Comparison of Propofol-Remifentanyl Versus Propofol-Ketamine Deep Sedation for Third Molar Surgery

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This study aimed to compare continuous intravenous infusion combinations of propofol-remifentanyl and propofol-ketamine for deep sedation for surgical extraction of all 4 third molars. In a prospective, randomized, double-blinded controlled study, participants received 1 of 2 sedative combinations for deep sedation for the surgery. Both groups initially received midazolam 0.03 mg/kg for baseline sedation. The control group then received a combination of propofol-remifentanyl in a ratio of 10 mg propofol to 5 µg of remifentanyl per milliliter, and the experimental group received a combination of propofol-ketamine in a ratio of 10 mg of propofol to 2.5 mg of ketamine per milliliter; both were given at an initial propofol infusion rate of 100 µg/kg/min. Each group received an induction loading bolus of 500 µg/kg of the assigned propofol combination along with the appropriate continuous infusion combination. Measured outcomes included emergence and recovery times, various sedation parameters, hemodynamic and respiratory stability, patient and surgeon satisfaction, postoperative course, and associated drug costs. Thirty-seven participants were enrolled in the study. Both groups demonstrated similar sedation parameters and hemodynamic and respiratory stability; however, the ketamine group had prolonged emergence (13.6 ± 6.6 versus 7.1 ± 3.7 minutes, $P=.0009$) and recovery (42.9 ± 18.7 versus 24.7 ± 7.6 minutes, $P=.0004$) times. The prolonged recovery profile of continuously infused propofol-ketamine may limit its effectiveness as an alternative to propofol-remifentanyl for deep sedation for third molar extraction and perhaps other short oral surgical procedures, especially in the ambulatory dental setting.

Key Words: Propofol; Ketamine; Remifentanyl; Deep sedation; TIVA.

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Surgical extraction of third molars is a common dental procedure performed under local anesthesia, often with moderate or deep sedation for additional patient comfort. The surgical treatment and patient populations are generally very homogenous. Because this surgical procedure is often performed in the dental office, it is best to tailor the anesthetic plan accordingly.

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Unlike the traditional hospital setting, most dental offices are not equipped with trained recovery personnel or sophisticated facilities where patients can recover for extended periods of time without negatively impacting office efficiency. In fact, it is common for many patients to recover in and be discharged directly from the dental chair if the anesthetic duration is tightly controlled. Therefore, it is practically and economically advantageous for practitioners to utilize anesthesia techniques that are capable of providing rapid recovery for safe discharge from the ambulatory setting.

The routine use of local anesthesia during dental or oral surgical procedures significantly inhibits noxious afferent surgical stimuli from reaching the central nervous system and thereby decreases the quantity of intravenous (IV) opioids or other anesthetics required during both the intraoperative and immediate postoperative periods. Anesthetic techniques that provide reliable hypnosis, anxiolysis, and amnesia; minimize patient movement and postoperative nausea and vomiting (PONV); and provide rapid recovery are ideal for ambulatory dental procedures. The ability to rapidly titrate profound but brief periods of analgesia/hypnosis is also key. This gives the anesthesia provider the ability to rapidly change the depth of anesthesia in accordance with the level of surgical stimulation. Whereas the pharmacokinetic and pharmacodynamic profiles of propofol make it a nearly ideal sedative, its lack of analgesic properties often necessitates concurrent administration of IV opioids, even when local anesthesia is provided. Fentanyl, alfentanil, and remifentanyl are commonly used opioid agonists that provide rapid onset, relatively short duration, and potent analgesia, all of which are useful during anesthetic induction, the injection of local anesthetic, and the stimulating portions of surgery. The short clinical half-lives of these opioids are particularly beneficial for ambulatory anesthesia, since patients tend to recover faster and have fewer side effects or complications once the drugs are either quickly redistributed or metabolized.

Infusion combinations of propofol and remifentanyl for induction and maintenance of deep sedation or non-intubated general anesthesia (DS/GA) have been shown to be safe and effective in providing analgesia, stable sedation/hypnosis, and satisfactory operating conditions along with a shorter recovery period than other conventional balanced anesthetic techniques.^{1–4} The use of propofol and remifentanyl as a total IV anesthetic or for deep sedation has become an extremely popular technique for ambulatory anesthesia by dentist anesthesiologists, but this approach is not without some potential drawbacks. The concurrent IV administration of propofol and opioids can lead to multiple intraoperative and postoperative complications, most significantly

respiratory and cardiovascular depression and an increased risk of PONV.^{2,4}

Propofol-opioid combinations can cause dose-dependent decreases in ventilation and perfusion.^{2,4,5} This depression can be clinically significant, possibly resulting in a need for short interruptions in surgery to support and stabilize the patient. The continuous infusion of propofol-remifentanyl is no exception and has been shown to cause significant decreases in respiratory rate and hypercarbia.^{2–4} In many cases, respiratory support caused by airway obstruction is required, often by means of simple airway repositioning.² Occasionally the patient's respiratory drive may be depressed enough to require active augmentation with positive pressure ventilation.² While this is not problematic for an endotracheal intubated patient, it does require interrupting the surgery briefly to provide positive pressure ventilation when using an open-airway total IV anesthetic technique.

Hemodynamic depression associated with propofol-opioid combinations usually manifests as bradycardia and hypotension.⁴ For healthy patients who are able to tolerate the reductions in heart rate and blood pressure, these changes may be clinically insignificant. Elderly or medically compromised patients, however, may be far less tolerant of these cardiovascular changes. When propofol-remifentanyl infusions are being used, cardiovascular depression typically responds favorably to a decrease in the anesthetic infusion rate, in addition to a modest fluid bolus or administration of a sympathomimetic agonist drug.

Opioids are known to increase the risk of PONV, which can negatively impact patient comfort, increase postoperative morbidity, and prolong the need for monitored postoperative care, all of which delay discharge of the patient from the dental office. These adverse effects may be mitigated by avoiding or minimizing opioid dosages or by utilizing a rapidly metabolized opioid such as remifentanyl.⁶ Continuous infusion of subhypnotic doses of propofol has been used successfully to prevent and treat PONV.^{7,8} Infusion of propofol in combination with remifentanyl has been demonstrated to decrease the incidence of PONV in comparison to an infusion of remifentanyl alone.⁹

Ketamine, a phencyclidine derivative, is an N-methyl-D-aspartate (NMDA) receptor antagonist that produces a state of dissociative anesthesia.^{10,11} This dissociative mechanism acts nonspecifically on the midbrain and thalamic pathways and is responsible for producing analgesia, amnesia, and the dissociated state, a form of unconsciousness.⁵ Ketamine causes an increase in central sympathetic tone in the normovolemic patient (masking its direct myocardial depressant effect), thereby producing a dose-dependent increase in afterload, heart rate, and cardiac output. Ketamine does not cause significant

depression of the respiratory drive and produces significant bronchodilation secondary to sympathetic stimulation. While ketamine does not prevent obstruction and airway compromise in an unconscious patient, airway reflexes tend to be better preserved than with other induction agents.⁵ The propensity for ketamine to retain laryngeal protective reflexes therefore permits laryngospasm to occur in deeply sedated, dissociated, or unconscious patients.

The combination of propofol and low-dose ketamine is potentially a viable anesthetic alternative capable of providing effective analgesia, high-quality sedation, good operating conditions, and a recovery profile that is perhaps similar to that of propofol and remifentanyl. Low-dose ketamine-propofol combinations used for deep sedation for female patients undergoing breast biopsy procedures were shown to provide significant analgesia, minimizing the need for supplemental opioids during the perioperative period; they also produced minimal hemodynamic changes and respiratory depression.¹² These desirable properties may provide a more physiologically stable sedation, leading to fewer surgical interruptions and increased surgeon satisfaction. Additionally, NMDA receptor antagonists such as ketamine may minimize postoperative pain by blocking “pain windup” (central sensitization) in the spinal dorsal horn and trigeminal nucleus caudalis.^{10,13}

In this era of cost-conscious health care, the relatively high cost of remifentanyl compared to that of ketamine may favor the use of ketamine as a more cost-effective anesthetic alternative to remifentanyl for ambulatory procedures while still allowing for good sedation quality and recovery parameters. This study aimed to compare the combinations of propofol-remifentanyl and propofol-ketamine when used to provide DS/GA for surgical extraction of all 4 third molars with local anesthesia. The present study sought to determine whether the addition of low-dose ketamine to propofol would provide sedation, analgesia, and operating conditions similar to those of remifentanyl with propofol while minimizing the potential for cardiovascular and respiratory depression intraoperatively and decreasing the need for oral analgesics during the immediate postoperative period (24 hours).

METHODS AND MATERIALS

Recruitment

Potential subjects who were offered the opportunity to participate in this institutional review board–approved study were required to be active patients of the Department of Oral and Maxillofacial Surgery within the Col-

lege of Dentistry, Ohio State University. Inclusion criteria included English speakers, ages 18–40 inclusive, with an American Society of Anesthesiologists physical status of I or II, who were men or nonpregnant women. Additionally, because of the possible psychotomimetic effects of ketamine, any patients with a history of psychiatric/psychological conditions were excluded, as were patients with any contraindications or allergies to the study medications. After the initial surgical consultation and acceptance of the treatment plan (extraction of all 4 third molars with DS/GA), a member of the research team introduced the study and requested participation. A payment of US\$20.00 was offered to those participants who completed all phases of the study. Those who agreed to participate reviewed and signed a consent form approved by the investigational research board of the Ohio State University and were scheduled for surgery and given appropriate preoperative instructions. Vital signs consisting of blood pressure, respiratory rate, heart rate, and room air hemoglobin oxygen saturation via pulse oximetry (SpO₂) were obtained, in addition to completion of a baseline preoperative Trieger connect-the-dots test and a 30-second 1-leg standing test, which is a standard roadside sobriety test, prior to discharge from the preoperative consult visit.

Randomization and Blinding

Using Excel, participants were assigned to either study group based on a random number table and their study identification number, which correlated to the order in which they were enrolled in the study. Both the study participants and the surgeons were blinded to the assigned study group. The dentist anesthesiologist was not tasked with providing any subjective opinions regarding the treatment and thus was not blinded.

Infusion Preparation

In a single 60-mL BD syringe, a mixture of propofol-remifentanyl or propofol-ketamine was prepared using an aseptic technique for delivery via an infusion pump. The combination of propofol-remifentanyl was prepared using 40 mL of propofol (1%) mixed with 1 mL of remifentanyl (200 µg/mL), which was reconstituted previously using normal saline. This yielded a propofol-remifentanyl mixture of 10 mg of propofol and 5 µg of remifentanyl per milliliter. The combination of propofol-ketamine was prepared using 40 mL of propofol (1%) mixed with 1 mL of ketamine (100 mg/mL), yielding a propofol-ke-

tamine mixture with 10 mg of propofol and 2.5 mg of ketamine per milliliter.

Surgical Procedure

On the scheduled day of surgery, participants were seated in the operating suite by the dental anesthesia resident member of the research team, where the patient's medical history, consent to treatment, status of no food by mouth, negative urine pregnancy test for women, and presence of an escort were all confirmed. Monitors, including a noninvasive blood pressure cuff, 5-lead electrocardiogram, pulse oximeter finger probe, Salter divided nasal cannula with an end-tidal carbon dioxide (EtCO₂) monitoring line connected to a Passport 2 with gas module SE (Datascope Corp), and pretracheal stethoscope, were all applied. Initial vital signs were recorded at this time. Supplemental oxygen (O₂) was then administered via the applied nasal cannula at 3 L/min. Intravenous access was obtained using a 20-gauge IV catheter, with or without intradermal local anesthesia, in a suitable hand or antecubital vein. After the IV line was secured, midazolam 0.03 mg/kg was immediately administered for baseline sedation. After 3 minutes, a priming bolus of the propofol solution with either remifentanyl or ketamine, depending on group, was delivered using a Baxter Infus OR Pump, dosed according to propofol concentration. An initial priming bolus of 300 µg/kg of the assigned combination, based on the propofol concentration, was followed with a continuous infusion at 100 µg/kg/min of the appropriate solution. Two minutes after completion of the priming bolus, vital signs were recorded (heart rate, blood pressure, respiratory rate, SpO₂, EtCO₂); a rubber bite block was placed intraorally; and an additional bolus of 500 µg/kg of the propofol solution was administered to facilitate the administration of local anesthetic (lidocaine, 2% with 1:100,000 epinephrine) by the surgeon. After 30 seconds, the depth of anesthesia was determined by evaluating the eyelid reflex. If still present, an additional 200 µg/kg bolus of the appropriate propofol mixture was administered every 30–60 seconds as needed to obtund the reflex before the surgeon was permitted to proceed with administration of the local anesthetic. The time of completion of the local anesthesia administration was recorded. Vital signs were recorded every 5 minutes thereafter. During the surgical procedure, the infusion was maintained at 100 µg/kg/min of the propofol component of the mixture. Additional 20-mg boluses of plain propofol were administered as needed from a separate syringe, guided by hemodynamic parameters and facilitation of adequate surgical conditions. Following 2

subsequent “emergency boluses” of propofol, the infusion rate of the combination was increased by 25 µg/kg/min of the propofol component. Parameters for adjusting the infusion rate by ± 25 µg/kg/min included maintenance of adequate spontaneous ventilation, a mean arterial pressure within 20% of baseline, and an adequate depth of sedation for the duration of the surgical procedure. Upon extraction of the last tooth or placement of the final suture, the infusion was terminated. The duration of the infusion and surgery, the total dose of propofol and ketamine or remifentanyl, and the number of additional plain propofol 20-mg boluses were recorded.

Recovery and Postanesthesia Care Unit Experience

Following termination of the infusion, the clinician gently shook the patient's shoulder and simultaneously asked the patient to open his or her eyes every minute until the patient was able to comply. The elapsed time for the participant to open his or her eyes upon command following discontinuation of the infusion was recorded as the emergence time. Participants were then immediately transferred via recovery recliner to the postanesthesia care unit (PACU), and the time of entry was recorded. While the patient was in the PACU, vital signs (heart rate, blood pressure, and SpO₂) were monitored continuously and recorded every 5 minutes. Beginning 10 minutes after arrival in the PACU, the patient was again asked to complete the same Trieger connect-the-dots test and the 30-second 1-leg standing test that had been completed preoperatively. These tests were repeated every 5 minutes thereafter until they were accomplished successfully. A patient was deemed ready for discharge once he or she was able to successfully complete both the Trieger test and the 30-second 1-leg standing test to the same level as at baseline, unless additional postoperative complications precluded discharge. The Trieger test was scored as 1 point taken away for each dot missed and for each millimeter by which each dot was missed. To be considered fully recovered, a patient had to attain a score equal to or better than the baseline presedation score. Likewise, the patient had to stand on 1 leg with the other foot extended somewhat forward for 30 seconds without losing balance to equal presedation success. Successful completion of these psychomotor tests was recorded as the discharge time for study purposes. Postoperative complications or untoward events that occurred during recovery were recorded and addressed. If a patient reported pain in a particular surgical site, local anesthetic was readministered (lidocaine 2% with 1:100,000 epinephrine). Additional

injections needed for postoperative pain were recorded. Ondansetron (4 mg) was administered IV as needed to treat incidents of PONV. Appropriate postsurgical instructions were given, the IV catheter and fluids were discontinued, and provisions were made for a follow-up telephone interview the following day. The patient was given 12 naproxen sodium (275-mg) tablets with the instruction to take 2 tablets every 12 hours for baseline analgesia. Additionally, 16 hydrocodone/acetaminophen (5 mg/500 mg) tablets were dispensed with instructions to take 1–2 tablets every 6 hours as needed for breakthrough pain. The patient was dismissed from the clinic in the care of the escort after any additional questions were answered. This dismissal time was recorded.

Surgeon Satisfaction

Immediately after the surgery, the surgeon was asked to rate his or her satisfaction with the sedation for the placement of the local anesthetic and for the surgical procedure as a whole using a standard 100-mm visual analog scale (VAS) on which 0 mm indicated “very satisfied” and 100 mm indicated “very dissatisfied.” The surgeons were verbally instructed to rate satisfaction with this sedation technique by comparing it only with other open-airway techniques they had experienced.

Patient Postoperative Survey

Participants were contacted via telephone the next day by a member of the research team and asked to complete a short questionnaire. They were asked whether they experienced any PONV within the last 24 hours, whether they had any additional complaints regarding the deep sedation, whether they took their pain medication as recommended, how much they took and at what time interval, and whether they had any recall of the local anesthesia injection or of the surgery. Finally, they were asked to rate their satisfaction with the deep sedation on a 5-point Likert scale. Upon completion of the telephone survey, participants were thanked for their participation and were mailed a check for \$20.00.

Statistical Analysis

Data were summarized and analyzed using SAS 9.2 (SAS Inc). Fisher exact tests and Wilcoxon rank sum tests (exact 2-sided) were used to verify that the 2 drug groups were not different with respect to baseline values

and demographics. Wilcoxon rank sum tests (exact 2-sided) were used to identify drug group differences for continuous outcomes such as age; weight; time of average infusion; average infusion rate; number of propofol rescue boluses required; total propofol delivered; total study drug delivered; hemodynamic and respiratory parameters (heart rate, respiratory rate, mean arterial pressure, etc); emergence and recovery times; and the number of postoperative oral analgesic tablets consumed. Fisher exact tests were used to compare the 2 groups for categorical outcomes such as sex, PONV, number of subjects requiring additional local anesthetic in the PACU, and patient and surgeon satisfaction.

RESULTS

Demographics

Thirty-seven patients between the ages of 18–40 years, all of whom met the inclusion criteria, were recruited and accepted for this study. One participant in the remifentanyl group was excluded after requiring a change in anesthetic techniques secondary to minor but persistent laryngospasm episodes that necessitated positive pressure ventilation. The study protocol was stopped; after a brief conference with the surgical team, endotracheal intubation was performed and a potent inhalation anesthetic was administered. No additional complications were noted during the surgery or during recovery. The patient was subsequently excluded from the study. The 36 remaining patients completed this study successfully. The demographics of the participants in both groups were very similar (Table 1), with no statistically significant differences.

Sedation Dosages

The data were evaluated regarding the average infusion time and rate, total number of plain propofol boluses, total dosage of propofol administered, total dosage of the experimental drug administered, and number of subjects who required additional local anesthesia once in the PACU. There were no statistically significant differences in infusion times, average infusion rates, number of propofol rescue boluses required, or the number of participants who required additional local anesthetic (Table 2). The total dose of propofol administered was statistically significantly different, with the ketamine group receiving 432.1 ± 155.0 mg and the remifentanyl group receiving 321.2 ± 122.7 mg, a difference of 110.9 mg ($P=.029$).

Table 1. Demographics

Parameter	Ketamine	Remifentanyl	P Value	Statistical Test
Age (y)	23.4 ± 3.4	21.7 ± 2.3	.149	Wilcoxon rank sum, exact 2-sided
Sex (male : female)	8 : 10	5 : 13	.489	Fisher exact, 2-sided
Weight (kg)	68 ± 11.1	63.2 ± 13.2	.199	Wilcoxon rank sum, exact 2-sided

Hemodynamic Stability

The measures of hemodynamic stability (heart rate, systolic and diastolic blood pressures, and mean arterial pressure) were statistically evaluated with regard to mean preoperative and intraoperative values (Table 3). The only statistically significant difference noted was in the changes in mean preoperative and intraoperative heart rates. The average change in heart rate for the remifentanyl group was $+4.1 \pm 7.3$ beats/min, and the average change was $+14.5 \pm 7.9$ beats/min for the ketamine group, a difference of 10.4 beats/min ($P=.0007$).

Respiratory Stability

Respiratory rate and SpO₂ data were evaluated using the Wilcoxon rank sum test, exact 2-sided (Table 4). The difference between the mean preoperative and intraoperative respiratory rates was statistically significant. The remifentanyl group had a decrease of 2.35 ± 4.4 breaths/min and the ketamine group showed an increase of 3.9 ± 3.7 breaths/min, a difference of 6.25 breaths/min ($P=.0002$). There was no significant difference in SpO₂ between the 2 groups.

Emergence and Recovery Times

Emergence time was defined as the duration from discontinuation of the infusion to sustained eye opening on command. Analysis of the mean emergence times using the Wilcoxon rank sum test, exact 2-sided (Table

5), revealed a statistically significant difference between the 2 groups. Emergence time for the remifentanyl group was 7.1 ± 3.7 minutes, and for the ketamine group it was 13.6 ± 6.6 minutes, a difference of 6.5 minutes ($P=.0009$).

Recovery time was defined as the time from PACU entry to determination of the patient being declared “street ready/fit” by successful completion of a Trieger test and 30-second 1-leg standing test. The differences in mean recovery times for both groups were evaluated using the Wilcoxon rank sum test (Table 5). Mean recovery time for the remifentanyl group was 24.7 ± 7.6 minutes, and mean recovery time was 42.9 ± 18.7 minutes for the ketamine group, a difference of 18.2 minutes ($P=.0004$). Additionally, none of the participants reported any negative behavioral effects such as dysphoria or hallucinations.

Satisfaction Surveys

The results of the patient and surgeon satisfaction surveys were evaluated using the Fisher exact test (Table 6). The 5-point Likert scale used the following points to measure patient satisfaction with the sedation: 1 indicated “very satisfied”; 2, “satisfied”; 3, “neutral”; 4, “dissatisfied”; and 5, “very dissatisfied.” The VAS used the 0-mm mark to indicate “very satisfied” and the 100-mm mark to indicate “very dissatisfied.” There were no statistically significant differences between the 2 groups for patient satisfaction with the sedation and surgeon satisfaction with administration of the local anesthesia and with sedation.

Table 2. Infusion Dosages

Parameter	Ketamine	Remifentanyl	P Value	Statistical Test
Average infusion (min)	32.3 ± 9.2	28.6 ± 12.8	.154	Wilcoxon rank sum, exact 2-sided
Average infusion rate (μg/kg/min)	151.9 ± 18.5	143.9 ± 29.0	.322	Wilcoxon rank sum, exact 2-sided
Propofol rescue boluses (no.)	4.9 ± 3.3	3.5 ± 2.1	.124	Wilcoxon rank sum, exact 2-sided
Total propofol (mg)	432.1 ± 155.0	321.2 ± 122.7	.029	Wilcoxon rank sum, exact 2-sided
Total study drug (mg or μg)	83.3 ± 28.2 mg	131.4 ± 48.1 μg	n/a	n/a
Additional local anesthesia in PACU* required (no. of subjects)	3	3	> .999	Fisher exact test

* PACU indicates postanesthesia care unit.

Table 3. Hemodynamic Stability

Parameter	Remifentanyl	Ketamine	P Values	Statistical Tests
Preop heart rate (bpm)	72.1 ± 10.8	67.6 ± 11.2	.35	Wilcoxon rank sum, exact 2-sided
Intraop heart rate (bpm) (change)	76.2 ± 10.3 (+4.1 ± 7.3)	82.0 ± 12.4 (+14.5 ± 7.9)	.0007	Monte Carlo estimate
Preop systolic (mm Hg)	121.8 ± 13.2	120.3 ± 17.9	.59	Wilcoxon rank sum, exact 2-sided
Intraop systolic (mm Hg)	110.7 ± 10.6	115.7 ± 8.5	.10	Wilcoxon rank sum, exact 2-sided
Preop diastolic (mm Hg)	72.8 ± 14.2	70.7 ± 10.6	.58	Wilcoxon rank sum, exact 2-sided
Intraop diastolic (mm Hg)	60.0 ± 5.4	63.5 ± 5.8	.075	Wilcoxon rank sum, exact 2-sided
Preop MAP* (mm Hg)	89.2 ± 12.1	87.2 ± 11.2	.74	Wilcoxon rank sum, exact 2-sided
Intraop MAP* (mm Hg)	76.9 ± 6.5	80.9 ± 6.5	.069	Wilcoxon rank sum, exact 2-sided
Change in MAP* (mm Hg)	−12.2 ± 12.5	−6.5 ± 9.9	.13	Wilcoxon rank sum, exact 2-sided

* MAP indicates mean arterial pressure.

Postoperative Oral Analgesic Requirements

Statistical analysis of the quantity of pain medication taken over the first 24 hours (Wilcoxon rank sum test, exact 2-sided) (Table 7) failed to demonstrate any statistically significant difference between the 2 groups.

Postoperative Nausea and Vomiting

PONV was evaluated during the immediate postoperative recovery period and again within the first 24-hour period using the patient telephone survey (Table 8). These data were analyzed using the Fisher exact test. There was 1 patient in the ketamine group who experienced nausea and vomiting during the immediate postoperative period, while the remifentanyl group had none, but this difference was not statistically significant ($P=1.0$). During the first 24-hour period, there were 6 participants in each group who reported nausea and/or vomiting, which was not statistically significant ($P=1.0$).

DISCUSSION

Sedation Dosages

The mean infusion times, mean infusion rates, and number of propofol rescue boluses were not statistically significantly different for the 2 groups, which were de-

mographically similar. However, the ketamine group did receive, on average, 110 mg more propofol than the remifentanyl group, which was statistically and probably clinically significant. This difference included the additional volume of rescue propofol (number of 20-mL boluses)—a mean of 4.9 ± 3.3 rescue boluses was required in the ketamine group versus 3.5 ± 2.1 in the remifentanyl group, resulting in overall volumes of 151.9 ± 18.5 µg/kg/min for ketamine and 143.9 ± 29.0 µg/kg/min for remifentanyl—and the longer average infusion time in the ketamine group (32.3 ± 9.2 min versus 28.6 ± 12.8 min for remifentanyl). While these factors contributed to the increased total dosage of propofol for the ketamine group, none individually were statistically significantly different between the groups. The total dose of propofol/min for the ketamine group was 13.4 mg/min, versus 11.2 mg/min for the remifentanyl group. These dosages are very similar. The differences could reflect the profound analgesia that occurs with the administration of remifentanyl at the dose used, which reduces the surgical stimulation to a higher degree than ketamine at the dose used, effectively lowering the propofol anesthetic requirements of the remifentanyl group. Additionally, the duration of the infusion was based entirely on the surgical procedure and was terminated as soon as the surgeon indicated that the last tooth was extracted or the last suture placed. Because the ketamine group had an emergence time that was 6.6 minutes longer than the remifentanyl group, it may

Table 4. Respiratory Stability

Parameter	Remifentanyl	Ketamine	P Values
Preop respiratory rate (breaths/min)	16.3 ± 3.9	15.2 ± 3.1	.197
Intraoperative respiratory rate (breaths/min) (change)	14.0 ± 2.2 (−2.35 ± 4.4)	19.1 ± 2.8 (+3.9 ± 3.7)	.0002
Preop SpO ₂ * (%)	99.3 ± 1.2	99.6 ± 0.6	.916
Intraop SpO ₂ * (%)	98.2 ± 1.7	98.7 ± 1.2	n/a

* SpO₂ indicates oxygen saturation as measured using pulse oximetry.

Table 5. Emergence and Recovery

Parameter	Remifentanyl	Ketamine	P Values
Emergence (min)	7.1 ± 3.7	13.6 ± 6.6	.0009
Recovery (min)	24.7 ± 7.6	42.9 ± 18.7	.0004

have been possible to terminate the ketamine infusion earlier to facilitate a more rapid emergence.

Most importantly, the difficulty of the surgical extractions was not evaluated preoperatively. The observed difference in infusion times may reflect a discrepancy in the distribution of difficult surgical cases between the groups. Additionally, several surgeons participated in the study and were randomly assigned to each group. Any differences in total propofol used may have been a result of differences between surgeons with respect to experience, gentleness of surgical technique, and surgical speed. Interestingly, both groups had 3 participants in whom the inferior alveolar nerve blocks failed, as self-reported in the PACU. These participants received supplemental nerve blocks, and all reported immediate resolution of pain following injection of the additional local anesthetic.

Lastly, both groups required an increase in the initial infusion rate of 100 µg/kg/min, with a mean increase of 43.9 µg/kg/min for remifentanyl versus 51.9 µg/kg/min for ketamine. The data suggest that 100 µg/kg/min as the initial infusion rate is not adequate and could easily be increased to 120 µg/kg/min or more.

Hemodynamic and Respiratory Stability

Prior to the study, it was believed that hemodynamic and respiratory stability might differ between the 2 groups. Specifically, it was considered likely that the ketamine group would have greater hemodynamic stability as a result of the offsetting effects of propofol-induced vasodilation and inhibition of baroreceptor reflexes with ketamine's mild (at these doses) sympathomimetic properties.¹¹ Likewise, it was believed that the remifentanyl group might have more hemodynamic and respiratory depression. However, there was remarkable hemodynamic and respiratory stability for both groups. The

Table 7. Analgesic Tablets Consumed in the First 24 Hours Postsurgery

Oral Analgesics	Remifentanyl	Ketamine	P Value
Naproxen 550 mg (no. of tablets)	2.6 ± 0.5	2.3 ± 0.8	.31
Acetaminophen/hydrocodone 5/500 mg (no. of tablets)	3.1 ± 2.7	4.1 ± 2.5	.25

only vital signs that were statistically significantly different were mean preoperative and intraoperative heart rates and respiratory rates.

While both groups demonstrated an increase in heart rate from preoperative to intraoperative, the ketamine group showed an increase of 14.5 ± 7.9 beats/min, while the difference for remifentanyl was only 4.1 ± 7.3 beats/min ($P=.0007$). This difference of approximately 10 beats/min was not clinically relevant in this study patient population and was well within 20% of baseline. The increases in heart rate, especially with ketamine, may pose more of a concern in patients with a history of cardiovascular concerns. Neither group required any hemodynamic interventions. Interestingly, both groups showed a decrease in all mean arterial blood pressure parameters and, although the decreases were greater in the remifentanyl group for all parameters, none were statistically significant. It would appear that the dose of ketamine used was not sufficient to significantly offset the depressant hemodynamic effects of propofol.

With respect to respiratory rate, the ketamine group demonstrated a mean increase of 3.9 ± 3.7 breaths/min, while the remifentanyl group demonstrated a mean decrease of 2.35 ± 4.4 breaths/min. This difference of 6.25 breaths/min was statistically significant ($P=.0002$), although not clinically significant, particularly in this patient population. The modest decrease in respiratory rate in the remifentanyl group would not be expected to produce clinically significant hypercapnia, especially for the short duration of these procedures. While many of the participants in both groups demonstrated hypopnea/apnea immediately following induction, it typically resolved once the patient was stimulated by the administration of the local anesthetic. As such, the often-noted hypopnea/apnea was of such

Table 6. Satisfaction Surveys

Satisfaction Survey	Remifentanyl	Ketamine	P Value
Mean patient satisfaction (5-pt Likert scale, 1 = very satisfied)	1.1 ± 0.2	1.3 ± 0.6	.34
Mean surgeon satisfaction: local anesthesia (100-mm VAS*)	13.9 ± 14.4	14.1 ± 17.7	.97
Mean surgeon satisfaction: sedation for surgery (100-mm VAS*)	12.8 ± 11.9	10 ± 14.9	.54

* VAS indicates visual analog scale.

Table 8. Postoperative Nausea and Vomiting

Parameter	Remifentanyl	Ketamine	P Values
Postop nausea	0	1	> .999
Postop vomiting	0	1	> .999
Nausea <24 h	6	6	> .999
Vomiting <24 h	2	3	> .999

extremely short duration that it was very difficult to quantify and not clinically relevant.

There was minimal change in either group with regard to preoperative or mean intraoperative SpO₂ readings. Both groups demonstrated SpO₂ readings of 98%–99%, which were considered neither significantly nor clinically different.

Both groups required respiratory interventions, mostly via occasional airway support/repositioning. Because of the need to stabilize the patient's head to better facilitate the surgical procedure, it was difficult to quantify the amount of additional airway support required for anesthetic concerns. This is a potential area of investigation for future studies. One participant in the remifentanyl group required placement of an airway adjunct (nasopharyngeal airway) to bypass nasal congestion caused by seasonal allergies. None of the participants in either group required positive pressure ventilation at any time, aside from the participant originally in the remifentanyl group excluded on the basis of persistent episodes of laryngospasm.

Emergence and Recovery

The study demonstrated that patients who received propofol-remifentanyl had a shorter emergence from anesthesia, a quicker recovery period, and quicker discharge than patients who received propofol-ketamine. The average emergence time in the ketamine group was almost twice that in the remifentanyl group (13.6 ± 6.6 minutes versus 7.1 ± 3.7 minutes; $P = .0009$). The prolonged emergence could reflect the longer context-sensitive half-life of ketamine compared to that of remifentanyl. However, the ketamine group received on average 110 mg more propofol than the remifentanyl group, although not for any specific reason. The longer (by 3.7 minutes) mean infusion time, the higher mean infusion rate of the propofol (by $8 \mu\text{g}/\text{kg}/\text{min}$), the fact that the ketamine group patients were an average of 5 kg heavier than the remifentanyl patients, and the additional 20-mg boluses of plain propofol (mean of 1.4 boluses) all undoubtedly contributed. It is likely that these factors account at least partially for the ketamine group's prolonged emergence. In a practical clinical scenario, the propofol-ketamine

combination would likely be initiated at a higher infusion rate and terminated earlier to improve on this emergence profile.

The ketamine group had a PACU recovery time that was almost twice as long as that experienced by the remifentanyl group (42.9 ± 18.7 minutes versus 24.7 ± 7.6 minutes; $P = .0004$). While the ketamine group received an average of 110 mg more propofol, the pharmacokinetic and pharmacodynamic profiles of propofol make it unlikely to account completely for the prolonged recovery period. One consideration that was noted by the primary researcher (KK) was that the limiting factor in discharge time was completion of the 30-second 1-leg standing test. Many participants would have been deemed “street fit/ready” even though they could not complete this particularly stringent psychomotor test. Had this test been changed to a 10- or 15-second test, discharge times may have been more comparable.

Also of note, none of the participants in the ketamine group reported negative behavioral effects such as dysphoria or visual hallucinations. In fact, many participants in this group displayed mild euphoria during recovery, which resolved prior to discharge. It is felt that this may have been a mild form of “emergence delirium” that was interpreted as elation rather than the negative disorientation more commonly reported with higher doses of ketamine. This phenomenon generally was not observed in the remifentanyl patients, who appeared either unimpaired or mildly sedated without euphoria.

Surgeon Satisfaction

No statistically significant difference was noted between the groups with respect to the surgeon's satisfaction with the sedation during the administration of local anesthesia or the surgical procedure. Of note, no measures were performed to validate intrarater or interrater reliability. A total of 4 surgeons participated in the study; 3 of the surgeons operated on 33 of the 36 participants.

Patient Satisfaction

There was no statistically significant difference between the groups with respect to patient satisfaction with the sedation (remifentanyl group, 1.1 ± 0.2 ; ketamine group, 1.3 ± 0.6 ; $P = .34$). While patients were asked to rate their satisfaction with the sedation on a scale of 1 (“very satisfied”) to 5 (“very dissatisfied”), they were not given any indicators or guidelines to assist with their decision. The use of guidelines such as “How likely would you be to

have this same sedation again”? would potentially have led to varying results. The investigators expected that there might be a difference only if there was a negative perioperative experience that the patients remembered about either sedation protocol. However, since all patients were deeply sedated and likely amnesic for the procedure, it was expected that patients would have high satisfaction levels.

Postoperative Pain Control

Ketamine is a potent antagonist to NMDA receptors, which has been identified as crucial in the induction and maintenance of central sensitization (ie, pain).^{10,11,14} Blocking of the NMDA receptors with ketamine prior to the initial potentially painful insult (surgery), thereby reducing pain wind-up and central sensitization, makes it possible to reduce postoperative pain (pre-emptive analgesia).¹⁰ The investigators theorized that the ketamine group may potentially demonstrate lower postoperative oral analgesic requirements because of ketamine's potential for pre-emptive analgesia. However, using the patients' reported frequency and dosage of oral pain medication consumed, statistical analysis failed to show any difference between the groups in the quantity of naproxen and acetaminophen/hydrocodone taken during the first 24 hours. The absence of any appreciable pre-emptive analgesia may reflect a lack of specificity by measuring the quantity of oral pain medication taken at 24 hours or simply that the dose of ketamine was too low to cause an effect. Importantly, because local anesthesia was used, the effects of the ketamine may have waned before the local anesthesia wore off. Thus, significant afferent noxious input may not have reached the central nervous system, thereby limiting any ketamine NMDA receptor blockade effects.

Postoperative Nausea and Vomiting

Regarding the incidence of PONV, there was no significant statistical or clinical difference between either group during the immediate postoperative period ($P > .999$). In fact, only 1 participant experienced nausea and vomiting during the immediate postoperative period and required administration of a single rescue dose of ondansetron (4 mg IV). This particular subject was in the ketamine group and was poorly compliant with instructions to bite firmly on the gauze surgical site dressings. While the emetic effects of ketamine may have caused the PONV, it was felt that this was more likely related to

poor patient compliance that led to swallowing blood. The mild euphoria that was common in the ketamine group may have contributed to the poor patient compliance. Following administration of the rescue antiemetic and strong encouragement of the patient to apply constant pressure to the surgical sites with the gauze packs, the mild hemorrhage quickly ceased. The participant had no recurrent episodes of PONV and was discharged home shortly thereafter.

Both groups had a number of subjects who reported nausea and/or vomiting during the first 24 hours. Several participants in each group reported nausea and/or vomiting that coincided temporally with the acetaminophen/hydrocodone tablets taken postoperatively for breakthrough pain. The PONV was likely caused by the postoperative opioid pain medication, as opioids have an established history of increasing the incidence of nausea and vomiting.¹² Postoperative bleeding may also have been a factor. It must be stated that all patients were given postoperative instructions that included eating soft foods, staying well hydrated, and avoiding taking pain medication on an empty stomach. However, many of the patients who reported PONV after taking the opioid pain medication admittedly did not follow the postoperative instructions.

Cost Analysis

The current market cost for remifentanyl is \$49.00 for a 1-mg vial, and ketamine costs \$9.35 per 500 mg/5-mL vial. Unit analysis yields a cost of \$0.05/ μ g of remifentanyl used and \$0.02/mg used of ketamine. Utilizing the mean total dosages for remifentanyl ($131.4 \pm 48.1 \mu$ g) and ketamine (83.3 ± 28.2 mg), the average cost per anesthetic dose of remifentanyl was \$6.57 and the average cost per dose of the ketamine was \$1.67. This cost analysis does not include the midazolam or propofol administered. While the remifentanyl cost \$4.90 more than the ketamine per average case, this cost difference may potentially be offset by the extra time needed to monitor and recover the ketamine patients and the additional amount of propofol required for the ketamine group. Remifentanyl is also marketed as a single-patient-use agent. It is not uncommon, however, for clinicians to use remifentanyl for multiple patients in a given treatment day using different sterile syringes drawn from the same vial. If used in this off-label manner, based on the number of cases performed each day, there may still be a significant waste of remifentanyl, as US Food and Drug Administration labeling requires that any unused remifentanyl be discarded within 24 hours of reconstitution. This may be significant if only 2 or 3 relatively short cas-

es per day utilize this anesthetic technique. Ketamine is available in a multiple-dose vial.

CONCLUSION

Continuous infusions of propofol-remifentanyl and propofol-ketamine provided remarkably comparable deep sedation for third molar extractions in this young, healthy patient population. The propofol-ketamine combination demonstrated a significantly prolonged emergence and recovery profile in comparison to the propofol-remifentanyl combination. Ketamine-based deep sedation produced a statistically and potentially clinically significant increase in mean heart rate of approximately 10 beats per minute. Ketamine, as utilized in this study, did not demonstrate a significant pre-emptive analgesic effect. The blinded surgeons and patients were very satisfied with both deep sedation regimens. There was no difference in PONV between the groups. Based on the data from this study, continuous infusions of ketamine in combination with propofol can be considered as another option in the anesthetic armamentarium for young, healthy patients undergoing third molar surgery, but this approach is likely to be associated with a more prolonged recovery profile compared to a combination of propofol and remifentanyl.

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