Comparison of Mixtures of Propofol-Remifentanil vs. Propofol-Ketamine for Deep Sedation for Third Molar Extraction Surgery (IRB # 2009H0306)

Thesis

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Abstract

The surgical extraction of third molars is a common dental procedure performed in conjunction with deep sedation for patient comfort. Dental anesthesia providers are constantly trying to better utilize current medications and techniques in order to facilitate a more comfortable and stable sedation experience with rapid recoveries for patients and surgeons. The combination of propofol and remifentanil, while not inexpensive or ideal, is often used because of the numerous advantages it provides. Ketamine is a unique drug that has several benefits not found with remifentanil. We performed this study to compare the combination of propofol-remifentanil with propofol-ketamine for deep sedation for surgical extraction of all four third molars. Patients were randomly assigned to one of two groups, each with 18 patients, and received deep sedation for the duration of the surgical procedure. In addition to evaluating emergence and recovery times, sedation parameters and hemodynamic and respiratory stability, we also assessed patient and surgeon satisfaction, incidence of postoperative nausea and vomiting, pre-emptive analgesia secondary to ketamine administration, presence of negative behavioral effects of ketamine and the cost analysis for each experimental drug for each group. While the ketamine and remifentanil groups both demonstrated hemodynamic and respiratory stability, the ketamine group had prolonged emergence and recovery times (p < .05). It appears that ketamine, while a viable, stable, cost-effective alternative to remifentanil,
did lead to longer recovery periods. This may prohibit its use as a replacement to remifentanil for combined propofol continuous infusions for deep sedations for dental surgical procedures.
This work is dedicated to my parents who supported me in all my endeavors and instilled in me the drive and motivation to achieve those dreams. It is also dedicated to my three children, Hunter, Aiden and Kendall, who have kept my feet firmly grounded, my mind sharp and my heart light with their laughter. Finally, I would like to dedicate this master’s thesis to my wonderful wife, Brianna, who has walked right by my side throughout my entire dental education. Your love and support has helped carry me through all the hard times.
Acknowledgments

I would like to thank all of the oral surgery faculty and residents who allowed me to include their patients in my research project. Without their help, my research project and master’s thesis would not have been possible. A thank you goes out to Dr. Bob Rashid, who guided me through all the statistical analysis and was always there if I had any questions. To Josh and Phil, I would like to thank you both for your assistance with my research project. I’m sure we will remain lifelong friends and I look forward to watching you both grow professionally. I would like to acknowledge Dr. Joel Weaver, who has been one of the most influential people in my education. You will forever be one of my professional and personal heroes and while I will never be able to repay you for your help, I will constantly work to pay it forward. Lastly, I would like to thank both of my faculty, Dr. Simon Prior and Dr. Steven Ganzberg. Dr. Prior is one of the most genuine people I have had the pleasure of knowing. His insights and assistance throughout my project and entire residency has been immeasurable. Dr. Ganzberg always had an open door and never tired of my endless questions, which still have not ceased. I am incredibly lucky and grateful to have had both of you as mentors and now as good friends.
Vita

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Major Field: Dentistry

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Introduction

Surgical extraction of third molars is a common oral surgery procedure performed under local anesthesia, often with 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 setting, an ambulatory anesthetic plan, with rapid awakening and recovery is highly desirable. Unlike the traditional hospital setting, most dental offices lack the staffing and equipment of a proper recovery room where patients can be monitored for extended periods of time. In fact, it is common practice for dental anesthesiologists and some oral surgeons to recover patients in, and discharge them directly from, the dental chair. As such, a patient requiring an extended postoperative stay will require continued supervision and will also keep the operatory occupied, possibly delaying the start of the subsequent case. Therefore, it is practically and economically advantageous for practitioners to utilize ambulatory anesthesia techniques that are capable of providing a rapid recovery and safe discharge from the dental office setting.

The ability to easily obtain profound local anesthesia during oral procedures plays a major role in reducing the anesthetic requirements of sedated dental patients. By blocking or significantly reducing the noxious surgical afferent stimuli, dental patients typically require significantly smaller quantities of intravenous opioids during both the
intraoperative and immediate postoperative periods than patients undergoing more extensive surgical procedures. Sedation techniques that provide a stable hypnotic level, anxiolysis, amnesia, analgesia, can minimize patient movement, have a brief recovery period with minimal postoperative nausea and vomiting (PONV) and also the ability to rapidly titrate profound, but brief periods of analgesia are ideal for outpatient dental procedures. This gives the dentist anesthesiologist or oral surgeon the ability to rapidly change the depth of sedation or anesthesia in accordance with the level of stimulation from the surgical procedure. While the pharmacologic and pharmacodynamic profiles of propofol make it an ideal drug for sedations, the lack of analgesic properties usually requires concurrent administration of intravenous opioids. Fentanyl, sufentanil, alfentanil or remifentanil, are commonly used opioids because they provide rapid onset, potent analgesia, initially useful during induction and for the injection of the local anesthetic. Once the local anesthetic has been successfully administered, there usually is minimal need for additional intraoperative opioids during most outpatient dental procedures. The short alpha half-lives of these opioids are beneficial especially when administering ambulatory anesthesia as patients tend to recover faster and have fewer side effects or complications once the drugs are either redistributed and/or metabolized.

The use of a combination of remifentanil and propofol for induction and maintenance of deep sedation has been shown to be a safe, effective technique, capable of providing analgesia, stable sedation/hypnosis and satisfactory operating conditions along with the benefit of a shorter recovery period than conventional balanced anesthetics.\textsuperscript{1-4} While propofol and remifentanil, used as a total intravenous anesthetic (TIVA), has become an
extremely popular technique for ambulatory anesthesia in dental offices, it is not a panacea. The concurrent intravenous administration of propofol and opioids, including remifentanil, can lead to multiple intraoperative and postoperative complications, most significantly respiratory and cardiovascular depression and increased risk of PONV.²,⁴

Propofol-opioid combinations can cause dose-dependent decreases in ventilation and perfusion.²,⁴,⁵ These decreases can be clinically significant, possibly even requiring short interruptions in surgery in order to support and stabilize the patient. The continuous infusion of propofol-remifentanil is no exception and has been shown to cause statistically significant decreases in respiratory rate and subsequent increases in CO₂ retention.²-⁴ In some cases this is secondary to airway obstruction and can be managed via simple airway repositioning by the dentist anesthesiologist or oral surgery assistant.² Occasionally the patient’s respiratory drive may be depressed enough to require active augmentation of the patient’s ventilation.² While this is not an issue for an intubated patient, it does require interrupting the surgery in order to mask ventilate the patient if using an open airway TIVA technique.

Hemodynamic depression associated with propofol-opioid combinations usually manifests as bradycardia and hypotension.⁴ For healthy patients able to tolerate the reduction in heart rate and afterload, these changes may be clinically insignificant. The elderly or medically compromised patient population is far less tolerant of these cardiovascular changes and may develop very significant hypotension and possibly cardiac dysrhythmias. In the typical TIVA setting utilizing propofol-remifentanil
infusions, this cardiovascular depression usually responds quickly to decreasing the infu-
sion rate, occasionally requiring a modest fluid bolus or administration of a sympatho-
mimetic.

Opioids are also well known to increase the incidence of postoperative nausea and vomiting (PONV), although with a rapidly metabolized agent, such as remifentanil, this may be less frequent. Continuous infusion of subhypnotic propofol has been used successfully to prevent PONV.\textsuperscript{6,7} It has also been used as a treatment for patients suffering from PONV.\textsuperscript{6} Therefore the use of a continuous propofol infusion combined with the use of short-acting opioids in typical dental procedures, including extraction of third molars, may make PONV less common. However, when it occurs, PONV can negatively impact patient comfort significantly, increase postoperative morbidity, prolong the need for monitored postoperative care and delay discharge from the dental office.

Ketamine, a phencyclidine derivative, is an N-methyl-D-aspartate (NMDA) receptor antagonist that produces a state of dissociative anesthesia.\textsuperscript{8,9} 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.\textsuperscript{5} Ketamine causes an increase in central sympathetic tone (masking a direct myocardial depressant effect), thereby causing a modest increase in afterload, heart rate and cardiac output. Additionally, ketamine does not cause depression of the respiratory drive and produces significant brochodilation. Of note, use of ketamine does
not prevent obstruction and airway compromise in an unconscious patient, but airway reflexes tend to be better preserved than with other induction agents.\textsuperscript{5}

The combination of propofol and low-dose ketamine is a viable anesthetic alternative that is able to provide effective analgesia, quality sedation, good operating conditions and a recovery profile similar to that of propofol and remifentanil. Badrinath, et al. reported that a low-dose ketamine-propofol combination used for deep sedation for female patients undergoing breast biopsy procedures under local anesthesia was shown to provide significant analgesia and to minimize the need for supplemental opioids during the peri-operative period.\textsuperscript{10} The ketamine-propofol combination also caused minimal changes in hemodynamics along with a notable lack of respiratory depression.\textsuperscript{10} These desirable properties may provide a more physiologically stable sedation, an advantage that could lead to fewer interruptions to the surgical team and thus shorter surgical procedures while allowing good patient and surgeon satisfaction with the sedative regimen. Additionally, NMDA receptor antagonists, like ketamine, may minimize post-operative pain by blocking “pain windup” in the spinal dorsal horn and Trigeminal Nucleus Caudalis and central sensitization.\textsuperscript{8,11}

The lesser cost of ketamine, when compared to remifentanil, is also of interest. Currently the cost of remifentanil is approximately 3 times that of ketamine when compared to doses that are used for deep sedation/non-intubated general anesthesia. If ketamine is capable of providing sedation similar or superior to remifentanil, in combination with
propofol, this would provide a more cost-effective anesthetic alternative for outpatient procedures requiring deep sedation and still allow for good recovery parameters. This study, therefore, aims to compare the combination of propofol-remifentanil to propofol-ketamine when used to provide deep sedation for surgical extraction of four third molars along with local anesthesia. We anticipate that the use of low-dose ketamine with propofol will provide sedation, analgesia and operating conditions similar to the remifentanil and propofol combination, but may minimize the potential for cardiovascular and respiratory depression in addition to a decreased need for oral analgesics in the immediate postoperative period (24 hours).
Methods and Materials

Recruitment

Potential subjects offered the opportunity to participate in this Institutional Review Board (IRB) approved study were required to be active patients of the Department of Oral and Maxillofacial Surgery within the College of Dentistry at the Ohio State University. Inclusion criteria included English speakers, American Society of Anesthesiologists (ASA) Physical Status I or II, non-pregnant adults, ages 18 to 40. Due to issues regarding study consent, patients below the age of 18 or those who were incarcerated were excluded from participation. Additionally, because of possible effects with ketamine, any patients with a history of psychiatric/psychological problems were also excluded from the study. Prior to being approached by a member of the research team, all patients attended a consultation appointment where they were evaluated by oral and maxillofacial surgery residents or faculty. After establishment and acceptance of the treatment plan consisting of extraction of all four third molars with deep sedation/non-intubated general anesthesia, a member of the research team would introduce the IRB approved study to the potential subject and request participation. If the subject agreed, they would be scheduled for surgery at a future date with appropriate preoperative instructions as per the usual departmental protocol. Before dismissal from the consultation appointment, consenting potential participants were asked to complete a
preoperative Trieger test and a 30 second one leg standing test. Vital signs consisting of
blood pressure, respiratory rate, heart rate and room air oxygen saturation were obtained.

Randomization
Using Excel to fabricate a random number table, patients were assigned to either study
group based on the sequence obtained from the random number table and their study ID
number which correlated to the order that they were enrolled in the study.

Propofol Mixture Preparation
In a single syringe, a mixture of propofol-remifentanil or propofol-ketamine was steriley
prepared as the primary intravenous anesthetic agent to be delivered via an infusion pump
for the duration of the surgical procedure. Regarding the propofol and remifentanil
mixture, 40 mL of propofol (10 mg/mL) was mixed in a BD 60 mL syringe together with
1 mL of remifentanil that was reconstituted in normal saline to a dilution of 200 mcg/mL.
This yielded a mixture with a ratio of 10 mg of propofol plus 5 mcg of remifentanil per 1
mL. For the propofol and ketamine mixture, 40 mL of propofol (10 mg/mL) was mixed
in the BD 60 mL syringe together with 1 mL of ketamine (100 mg/mL), yielding a
mixture with a ratio of 10 mg of propofol plus 2.5 mg of ketamine per 1 mL.

Surgical Procedure
On the scheduled day of surgery participants were escorted to the operating suite by the
dental anesthesia resident, a member of the research team. Once seated in the standard
dental chair designed for oral surgical procedures, the patient’s medical history was
reviewed, consents for the surgical procedure and IRB approved study obtained, NPO status and presence of an escort confirmed. Negative pregnancy status was confirmed using a urine HCG test for any female patient. ASA monitors consisting of a non-invasive blood pressure monitor, 5-lead electrocardiogram, pulse oximeter finger probe (Passport 2 with gas monitor SE, Datascope Corp.) and pretracheal stethoscope were all applied. Initial vital signs were recorded at this time. Using a Salter divided nasal cannula, supplemental oxygen (O₂) was administered at 3 L/min while simultaneously monitoring end tidal carbon dioxide (EtCO₂). Intravenous access was obtained using a 20 gauge IV catheter, with or without subdermal local anesthesia, in a suitable hand or anticubital vein in order to administer normal saline and medications. After securing the IV line, midazolam 0.03 mg/kg was immediately administered to help alleviate preoperative anxiety. After three minutes a priming bolus of the propofol-remifentanil or propofol-ketamine mixture, depending on the randomly assigned experimental group, was delivered using a Baxter Infus OR Pump. The dosage of the initial priming bolus administered was 300 mcg/kg (propofol) after which an infusion rate of 100 mcg/kg/min (propofol) was started. As stated in the preparation section, the propofol-remifentanil (ratio of 10 mg-5 mcg/mL) or the propofol-ketamine (ratio of 10 mg-2.5 mg/mL) was combined in one BD 60 mL syringe for delivery with the infusion pump. After two minutes, vital signs were recorded (HR, BP, RR, SpO₂), a rubber bite block was placed intra-orally and an additional bolus of 500 mcg/kg of the propofol mixture was administered to facilitate the administration of local anesthetic solution (2% lidocaine with epinephrine 1:100,000 epinephrine) by the surgeon. After 30 seconds, sufficient depth of anesthesia was tested by loss of the eyelid reflex. If the eyelid reflex was still
present, an additional 200 mcg/kg bolus of propofol mixture was administered every 30 – 60 seconds as needed to obtund the eyelid reflex before allowing the surgeon to proceed with the administration of local anesthesia. The time of completion of the local anesthesia administration was recorded. Vital signs were recorded every five minutes thereafter. During the surgical procedure the propofol mixture infusion was maintained at 100 mcg/kg/min (propofol). Additional 20 mg boluses of plain propofol were administered as needed from a separate syringe, guided by hemodynamic parameters and to facilitate adequate surgical conditions. The infusion rate was adjusted, +/- 25 mcg/kg/min as needed, to facilitate maintenance of 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 remifentanil and the number of additional plain propofol 20 mg boluses were recorded.

Post-Anesthesia Care Unit (PACU) Recovery

Following termination of the infusion, the patient’s shoulder was gently shaken while simultaneously asking them to open their eyes every 60 seconds until they were able to comply. The elapsed time for the participant to open their eyes upon command following infusion discontinuation was recorded and listed as “emergence time”. Participants were then transferred via recovery recliner to the PACU and the time of entry into the PACU was recorded. While in the PACU, the patient’s vital signs (HR, BP and SPO₂) were continuously monitored by the anesthesiologist and recorded every 5 minutes.
Beginning 10 minutes after arrival to the PACU, the patient was asked to complete a Trieger Test and 30 second one leg standing test. These tests were repeated every 5 minutes thereafter until successful completion. Once the patient was able to complete both the Trieger test and 30 second one leg standing test, they were deemed ready for discharge unless they were hemodynamically unstable or had any additional postoperative complication that precluded discharge. This time was recorded as the discharge time for study purposes. We recorded and addressed any postoperative complications or untoward events that occurred during the recovery period, including more common events such as surgical pain, nausea or vomiting. If the patient reported pain in a particular quadrant, they were given an additional injection of local anesthetic (2% lidocaine w/ 1:100,000 epinephrine). Any additional injections needed for postoperative pain were recorded. Ondansetron 4 mg via IV was administered as needed to treat incidents of nausea or vomiting while the patient was in the PACU. Patients and their escorts received appropriate post-surgical instructions, the IV catheter and fluids were discontinued and provisions made for a follow-up telephone interview the following day once recovered in PACU.

Immediately prior to dismissal, the patient was given twelve naproxen sodium 275 mg tablets with the instruction to take 2 tablets every 12 hours “by the clock” for 36 – 48 hours. Additionally, sixteen hydrocodone 5 mg/acetaminophen 500 mg tablets were dispensed to be taken 1-2 tablets every 6 hours only as required for post-operative analgesia. Participants and escorts were instructed to take the naproxen sodium for baseline pain coverage and the hydrocodone/acetaminophen for any breakthrough pain.
Once the patient received the postoperative pain medication, postoperative instructions and all questions answered, the patient was dismissed from the clinic. This dismissal time was recorded for medico-legal reasons.

Surgeon Satisfaction
No later than 10 minutes after completion of the surgery, and using a standard 100 mm visual analog scale, the surgeon was asked to rate their satisfaction with the sedation for the placement of the local anesthetic and for the surgical procedure as a whole. They were verbally instructed to rate their satisfaction with this sedation technique by comparing it with other open airway sedation techniques.

Post-op Day One Survey
The following day, the participant was contacted via telephone by a member of the research team, as arranged, and asked to complete a short questionnaire consisting of 7 questions. They were asked if they experienced any post-operative nausea or vomiting within the last 24 hours; if they had any additional complaints regarding the anesthesia; if they took their pain medication as recommended; how much they took and at what time interval; if they have any recall of the local anesthesia or of the surgery; and finally to rate their satisfaction with the anesthesia on a 5 point Likert scale. Each response was recorded on their individual study data sheet. Upon completion of the telephone survey, they were told that they had fulfilled their requirements for successful completion with the study, were thanked for their participation, and confirmation of their mailing address was obtained in order to mail each subject a check for $20.00.
Statistical Analysis

Data were summarized and analyzed using SAS 9.2 (SAS, Inc.; Cary, NC). Fisher Exact Tests and Wilcoxon Rank Sum Tests (Exact Two-sided) were used to verify that the two drug groups were not different with respect to starting values and demographics.

Wilcoxon Rank Sum Tests (Exact Two-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 two groups with respect to categorical outcomes such as sex and postoperative nausea and vomiting, the number of subjects who required additional local anesthetic in PACU and to compare the two groups with respect to patient and surgeon satisfaction.
Results

Demographics
Thirty-seven total patients between the ages of 18-40, all meeting the inclusion criteria for participation were recruited and accepted for this Institutional Review Board-approved study. One participant was excluded after requiring a change in anesthetic techniques secondary to minor airway complications. All remaining thirty-six patients successfully completed this study. The demographics of the participants in both groups were very similar (Table 1). There were no statistically significant differences in age (p = 0.149, Wilcoxon Rank Sum Test, Exact Two-sided), sex (p = 0.489, Fisher’s Exact Test, Two-sided) or weight (p = 0.199, Wilcoxon Rank Sum Test, Exact Two-sided).

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (Years)</th>
<th>Sex (Male:Female)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>23.4 ±</td>
<td>8:10</td>
<td>68 ± 11.1</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>21.7 ±</td>
<td>5:13</td>
<td>63.2 ± 13.2</td>
</tr>
<tr>
<td>p value</td>
<td>0.149</td>
<td>0.489</td>
<td>0.199</td>
</tr>
</tbody>
</table>

Table 1. Demographics

Sedation Dosages
The data was evaluated regarding the average infusion time, average infusion rate, total number of rescue plain propofol boluses, total dosage of propofol received and total dosage of the experimental drug received (ketamine or remifentanil) using the Wilcoxon Rank Sum Test (Exact Two-sided). The number of subjects who required additional
local anesthesia once in recovery was evaluated using Fisher’s Exact Test. There were no statistically significant differences in any measure of infusion time, average infusion rate or number of propofol rescue boluses required or the number of participants who required additional local anesthesia (Table 2). There was a statistically significant difference between the groups with respect to the total propofol received ($p = 0.029$).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Ketamine Group</th>
<th>Remifentanil Group</th>
<th>$p$ values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Infusion (min)</td>
<td>32.3 ± 9.2</td>
<td>28.6 ± 12.8</td>
<td>0.154</td>
</tr>
<tr>
<td>Average Infusion Rate (mcg/kg/min)</td>
<td>151.9 ± 18.5</td>
<td>143.9 ± 29.0</td>
<td>0.322</td>
</tr>
<tr>
<td>Propofol Rescue Boluses (Number)</td>
<td>4.9 ± 3.3</td>
<td>3.5 ± 2.1</td>
<td>0.124</td>
</tr>
<tr>
<td>Total Propofol (mg)</td>
<td>432.1 ± 155.0</td>
<td>321.2 ± 122.7</td>
<td>0.029</td>
</tr>
<tr>
<td>Total Study Drug (mg or mcg)</td>
<td>83.3 ± 28.2 mg</td>
<td>131.4 ± 48.1 mcg</td>
<td></td>
</tr>
<tr>
<td>Subjects Requiring Additional Local Anesthesia in PACU (Number)</td>
<td>3</td>
<td>3</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Table 2. Infusion Dosages

Hemodynamic Stability

The results of measures of hemodynamic stability (heart rate, systolic, diastolic and mean arterial pressure) were evaluated using the Wilcoxon Rank Sum Test (Exact Two-sided) with regards to preoperative and mean intraoperative values along with the difference between the two (Tables 3 and 4). The ketamine group had an average preoperative heart rate of $67.6 \pm 11.2$ bpm while the remifentanil group had an average preoperative heart rate of $72.1 \pm 10.8$ bpm. However, the difference between the groups was not
statistically significant ($p = 0.35$). The average change in heart rate for the remifentanil group was $+4.1 \pm 7.3$ bpm and $+14.5 \pm 7.9$ bpm for the ketamine group. The difference in the increase in heart rate was statistically significant ($p = .0007$, Monte Carlo Estimate). There was no statistically significant difference between the groups with respect to the preoperative or intraoperative measurements for systolic ($p = 0.59$; $p = 0.10$), diastolic ($p = 0.58$; $p = 0.075$) or MAP ($p = 0.74$; $p = 0.069$). While both groups demonstrated an average decrease in MAP, $-12.2 \pm 12.5$ mmHg for the remifentanil group and $-6.5 \pm 9.9-6$ mmHg for the ketamine group, that difference was not statistically significant ($p = 0.13$).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Remifentanil Group</th>
<th>Ketamine Group</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop Heart Rate (bpm)</td>
<td>72.1 ± 10.8</td>
<td>67.6 ± 11.2</td>
<td>0.35</td>
</tr>
<tr>
<td>Intraop Heart Rate (bpm)</td>
<td>76.2 ± 10.3</td>
<td>82.0 ± 12.4</td>
<td></td>
</tr>
<tr>
<td>Change in Heart Rate (bpm)</td>
<td>4.1 ± 7.3</td>
<td>14.5 ± 7.9</td>
<td>.0007</td>
</tr>
</tbody>
</table>

Table 3. Heart Rate Stability
<table>
<thead>
<tr>
<th>Variable</th>
<th>Remifentanil Group</th>
<th>Ketamine Group</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop Systolic (mmHg)</td>
<td>121.8 ± 13.2</td>
<td>120.3 ± 17.9</td>
<td>0.59</td>
</tr>
<tr>
<td>Intraop Systolic (mmHg)</td>
<td>110.7 ± 10.6</td>
<td>115.7 ± 8.5</td>
<td>0.10</td>
</tr>
<tr>
<td>Preop Diastolic (mmHg)</td>
<td>72.8 ± 14.2</td>
<td>70.7 ± 10.6</td>
<td>0.58</td>
</tr>
<tr>
<td>Intraop Diastolic (mmHg)</td>
<td>60.0 ± 5.4</td>
<td>63.5 ± 5.8</td>
<td>0.075</td>
</tr>
<tr>
<td>Preop MAP (mmHg)</td>
<td>89.2 ± 12.1</td>
<td>87.2 ± 11.2</td>
<td>0.74</td>
</tr>
<tr>
<td>Intraop MAP (mmHg)</td>
<td>76.9 ± 6.5</td>
<td>80.9 ± 6.5</td>
<td>0.069</td>
</tr>
<tr>
<td>Change in MAP (mmHg)</td>
<td>-12.2 ± 12.5</td>
<td>-6.5 ± 9.9</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Table 4. Blood Pressure Stability

Respiratory Stability

The results regarding respiratory stability, specifically respiratory rate and oxygen saturation (SpO₂) were evaluated using the Wilcoxon Rank Sum Test (Exact Two-sided) and are illustrated in Table 5. There was no statistically significant difference between the groups with respect to preoperative respiratory rate (p = 0.197) or preoperative SpO₂ (p = 0.916). There was a statistically significant difference between the groups regarding the change between preoperative and mean intraoperative respiratory rate. The remifentanil group had a decrease of -2.35 ± 4.4 breaths per minute while the ketamine group had a respiratory rate increase of +3.9 ± 3.7 breaths per minute (p = .0002). While there was a slight decrease noted between preoperative and mean intraoperative SpO₂ measurements for both groups, the difference (99% vs. 98%) was not significant.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Remifentanil Group</th>
<th>Ketamine Group</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop Respiratory Rate</td>
<td>16.3 ± 3.9</td>
<td>15.2 ± 3.1</td>
<td>0.197</td>
</tr>
<tr>
<td>Rate (breaths/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraop Respiratory Rate</td>
<td>14.0 ± 2.2</td>
<td>19.1 ± 2.8</td>
<td></td>
</tr>
<tr>
<td>Rate (breaths/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in Respiratory Rate</td>
<td>-2.35 ± 4.4</td>
<td>3.9 ± 3.7</td>
<td>.0002</td>
</tr>
<tr>
<td>Rate (breaths/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop SpO₂ (%)</td>
<td>99.3 ± 1.2</td>
<td>99.6 ± 0.6</td>
<td>0.916</td>
</tr>
<tr>
<td>Intraop SpO₂ (%)</td>
<td>98.2 ± 1.7</td>
<td>98.7 ± 1.2</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Respiratory Stability

**Emergence and Recovery Time**

Emergence time was defined as the duration from discontinuing the infusion to successful sustained eye opening on command. The mean emergence time for the propofol-remifentanil group was 7.1 ± 3.7 minutes and for the propofol-ketamine group was 13.6 ± 6.6 minutes (Figure 1). This data was analyzed using the Wilcoxon Rank Sum Test (Exact Two-sided) and it was determined that the difference between the groups was statistically significant (p = .0009).

Recovery time was defined as the time from entry to the post anesthesia care unit (PACU) to establishment of patient being declared “street ready/fit” by successful completion to a Trieger test to near baseline levels and completion of a 30 second one leg standing test. This data was evaluated using the Wilcoxon Rank Sum Test. The difference in mean recovery times, 24.7 ± 7.6 minutes for the remifentanil group and 42.9 ± 18.7 minutes for the ketamine group, was statistically significant (p = .0004). While the propofol-ketamine group had a significantly longer emergence and recovery period,
the participants did not report any negative behavioural effects such as dysphoria or hallucinations (Figure 1).

Figure 1. Emergence and Recovery

Satisfaction Surveys

The results of the patient and surgeon satisfaction surveys were evaluated using Fisher’s Exact Test and are presented below (Table 6). The 5 point Likert scale used the following points to measure patient satisfaction with the sedation: 1 - very satisfied, 2 - satisfied, 3 - neutral, 4 - dissatisfied and 5 - very dissatisfied. The VAS scales used the 0 mm mark as very satisfied and the 100 mm mark as very dissatisfied. Statistical analysis failed to demonstrate any significant difference between the two groups with regards to patient satisfaction with the sedation (p = 0.34), surgeon satisfaction for administration of the local anesthesia (p = 0.97) and for the sedation (p = 0.54).
Satisfaction Survey

Mean Patient Satisfaction (5 pt Likert scale, 1 = very satisfied)

<table>
<thead>
<tr>
<th></th>
<th>Remifentanil Group</th>
<th>Ketamine Group</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.1 ± 0.2</td>
<td>1.3 ± 0.6</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Mean Surgeon Satisfaction Sedation for Local Anesthesia (100 mm VAS)

|                          | 13.9 ± 14.4        | 14.1 ± 17.7    | 0.97     |

Mean Surgeon Satisfaction Sedation for Surgery (100 mm VAS)

|                          | 12.8 ± 11.9        | 10 ± 14.9      | 0.54     |

Table 6. Satisfaction Surveys

Postoperative Oral Analgesic Requirements

Using the Wilcoxon Rank Sum Test (Exact Two-sided), statistical analysis of the quantity of pain medication reported by the patient as taken over the first 24 hours is presented in Table 7. Both groups were similar with respect to the number of naproxen 550 mg tablets (p = 0.31) and acetaminophen/hydrocodone 5/500 mg tablets (p = 0.25) taken during the first 24 hour period.

<table>
<thead>
<tr>
<th>Pain Medication</th>
<th>Remifentanil Group</th>
<th>Ketamine Group</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen 550 mg (Number of tablets)</td>
<td>2.6 ± 0.5</td>
<td>2.3 ± 0.8</td>
<td>0.31</td>
</tr>
<tr>
<td>Acetaminophen/hydrocodone 5/500 mg (Number of tablets)</td>
<td>3.1 ± 2.7</td>
<td>4.1 ± 2.5</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Table 7. Oral Analgesic Requirements
Postoperative Nausea and Vomiting

Postoperative nausea and vomiting was evaluated during the immediate postoperative recovery period and again within the first 24 hour period during the patient telephone survey (Figure 2). This data was analyzed using Fisher’s Exact Test. There was one patient in the ketamine group who had both nausea and vomiting during the immediate postoperative period, while the remifentanil group had none. This difference, however, was not statistically significant (p = 1.0). During the first 24 hour period, there were six participants in each group who reported nausea and/or vomiting, which was not a statistically significant difference (p = 1.0).

Figure 2. Postoperative Nausea & Vomiting
Discussion

Demographics

The participants in the two groups for this study were found to be similar with respect to patient demographics (age, sex, weight). The population who receives deep sedation for surgical extraction of all four third molars is fairly homogenous and the study sample adequately reflects a young, generally healthy group. Regarding the inclusion criteria, the difficulty of the surgical extraction of the four third molars was not evaluated. Participants may have had four completely erupted third molars or four full bony impacted third molars. If one group by chance had significantly less difficult extractions, this may have skewed some results.

Sedation Dosages

While the mean infusion time, mean infusion rate and number of propofol rescue boluses were not found to have any differences that were statistically significant, the ketamine group did receive on average 110 mgs more propofol than then remifentanil group. This difference was statistically and clinically significant. This difference reflects the additional 30 mgs from the extra propofol rescue boluses, the slightly higher infusion rate and the slightly longer mean infusion rate. The ketamine group required a higher mean infusion rate (151.9 ± 18.5) versus the remifentanil group (143.9 ± 29.0) in addition to an
increased number of propofol rescue boluses (4.9 ± 3.3 versus 3.5 ± 2.1). The differences are theoretically secondary to the profound analgesia that occurs with the administration of opioids, reducing the surgical stimulation to a higher degree than ketamine and effectively lowering the anesthetic requirements of the remifentanil group. Both groups had three participants in whom the initial local anesthetic blocks either missed or failed, that reported pain while in recovery, and were given additional local anesthetic. All of these participants reported immediate resolution of the pain after administration of the additional local anesthetic. Also of note was that both groups required an increase in the initial infusion rate of 100 mcg/kg/min (+43.9 mcg/kg/min remifentanil and +51.9 mcg/kg/min ketamine). The data suggests that 100 mcg/kg/min as the initial infusion rate is not adequate and could easily be increased to 125 mcg/kg/min. The ketamine group (32.3 ± 9.2 minutes) had a slightly longer mean infusion time than the remifentanil group (28.6 ± 12.8 minutes), however this difference was not statistically significant (p = 0.154). As the ketamine group had an emergence time that was 6.6 minutes more than the ketamine group, it would be possible to terminate the ketamine infusion earlier in order to facilitate a more rapid emergence. The duration of the infusion was based entirely on the surgical procedure and was terminated as soon as the surgeon indicated the last tooth was extracted or the last suture placed. It must be discussed that the difficulty of the surgical extractions was not evaluated preoperatively. This difference in infusion times may reflect a discrepancy in the distribution of difficult surgical cases within the ketamine group. Additionally, as a variety of surgeons participated in the study and were randomly assigned to each group depending on their patient’s randomized
assignment to one of the groups, this may reflect the difference between surgeons with respect to their experience, gentleness of surgical technique and surgical speed.

Cost Analysis
The current market cost for remifentanil is $49.00 for a 1 mg vial of remifentanil and $9.35 per 500 mg/5 mL vial of ketamine. Unit analysis yields a cost of $0.05 per mcg of remifentanil and $0.02 per mg of ketamine. Including the mean total dosages for remifentanil (131.4 ± 48.1 mcg) and ketamine (83.3 ± 28.2 mg) brings the mean cost for each participant to $6.57 for the remifentanil and $1.67 for the ketamine. This cost analysis does not include the midazolam or propofol administered. While the remifentanil costs $4.90 more than the ketamine, this cost difference would most likely be offset by the extra time needed to monitor and recovery the ketamine patients.

Hemodynamic and Respiratory Stability
Prior to the study, the investigators thought that hemodynamic and respiratory stability might be different between the two groups. Specifically, we considered it likely that the ketamine group would have greater hemodynamic stability due to the offsetting effects of propofol-induced vasodilation and inhibition of baroreceptor reflexes by ketamine’s mild (at these doses) sympathomimetic properties. Likewise, we felt the remifentanil group might have more hemodynamic and respiratory depression. However, there was remarkable hemodynamic and respiratory stability for both groups. The only parameters which were statistically significant were the difference between preoperative and mean
intraoperative heart rate and respiratory rate. While both groups demonstrated an increase in heart rate, the ketamine group had a difference between preoperative and mean intraoperative values of 14.5 ± 7.9 bpm, while the difference for remifentanil was only 4.1 ± 7.3 bpm. This difference was statistically significant (p = .0007). In regards to respiratory parameters, the ketamine group demonstrated a mean increase of 3.9 ± 3.7 breaths per minute while the remifentanil group demonstrated a mean decrease of 2.35 ± 4.4 breaths per minute. This difference was found to be statistically significant (p = .0002) although not clinically significant. There was minimal change for either group with regards to preoperative or mean intraoperative SpO₂ readings. Both groups demonstrated pulse oximeter readings of 99-98% which were not considered statistically or clinically relevant. The remaining hemodynamic and respiratory variables measured during the study, specifically systolic, diastolic and mean arterial pressure (MAP) demonstrated average intraoperative values that were within 20% of preoperative values for both groups and were not statistically different. Both groups had decreased mean intraoperative values compared with preoperative values with regards to the systolic, diastolic and mean arterial pressure (MAP). The remifentanil group demonstrated a larger decrease in MAP than the ketamine group however the difference was not statistically significant (p = 0.13).

As a whole, the propofol-remifentanil group did have a lower heart rate, MAP and respiratory rate; however the difference was within 20% of baseline and therefore did not require any additional intervention beyond occasional airway support/repositioning,
which was also administered to the ketamine group. None of the participants in either group required positive pressure ventilation at any time, aside from the one participant originally in the remifentanil group, who was excluded from the study after multiple laryngospasms. This participant was ultimately converted successfully to an intubated general anesthetic for the duration of the surgical procedure and was removed from the study. There was one participant in the remifentanil group who required placement of an airway adjunct (nasopharyngeal airway) in order to bypass nasal congestion due to seasonal allergies. Due to the need to stabilize the patient’s head in order to better facilitate the surgical procedure, it was difficult to quantify the amount of additional airway support required. This is an area of needed improvement for future studies. The larger decrease in vital signs for the remifentanil group was felt to be due to the reduction in sympathetic tone secondary to the pharmacologic effects of remifentanil and potentiation of propofol. Alternatively, the ketamine group demonstrated an increase in heart rate and respiratory rate along with a smaller reduction in MAP. The increase in heart rate and respiratory rate was well within 20% of baseline and was attributed to the sympathomimetic effects of ketamine. There was no significant difference in oxygen saturation (SpO₂) for either group for the duration of the surgical procedure. While many of the participants in both groups demonstrated hypopnea/apnea immediately following induction, this resolved as soon as the patient was stimulated during the administration of the local anesthetic. As such, the often noted hypopnea/apnea was of such extremely short duration that it was very difficult to quantify and was not clinically relevant. Pulse oximetry was a poor indicator of respiratory stability because of a lack of specificity.
This was mainly due to the natural lag or time delay between the apneic or hypopneic event and decrease in SpO2. Additionally, the rapid rebound in oxygen saturation following an apneic event can occur so quickly that the momentary decrease in SpO2 may be difficult to capture.

**Emergence and Recovery**

The results of the study demonstrate that patients who receive a combination of propofol-remifentanil had a shorter emergence from anesthesia, quicker recovery periods and were discharged sooner than patients who received a combination of propofol-ketamine. Patients who were assigned to the ketamine group had an average emergence time that was 1.92 times longer than the remifentanil group (13.6 ± 6.6 minutes versus 7.1 ± 3.7 minutes, \( p = .0009 \)). The prolonged emergence could reflect the pharmacodynamic profile of ketamine versus remifentanil. However, the ketamine group received on average 110 mgs more propofol than the remifentanil group, a result of the 3.7 minutes longer mean infusion time, additional 28 mgs of plain propofol and the 8 mcg/kg/min higher mean infusion rate. This may also explain the prolonged emergence of the ketamine group. Patients assigned to the ketamine group had a recovery time that was 1.74 times longer than the remifentanil group (42.9 ± 18.7 minutes versus 24.7 ± 7.6 minutes, \( p = .0004 \)). While the ketamine group received an average of 110 mgs more propofol, the pharmacokinetic and pharmacodynamic profiles of propofol make it unlikely to account completely for the prolonged recovery period. Also of note, none of the participants in the ketamine group reported negative behavioural effects, such as
dysphoria or visual hallucinations. In fact, many participants in this group were observed displaying mild euphoria, possibly a mild form of the emergence delirium often reported with higher doses of ketamine, after transportation to PACU, which resolved prior to discharge. This phenomenon generally was not observed with the remifentanil group who appeared either unimpaired or mildly sedated without euphoria. We believe that some of the ketamine effects persisted after emergence causing the mild euphoria most likely due to the prolonged clinical effects of ketamine when compared to remifentanil. We believed that the remifentanil was metabolized so quickly that the patients quickly returned to baseline and demonstrated no persistent effects.

Surgeon Satisfaction

There was no statistical significant difference noted between the groups with respect to surgeon’s satisfaction with the sedation during the administration of the local anesthesia. Additionally, no significant statistical difference was noted between the groups with respect to the surgeon’s satisfaction with the sedation for the duration of the surgical procedure. Overall, the surgeons were satisfied with the ketamine and the remifentanil techniques for both the administration of the local anesthesia and the sedation for the surgery. Of note, the surgeons were simply given the VAS scales with instructions to complete forms. There were no measures taken to validate intra-rater reliability. Also, due to time constraints, it was not possible limit the number of participating surgeons in order to eliminate or reduce inter-rater reliability issues. A total of four surgeons participated in the study. Three of the surgeons operated on 33 of the participants.
Patient Satisfaction

There was no statistical significance between the groups with respect to patient satisfaction with the sedation (remifentanil group 1.1 ± 0.2 versus ketamine group 1.3 ± 0.6, p = 0.34). 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 there might be a difference only if there was something negative either immediately preoperatively or postoperatively that the patients experienced and remembered about either sedation protocol. However, since all patients were amnestic for the procedure, we expected high satisfaction levels otherwise.

Postoperative Pain Control

Ketamine is a potent NMDA receptor antagonist. Several clinical studies have identified NMDA receptors as being crucial to the induction and maintenance of central sensitization (i.e. pain). By blocking the NMDA receptors with ketamine prior to the initial painful insult (surgery), thereby reducing pain wind-up and central sensitization, it is possible to reduce postoperative pain (pre-emptive analgesia).8 The investigators theorized that the ketamine group may potentially demonstrate lower postoperative oral analgesic requirements due to ketamine’s potential for pre-emptive analgesia. Statistical analysis failed to show any difference between the remifentanil or ketamine group with respect to the postoperative oral analgesic requirements. This was evaluated using the
patient’s reported frequency and dosage of oral pain medication. The data failed to show any difference between the groups with regards to the quantity of naproxen and acetaminophen/hydrocodone 5/500 taken during the first twenty four hours. The reported number of naproxen taken was 2.6 ± 0.5 tablets for the remifentanil group and 2.3 ± 0.8 tablets for the ketamine group, which was not clinically significant. The p value of 0.31 demonstrates that there was no statistical significant difference between the groups. While the ketamine group reported taking a higher number of acetaminophen/hydrocodone tablets than the remifentanil group (4.1 ± 2.5 tablets versus 3.1 ± 2.7 tablets). The p value of 0.25 failed to demonstrate any statistically significant difference between the groups. Based on the lack of statistical significance between the two groups with regards to oral pain medication requirements at twenty four hours, there appears to be no benefit to the ketamine group with respect to the pre-emptive analgesia. While there may truly not have been any difference with either group, this may reflect a lack of specificity by measuring the quantity of oral pain medication taken at twenty four hours. A shorter interval, possibly 6-12 hours) may have revealed a difference between the groups. Additionally, as 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 CNS limiting central sensitization phemonena.
Postoperative Nausea and Vomiting

Regarding the incidence of postoperative nausea and vomiting (PONV), there was no significant difference between either group during the immediate postoperative period ($p = 1.0$). In fact, there was only one participant who experienced nausea and vomiting during the immediate postoperative period and required administration of a single rescue dose of ondansetron 4 mg IV. While this particular subject was in the ketamine group, it was felt that the PONV reflected the participant’s poor compliance regarding continuously biting firmly on the gauze surgical site dressings. Following administration of the rescue antiemetic, in addition to strongly encouraging the participant to apply constant pressure to the surgical sites with the gauze packs, the mild haemorrhage quickly ceased. The participant had no recurrent episodes of PONV and was discharged home shortly thereafter.

With regards to PONV after the immediate postoperative period, both groups had a number of subjects who reported nausea and/or vomiting during the first 24 hours. Both groups had several participants who reported nausea and vomiting while taking the acetaminophen/hydrocodone 5/500 mg tablets postoperatively for breakthrough pain. This was most likely due to the postoperative pain medication, specifically the hydrocodone, as opioids have an established history of increasing incidence of nausea and vomiting $^{10}$. After thoroughly questioning each patient who reported PONV, it became apparent that the PONV typically correlated with the patient taking the hydrocodone 5 mg/acetaminophen 500 mg (Vicodin). It must be stated that all patients
were given postoperative instructions that included staying well hydrated, being sure to
eat and to avoid taking their pain medication on an empty stomach. However, many of
the patients who reported PONV after taking the Vicodin admittedly did not follow the
postoperative instructions.
Conclusion

The use of ketamine as an anesthetic adjunct when combined with continuous infusions of propofol during deep sedations for surgical extractions of third molars demonstrated a significantly prolonged emergence and recovery profile when compared to the use of remifentanil-propofol combinations. This potentially could be easily offset by discontinuing the ketamine-propofol infusion a few minutes before completion of the surgery. While the current market has created a significant cost discrepancy between ketamine and remifentanil, the cost savings would potentially be offset by the increase in monitored emergence and recovery time, should ketamine be substituted for remifentanil. Ketamine added to propofol did lead to slightly higher heart rates which were not clinically significant for this patient population. For an older population with coronary artery disease, for instance, one would have to take into consideration this slightly elevated heart rate when determining the anesthetic plan. Changes in respiratory rate, while statistically significant, were not clinically significant and all patients maintained adequate oxygen saturation. Neither group demonstrated clinically significant alterations in vital signs. Neither ketamine nor remifentanil lead to an increased incidence of nausea and vomiting during the immediate postoperative period. There was no appreciable pre-emptive analgesic effect noted with the ketamine group as neither group demonstrated any significant differences with respect to postoperative oral
analgesic requirements within the first 24 hours. Finally, patients and surgeons demonstrated no significant preference to either the remifentanil or ketamine group. Ketamine combined with propofol can be considered another option in the anesthetic armamentarium for young, healthy patients undergoing third molar surgery.
References


