained. Exclusion criteria included morbid obesity (>100 lb above ideal body weight), history of psychological problems, use of drugs that affect the central nervous system, substance abuse, chronic pain, pregnancy, seizure disorders, increased intracranial pressure, and cardiovascular, hepatic, renal, or psychiatric disease. Patients were then randomly assigned to one of two groups according to a computer-generated randomization schedule. The Propofol group ($n = 20$) received propofol alone, and

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the Coadministration group ($n = 20$) received a combination of propofol and small-dose ketamine for sedation. The study drug solutions consisted of propofol (10 mg/mL), or propofol (9.8 mg/mL) with ketamine (0.98 mg/mL).

Midazolam, 1–3 mg IV, was given as premedication. Fentanyl, 50 μ g IV, was given on arrival in the operating room. Before the injection of local anesthetics, 1–3 mL of the study drug solution was administered IV. Sedation was maintained by using an IV infusion of the study solution at a rate of 0.3–0.5 mL \cdot kg⁻¹ \cdot min⁻¹. The infusion rate was adjusted to attain the Observer's Assessment of Alertness/Sedation (OAA/S) score of 4 (9). Fentanyl was given in 50- μ g increments for complaints of pain during surgery.

In the postanesthesia care unit (PACU), patients received morphine, 2 mg IV, for pain (visual analog scale [VAS] score >30 mm). Nausea was treated with ondansetron, 4 mg IV. Patients were discharged from PACU to Phase 2 of recovery when both pain and nausea were mild (VAS <30 mm) and patients could tolerate oral liquid intake and sit up. Those who met these criteria at the end of surgery were sent directly to the Phase 2 facility. Patients were discharged home with a prescription for hydrocodone, 7.5 mg when they could walk without dizziness, pain, and nausea.

Ventilation was assessed by recording respiratory rate (RR; min⁻¹), end-expiratory carbon dioxide (Pco₂ [mm Hg], monitored via a plastic catheter inserted through a nasal prong into a nostril), and hemoglobin oxygen saturation. Pain intensity was assessed by using a 100-mm VAS, with 0 = "no pain" and 100 = "worst possible pain." Sedation was assessed by using the five-point OAA/S scale. Drowsiness was assessed by a VAS, with 0 = "wide awake" and 100 = "patients could hardly keep their eyes open" (5). Nausea was assessed by a VAS, with 0 = none and 100 = retching or vomiting.

Perceptual change was assessed in eight categories (i.e., body, surroundings, time, reality, colors, sound, voices, and meaning) by using a VAS anchored by "normal" at one end and "extremely" at the other end (5). Mood states (anxious/composed, hostile/agreeable, depressed/elated, unsure/confident, tired/energetic, and confused/clearheaded) were assessed by using a VAS anchored by "not at all" at one end and "extremely" at the other end (5). Cognition was assessed by using MMSE (0–30) (10). Thought control and the content of thought (i.e., "I have difficulty in concentrating on a thought" and/or "have a flight of ideas"), paranoia (suspicion), and weird (strange) feeling were assessed by using a VAS anchored by "extremely" at one end and "none" at the other end (5). After discharge home, pain intensity at rest and during physical activity was assessed by using a five-point rating scale: 1 = no pain, 2 = mild, 3 = moderate, 4 = severe, and 5 = unbearable.

Physical activity level was assessed by also using a five-point rating scale: 1 = chairbound, 2 = minimal (i.e., can go to the bathroom), 3 = moderate (i.e., can go around the house and garden), 4 = almost normal, and 5 = normal.

Baseline assessments of pain, drowsiness, nausea, mood states, perception, thought process, paranoia, strange or weird feeling; the scores for MMSE, OAA/S, Aldrete Post Anesthesia Recovery Scores (APARS; 0–10); and blood pressure (BP), heart rate (HR), end-expiratory Pco₂, and RR were performed before premedication. Assessments of drowsiness and OAA/S score, as well as BP, HR, end-tidal Pco₂, and RR were repeated every 15 min during surgery. Intraoperative adverse events (i.e., restlessness, violent behavior, hypoventilation [RR <8 /min], apnea, nausea/vomiting, aspiration, chest pain, etc.) were recorded. The assessment of VAS scores, vital signs, and OAA/S was repeated on arrival to the PACU, and every 15 min thereafter, until discharge to Phase 2 recovery. MMSE was repeated 15 min after arrival to the PACU. After discharge home, pain intensity at rest and during physical activity, the amount of hydrocodone, and physical activity were assessed daily for 5 days by telephone. Patients were asked at the fifth postoperative day assessment whether or not the sedation was satisfactory and whether they would prefer the same sedation for a future operation.

Differences between the groups in mean BP, HR, RR, end-tidal Pco₂, oxygen saturation, and Bispectral index were tested by using analysis of variance for repeated measures. These data were tested further by using Student's *t*-test with Bonferroni corrections. Perioperative drug doses, pain score on arrival to the PACU, mood scores, and MMSE scores were analyzed by using the Wilcoxon's Mann-Whitney *U*-test. Pain and activity scores and the amount of hydrocodone consumed after discharge were analyzed by using the Kaplan-Meier product-limit survival method and the log-rank test. Fisher's exact test and its extension to contingency tables were used for the analysis of the data for the first postoperative day. $P = 0.05$ was considered to be statistically significant.

Results

There were no differences in age, body weight, height, gender, type and duration of surgery, or in the amounts of propofol and fentanyl used between the two groups (Table 1).

End-expiratory Pco₂ was lower during the coadministration than during infusion of propofol alone ($P < 0.0001$) (Fig. 1). RR was more frequent in the Coadministration group at 45 min and 60 min during surgery (13.6 ± 0.4 min⁻¹ and 13.8 ± 0.5 min⁻¹ in the Propofol group versus 15.4 ± 0.4 min⁻¹ and $16.0 \pm$

Table 1. Demographic Data for the Two Study Groups

	Propofol (n = 20)	Coadministration (n = 19)
Age (yr)	42.4 ± 14.7	38.0 ± 16.4
Weight (kg)	74.7 ± 13.7	77.1 ± 17.4
Male/female	2/20	4/19
Surgery time (min)	36.4 ± 12.0	36.6 ± 8.2
Laparoscopic BTO	2	1
Cervical conization	1	2
Superficial surgery ^a	17	16
Propofol (mg/kg)	2.2 ± 1.7	2.0 ± 1.1
Fentanyl (μg/kg)	1.1 ± 0.5	1.1 ± 0.5
Ketamine (mg/kg)	0	0.24 ± 0.13

Values are mean ± SD or number (n).

BTO = bilateral tubal occlusion.

^a Includes biopsies, excision of skin lesions, scar revision, small ventral hernias, and minor surgeries of the wrist, hand, and fingers.

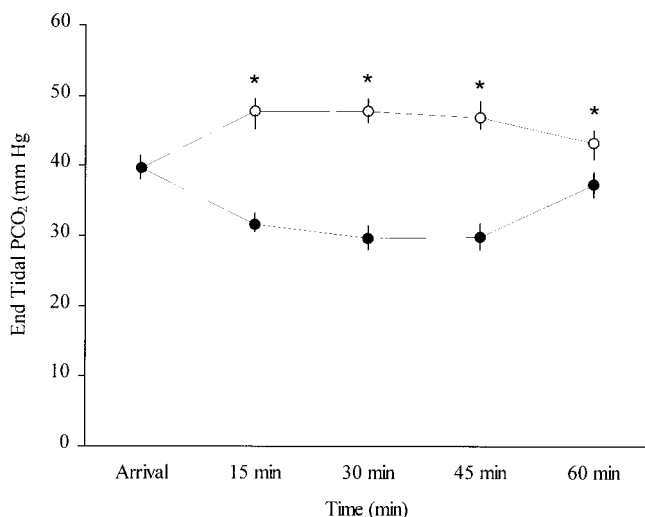


Figure 1. End-tidal PCO₂ (mean with 95% confidence intervals) during monitored anesthesia care in the Propofol (○, n = 20) and Coadministration (●, n = 19) groups. **P* < 0.0001 between the groups.

0.5 min⁻¹ in the Coadministration group, respectively) (*P* < 0.05). There were no group differences in the mean BP, HR, oxygen saturation, OAA/S score, and number of adverse events (there was only one event, i.e., transient restlessness, in the Propofol group).

Seven patients (three in the Propofol group and four in the Coadministration group) had an OAA/S score of four at the end of the operation and were admitted to the PACU recovery facility. The remaining 32 patients were admitted directly to the Phase 2 facility. There was no group difference in the duration of Phase 2 recovery (the Propofol group, 41 ± 11 min, and the Coadministration group, 43 ± 14 min). Pain VAS score on arrival to the Phase 2 facility was higher in the Propofol group (the propofol group, 20 [2.0–20.0] [median with quartile ranges], and the Coadministration group, 0 [0.0–0.0], *P* < 0.0001). However, there were no differences in the amount of opiate medication administered after surgery.

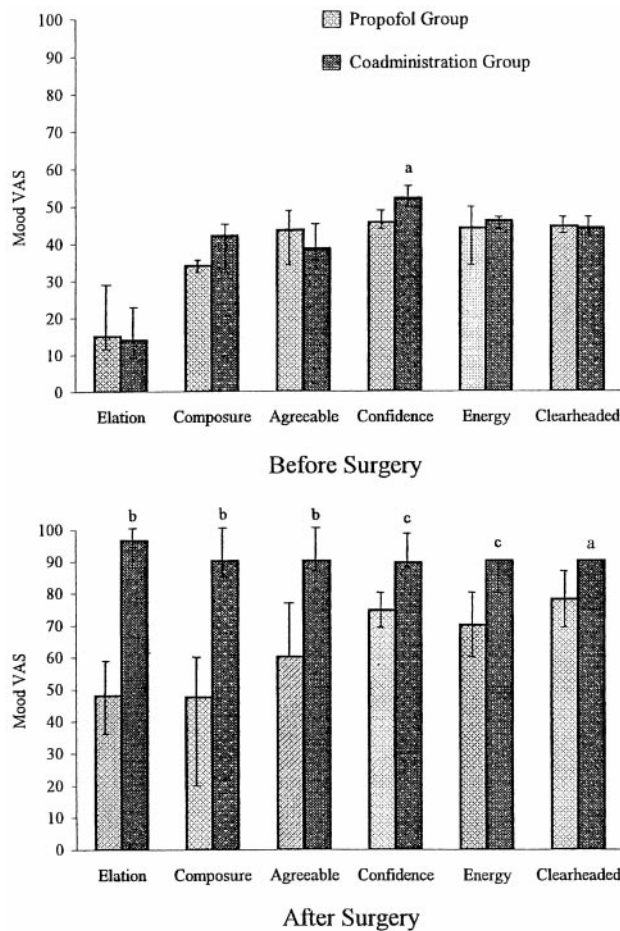


Figure 2. Six subsets of mood states (median with 25 and 75 percentile ranges) before and after surgery in the Propofol (n = 19) and Coadministration (n = 20) groups. ^a*P* = 0.001 versus the Propofol group. ^b*P* < 0.0001 versus the Propofol group. ^c*P* = 0.0004 versus the Propofol group.

There were no group differences in the preoperative scores for mood states except for the subset (i.e., unsure/confident) that was higher in the Propofol group (*P* = 0.001). In both groups, mood scores 15 min after arrival at the PACU were higher than the preoperative scores, and the postoperative scores in the Coadministration group were higher than those in the Propofol group for all mood states (Fig. 2). Preoperative MMSE values were normal in both groups. Postoperative MMSE scores were lower in the Propofol group than in the Coadministration group in three domains of cognitive function (i.e., orientation, *P* < 0.001; attention, *P* < 0.02; and recall, *P* < 0.05) (Table 2). There were no changes in the suspicion (paranoia), weird feeling, or thought process VAS scores in either group. Mild perceptual changes (VAS scores ≤ 20) in surroundings, time, colors, and sounds were observed in four patients in the Propofol group, which were absent 30 min after surgery.

Pain scores at rest and during activity were lower (*P* = 0.0004 and *P* < 0.01, respectively), the amount of

Table 2. Mini-Mental State Examination Scores Before and After Surgery

	Propofol group (n = 20)			Coadministration group (n = 19)			P value*
	Before	After	Difference	Before	After	Difference	
Orientation	10 (10, 10)	8 (7, 8)	-2 (-2, -3)	10 (10, 10)	10 (10, 10)	0 (0, 0)	0.001
Registration	3 (3, 3)	3 (2.25, 3)	0 (-0.75, 0)	3 (3, 3)	3 (3, 3)	0 (0, 0)	
Attention	5 (5, 5)	4 (2.25, 5)	-1 (-2.75, 0)	5 (5, 5)	5 (4.5, 5)	0 (-0.5, 0)	0.011
Recall	3 (3, 3)	2 (2, 3)	-1 (-1, 0)	3 (3, 3)	3 (3, 3)	0 (0, 0)	0.044
Language	9 (9, 9)	9 (8, 9)	-1 (-1, 0)	9 (9, 9)	9 (9, 9)	0 (0, 0)	
Total score	30 (30, 30)	25 (23, 28)	-5 (-7, 2)	30 (30, 30)	30 (30, 30)	0 (0, 0)	0.001

Data expressed as median (25th, 75th percentile ranges).

* Wilcoxon's Mann-Whitney U-test.

hydrocodone was smaller ($P < 0.0001$), and the physical activity level was higher ($P = 0.0001$) in the Coadministration group than in the Propofol group on the first postoperative day. Time (day) to normalization (i.e., score 0 for pain, 0 mg for amount of hydrocodone taken, and score 5 for physical activity) was shorter in the Coadministration group than in the Propofol group for pain at rest ($P = 0.0001$) and activity ($P = 0.0001$), analgesic use ($P = 0.0001$), and physical activity ($P = 0.0001$) (Table 3). All patients rated the sedation as satisfactory.

Discussion

These results confirm the previous reports (7,8), suggesting that the coadministration of small-dose ketamine with propofol improves ventilation during sedation and reduces opioid requirement in the recovery period. No psychotomimetic or perceptual symptoms were observed after surgery. In addition, the patient's mood was significantly better in the recovery room and cognitive function recovered more rapidly in the Coadministration group than in those given propofol alone.

In this study, end-expiratory PCO_2 significantly increased during propofol sedation, but decreased significantly during the coadministration of propofol and ketamine. Because the doses of propofol and fentanyl given during sedation, as well as the premedication, were comparable in both groups, significantly improved ventilation appears to result from the addition of ketamine. Ketamine-induced sympathoadrenal activation may account for improved ventilation (11). However, arousal secondary to the subjective side effects of ketamine (e.g., perceptual changes and anxiety) may also contribute (12).

Subanesthetic doses of racemic ketamine and (S)-ketamine produce a "high" feeling in volunteers and appear to be anxiolytic at smaller dosages (4). The similarity of the feelings produced by ketamine and alcohol has been suggested to be a result of by the N-methyl-D-aspartate (NMDA)-receptor antagonist property of each drug (4). Propofol has also produced

that feeling in volunteers (2,13), and more positive mood in surgical patients than methohexital, thiopental, or midazolam (14-16). Propofol inhibits NMDA receptors in hippocampal neurons (17), and this may have contributed to the positive effects on the mood state (e.g., more elated, energetic, and clearheaded) observed in the Propofol group after operation. It appears to be possible that positive mood alteration observed after the coadministration may have been mediated by the interaction of both propofol and ketamine with the NMDA receptor.

Propofol in sedative doses impairs delayed word recall (13). Postoperative memory impairment in the Propofol group was associated with impaired attention and disorientation, suggesting that the propofol-induced memory impairment may be related to generalized neural inhibition (18). Subanesthetic doses of ketamine also produce a dose-dependent impairment in delayed word recall, frontal lobe function (e.g., vigilance and verbal fluency), and thought processing (4). This memory impairment is not related to concomitant attention or behavioral changes (19). However, ketamine in sedative doses is associated with "busy or racing thoughts," flight of ideas, and electroencephalographic activation (3,20). Furthermore, small-dose ketamine increases thalamic sensory output and arousal (21,22). Our data suggest that sedative effects of propofol may be partially antagonized by the arousal effects of ketamine. This conclusion is consistent with a report showing that propofol inhibits ketamine-induced *c-fos* expression in the rat posterior cingulate cortex, the site that may be responsible for ketamine-induced psychotomimetic activity (23).

The combination of propofol and ketamine significantly improved postoperative analgesia. Patients in the Coadministration group had less pain, required less analgesic medication, and were physically more active after discharge. Both hyperalgesia secondary to tissue injury and opiate tolerance involve activation of NMDA receptors, and subsequent biochemical processes that lead to central sensitization (24). Our results are consistent with a previous study that suggested that small doses of ketamine, an NMDA

Table 3. Time (Day) to Normalization for Pain (Score 0), Amount of Hydrocodone (0 mg), and Physical Activity (Score 5)

	Propofol group (n = 20)	Coadministration group (n = 19)	P value*
Pain at rest	5 (4, 5) 2	3 (2, 4) 0	0.0001
Pain at activity	4 (4, 4) 2	3 (2, 4) 0	0.0001
Activity level	4 (3, 4) 1	2 (1, 3) 0	0.0001
Hydrocodone	4 (4, 4) 1	3 (2, 4) 0	0.0001

Data presented as median (quartile ranges) number of censored observation at postoperative day 5.

* Log-rank test.

antagonist, might exert a prolonged antinociceptive effect in the postoperative period (6,8).

In conclusion, a mixture of propofol and ketamine provided adequate sedation and ventilation during monitored anesthesia care and produced a positive mood state during the recovery period without side effects. The combination also appeared to prompt early recovery of cognitive function and to provide prolonged pain relief. Therefore, the coadministration of propofol and small-dose ketamine appears to be a safe and useful technique for monitored anesthesia care in the ambulatory setting.

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