A comparison of fospropofol to midazolam for moderate sedation during outpatient
dental procedures

THESIS

Presented in Partial Fulfillment of the Requirements for the Degree Master of Science in
the Graduate School of The Ohio State University

By

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Abstract

Introduction. Moderate intravenous (IV) sedation combined with local anesthesia is common for outpatient oral surgery procedures. An ideal sedative agent must be safe and well tolerated by patients and practitioners. This study evaluated fospropofol, a relatively new sedative/hypnotic, in comparison to midazolam, a commonly used benzodiazepine, for IV moderate sedation during oral and maxillofacial surgery.

Methods. Sixty patients were randomly assigned to either the fospropofol or the midazolam group. Each participant received 1 mcg/kg of fentanyl prior to administration of the selected sedative. Those in the fospropofol group received an initial dose of 6.5 mg/kg, with 1.6 mg/kg supplemental doses as needed. Those in the midazolam group received initial doses of 0.05 mg/kg, followed by 0.02 mg/kg supplemental doses. The quality of sedation in each patient was evaluated with regards to (1) onset of sedation, maintenance, and recovery profile; (2) patient and surgeon satisfaction; and (3) hemodynamic stability and adverse effects.

Results. The fospropofol group demonstrated shorter physical recovery times than midazolam patients, taking a mean of 11.6 minutes versus 18.4 minutes for physical recovery (p=0.007). Cognitive recovery comparison did not find any difference with a mean of 7.5 minutes versus 8.8 minutes between the two drug groups (p=0.123). The fospropofol group had a higher rate of local anesthetic recall (90.5% versus 44.4%, p =
0.004). Other parameters of recall were comparable. Two adverse effects demonstrated significance, with more patients in the midazolam group experiencing tachycardia (48.2% vs. 9.4%, p = 0.001), and more patients in the fospropofol group experiencing paresthesia (40.6% versus none, p<0.001). No significant difference was found in any other measures of sedation safety, maintenance, or satisfaction.

Conclusion. Fospropofol can be considered as a safe, well tolerated alternative to midazolam for IV moderate sedation during oral and maxillofacial surgery and other dental procedures.
I would like to thank Dr. Prior, Dr. Johnston, Dr. Smiley, and Dr. Thikkurissy for their guidance and unrelenting support that carried me through this project. Their intelligence and ability is paramount for the institution of education at The Ohio State.
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Chapter 1 Introduction

Moderate sedation is an anesthetic technique that aims to offer improved comfort and relaxation to patients while remaining safe and readily accessible to qualified healthcare personnel. This balance can be achieved when the drugs administered offer such advantages without significant compromise.

A combination of sedation and local anesthesia is often employed during a variety of minor oral surgery procedures, most notably the removal of third molars. The multitude of techniques and drug combinations that are used reflects the lack of a single ideal technique. Additionally, the need and demand for sedation services is on the rise\textsuperscript{12}. The search of an ideal sedative agent is centered on the ability to provide amnesia, anxiolysis and analgesia while providing both practitioner and patient satisfaction. Rapid onset and offset, ease in adjustability, wide margin of safety, and a high quality procedural sedation are other desirable features. Fospropofol, which is a new sedative/hypnotic agent, is being evaluated for potential benefits over existing drugs. It is being compared to a well known and widely used agent, midazolam, as an IV moderate sedation medication.

Midazolam provides anxiolysis, sedation, anterograde amnesia, and skeletal muscle relaxation with a wide therapeutic index, and can be administered by a variety of routes. A key feature that confers a greater degree of safety is the availability an antagonist drug
in the form of flumazenil, which can help reverse the effects of benzodiazepine overdose. The major drawbacks with midazolam are; its slow onset, inadequate alleviation of procedure-related discomfort, increased depth of sedation required for amnesia, and potentially prolonged recovery time.\textsuperscript{1,2}

Propofol is a sedative/hypnotic agent known for its rapid onset, short duration of action, as well as anti-emetic, amnestic, and hypnotic effects. There are several limitations with routine usage of propofol, the most crucial being that in certain patients, propofol can cause cardiac and respiratory depression with possible loss of airway reflexes in doses commonly used for moderate sedation\textsuperscript{3}. Administering unintended deeper level of sedation is a danger that is not unlikely to occur, since doses for moderate and deep sedation can overlap, especially with the narrow therapeutic range of propofol. Per its manufacturer and the Food and Drug Administration (FDA), propofol is recommended for use only by those trained in administering general anesthesia; it is also not advised for use by practitioners who act as both the anesthetist and the surgeon\textsuperscript{1}. Thus, propofol is not necessarily appropriate for the operator – anesthetist model for moderate sedation, in which the surgeon and anesthetist are one and the same. Additional limitations of propofol include its lipid-emulsion formulation, which frequently causes pain on injection\textsuperscript{2}. Water soluble intravenous medications typically do not elicit this pain response. The lipid- emulsion contains egg lecithin, soybean extract, glycerol, and antimicrobial additives, which have the potential to induce allergic reactions in susceptible individuals\textsuperscript{3}. Additionally, propofol supports a greater risk of bacteria growth.
and subsequent risk of infection to the patient. To guard against this a short time of usage is prescribed after opening of the container\(^2\). Thus, the pursuit of an ideal agent continues—one that can easily, safely, and pleasantly be titrated to a moderate level of sedation.

Fospropofol, a prodrug of propofol, is a newer moderate sedation drug. After intravenous administration, fospropofol is hydrolyzed by alkaline phosphatases present in blood plasma and tissues to propofol, phosphate, and formaldehyde\(^4\). Plasma concentration of formaldehyde and phosphate do not exceed endogenous levels following standard doses, and thus pose little risk of toxicity\(^4\). According to the Lusedra™ (brand name) package insert, after intravenous administration of fospropofol, the median time to peak propofol concentration is 12 minutes, and median onset of sedation is 4 to 8 minutes, and the median time to the patient being fully alert after the procedure is 5 minutes. Initial dose-finding research of fospropofol suggests that the optimal balance of safety and efficacy for healthy adult patients is achieved by using initial doses of 6.5 mg/kg, followed by supplemental doses of 1.6 mg/kg\(^4\). The recommended maximum dose of fospropofol is 12.5 mg/kg\(^4\).

Fospropofol’s potential advantages over propofol are related to its pharmacokinetic properties and its water soluble formulation. Due to the necessary enzymatic conversion, the blood concentration of propofol liberated from fospropofol increases at a slower rate, exhibits a longer duration, and does not reach the same peaks, as direct injections of propofol\(^1,5,6\). The rate of increase of the liberated propofol depends more on the rate-
limited metabolism of fospropofol, than on the rate of the injection of the prodrug itself\textsuperscript{7}. These pharmacokinetic properties retard the negative side effects of propofol and potentially create a wider margin of safety. Fospropofol is associated with less cardiopulmonary depression than propofol\textsuperscript{1}. In one safety and efficacy study of patients receiving 6.5 mg/kg doses of fospropofol, less than 1% experienced apnea, 4% demonstrated hypoxemia, and 4% became hypotensive\textsuperscript{4}. This slow and steady release of propofol from fospropofol may reduce the risk of over sedation and thus makes the safety profile of fospropofol potentially superior to that of propofol\textsuperscript{3}. Furthermore, fospropofol does not burn on injection, contain allergens in the form of egg lecithin, soy or preservatives, or carry the same threat of bacterial contamination\textsuperscript{3}.

Fospropofol has potential benefits over midazolam when used for moderate sedation as well. Fospropofol has been shown to have a faster onset and more rapid recovery\textsuperscript{8}. Researchers have demonstrated higher rates of sedation success, less need for supplemental pain medication during sedation, and increased patient and physician satisfaction\textsuperscript{8,9,10,11}. Sedation success rates of 87-89% for fospropofol have been cited, versus approximately 69% for midazolam\textsuperscript{5,9}. Patient satisfaction was found to be 92.3% with fospropofol compared to 69.2% with midazolam, and physician satisfaction was almost three times higher with fospropofol\textsuperscript{5,9}. To date, published studies have focused on comparing the two sedative agents during either colonoscopy or bronchoscopy procedures; the use of such drugs in dentistry has yet to be studied.
A pilot study was completed by Cara Riley in the thesis titled: A Single-Center, Randomized, Blinded Clinical Trial of Fospropofol Versus Midazolam for Moderate Sedation in Patients Undergoing Oral Surgery of 30-45 Minute Duration. The data from this study provided evidence that fospropofol was indeed a reliable alternative to midazolam in the given setting. This master’s thesis was accepted by The Ohio State University Graduate School in 2011. The data gathered from Dr. Riley’s study was combined with our results to attain a greater sample size. In addition, the study was further extended to incorporate the evaluation of memory and recall in the protocol. The implications of such changes are considered in the discussion section.
Chapter 2 Materials and Methods

**Overall Objective**

The overall objective of this study was to determine if fospropofol and fentanyl provide superior moderate sedation in comparison to midazolam and fentanyl in patients undergoing minor oral surgery procedures. This was evaluated by comparing the two study groups with regards to 18 specific aims:

1. Time (minutes) to onset of sedation, as defined by two consecutive Modified Observer’s Assessment of Alertness/Sedation (MOAA/S) scale scores <4. The MOAA/S scale is a commonly used instrument in sedation research that conforms to the American Society of Anesthesiologists (ASA) definition of moderate sedation. The review consists of five response levels to stimulation as shown in Table 1.

Table 1. Modified Observer's Assessment of Alertness/Sedation Scale

<table>
<thead>
<tr>
<th>Response Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responds readily to name spoken in normal tone</td>
<td>5</td>
</tr>
<tr>
<td>Lethargic response to name spoken in normal tone</td>
<td>4</td>
</tr>
<tr>
<td>Responds only after name is called loudly/repeatedly, or light tactile stimulus</td>
<td>3</td>
</tr>
<tr>
<td>Responds only after prodding or shaking</td>
<td>2</td>
</tr>
<tr>
<td>Does not respond to prodding or shaking</td>
<td>1</td>
</tr>
</tbody>
</table>
2. Supplemental dosage of sedative agent needed, defined as the number of doses required after the initial bolus to maintain the patient at a MOAA/S scale score <4.
3. Time in minutes to cognitive recovery, as defined by three consecutive MOAA/S scale scores of 5.
4. Time in minutes to physical recovery, as defined by ability to hold a one-leg stand for 10 seconds.
5. Proportion/percentage of patients who did not recall the local anesthetic injections
6. Proportion/percentage of patients who did not recall the image shown to them after MOAA/S score <4 was achieved.
7. Proportion/percentage of patients who did not recall anything unpleasant during the surgery (pain, pressure, etc.)
8. Patient satisfaction with the procedure, defined as the Visual Analog Scale (VAS) score measured on a 100mm continuous scale with far left representing “extremely dissatisfied” and far right representing “extremely satisfied.”
9. Proportion/percentage of patients willing to repeat the procedure as completed.
10. Surgeon satisfaction with the sedation, defined as the VAS score measured on a 100mm continuous scale with far left representing “extremely dissatisfied” and far right representing “extremely satisfied.”
11. Blood pressure instability, defined as proportion/percentage of patients with mean arterial pressure (MAP) at plus or minus 20% of the preoperative level at any time during the sedation.

12. Proportion/percentage of patients requiring intervention for a blood pressure change.

13. Bradycardia, defined as proportion/percentage of patients with heart rate decrease >20% from baseline or <50 beats/minute and a MAP >20% decrease from the preoperative level at any time during the sedation.

14. Tachycardia, defined as proportion/percentage of patients with heart rate >100 beats/minutes at any time during the sedation.

15. Proportion/percentage of patients requiring intervention for a heart rate change.

16. Proportion/percentage of patients experiencing hypoxemia, defined as an SpO₂ <93% for >60 seconds or any SpO₂ <80%.

17. Proportion/percentage of patients requiring airway assistance, including head tilt/chin lift/jaw thrust, or any exogenous airway adjunct.

18. Proportion/percentage of patients that have a MOAA/S score <2 at any point during the sedation.

**Study Design**

This study was a single-center, randomized, single blinded clinical trial involving patients scheduled and consented for oral surgery anticipated to last 30-60 minutes with local anesthesia and IV moderate sedation at the Ohio State University Oral and Maxillofacial
Surgery Clinic. The research protocol was approved by the Ohio State University Institutional Review Board before the initiation of the study. Our protocol was reviewed and granted approval under IRB protocol number 2011H0031. Prior to the administration of any study treatment, the research staff reviewed the patient’s past medical history (including major illnesses and hospitalization, medications, allergies, prior surgeries, experiences with anesthesia, family and social history, and demographics) and conducted a focused anesthesia examination of the heart, lungs, and airway, including vital signs. The 10-second one-leg standing test was assessed in each subject to ensure ability to perform the action post-operatively when it was used for evaluation of physical recovery from sedation. Fasting requirements were discussed with the patients: nil per os for eight hours prior to the procedure, with the exception that any necessary medications may be taken with a small amount of clear liquids up to two hours before anesthesia.

On the day of surgery, NPO status and the presence of an escort were confirmed. A urine pregnancy test was performed for any female patient whose pregnancy status was unknown. The medical history and physical examination were reviewed. Patients were transferred to a general anesthesia suite with full operating room capabilities including emergency mediations, crash cart, and drugs/equipment needed for endotracheal intubation. Standard ASA monitors (Non-Invasive Blood Pressure, Pulse oximetry, electrocardiography, temperature, capnography via nasal cannula) as well as a pre-tracheal stethoscope were applied. Baseline vital signs were recorded. A 20 or 22 gauge IV catheter was placed in an appropriate upper extremity vein and secured. A slow
infusion of normal saline was started.

Patients were randomly assigned in a 1:1 ratio by the predetermined randomization list to the two study groups. Each group received 1mcg/kg of fentanyl in two divided doses 30 seconds apart. Two minutes later, the first group received an initial dose of 6.5 mg/kg of fospropofol. The second group (controls) received 0.05 mg/kg of midazolam. In both groups, the MOAA/S (Modified Observers Assessment of Alertness/Sedation) score was determined every two minutes for the duration of the procedure. This is a six level scale (0-5) that is outlined in Table 1. If the patient was not at an MOAA/S score <4 (e.g. the patient responded to verbal stimulation in a normal tone) at four minutes, supplemental sedative agent was given in a dose of 1.6 mg/kg fospropofol for the fospropofol group or 0.02 mg/kg midazolam for the midazolam group, and in any four minute increments thereafter in order to reach or maintain the desired level of sedation. The oral surgeon administered local anesthesia using a dental aspirating syringe of 2% lidocaine with 1:100,000 epinephrine as dictated by the innervation of the structures being surgically manipulated. An image was then shown to the patient, and the patient was asked to identify the image (duck or dog). If, during the surgery, the patient required greater control over pain, additional local anesthetic was administered up to a maximum of 6 mg/kg based on lidocaine dose. Total local anesthetic dose as well as surgical start and stop times were recorded.

Sedative administration and monitoring was performed by a qualified dentist
anesthesiologist in compliance with the American Society of Anesthesiologists guidelines. Medications, physiological parameters, and any adverse events were noted on a standard anesthetic record starting preoperatively and ending at patient discharge. Any minor airway interventions, such as head tilt, jaw thrust, or airway adjunct placement, needed to maintain spontaneous ventilation were recorded.

To meet the conditions of recovery from sedation, the patients were required to attain three consecutive MOAA/S scores of 5 (measured every two minutes) as well as achieve a 10-second one-leg stand (measured every five minutes). Just prior to discharge, the patient was asked to rate his or her satisfaction with the sedation on a VAS from “extremely dissatisfied” to “extremely satisfied,” whether or not s/he could recall any part of the surgery, the local anesthetic injections, or the image that was shown to them, and finally, whether s/he would be willing to repeat the procedure in the same manner (refer to Appendix A: Survey). These same inquiries were also recorded by the participant one day postoperatively and returned to the investigators via regular mail (a self-addressed stamped envelope was provided to each subject). Surgeon satisfaction with the sedation was determined using an identical VAS measurement, along with surgeon willingness to repeat the sedation, directly following surgery.

Withdrawal Criteria

Participants had the right to withdraw from the study at any point, for any reason, without penalty, with no effect on the patient’s relationship with The Ohio State
University. The research team could also remove a participant from the study for the following reasons: an adverse event of any severity, the patient’s desire, noncompliance or insufficient cooperation of the patient, and/or any clinically significant abnormality or change in the patient’s condition that render further treatment unreasonable according to the judgment of the anesthesiologist.

**Study Population**

The target population for this research was patients presenting for outpatient oral and maxillofacial procedures requiring moderate intravenous sedation. The sample population included healthy (ASA 1 and 2), consenting volunteers between the ages of 18 and 50 who were not pregnant or breastfeeding, scheduled for oral and maxillofacial surgery (including but not limited to tooth extractions, implant placements, biopsies, and alveoplasty) at The Ohio State University Oral and Maxillofacial Surgery Clinic. An anesthesia consultation was performed prior to enrollment in the study to determine eligibility.

**Inclusion criteria.** Subjects were required to meet all of the criteria below for entry into the study:

1. Ages 18-50 years.
2. Provides written informed consent to participate in the study.
3. Non-pregnant.
4. ASA physical status 1 or 2.
5. Scheduled to undergo oral surgery, anticipated to last 30-60 minutes, under local anesthesia with IV moderate sedation.

**Exclusion criteria.** Subjects meeting any of the following criteria were ineligible for entry into the study:

1. Limited decision-making capacity and/or lacking the ability to consent.
2. Non-English speakers.
3. History of allergic/hypersensitivity reaction to benzodiazepines, fospropofol, fentanyl, or local anesthetic.
4. Pregnant and/or breastfeeding females.
5. Violation of the eight-hour fasting policy.
6. Involvement with a clinical trial of an investigational drug within 30 days of enrollment into this study.
7. Anticipated difficult intubation according to the judgment of the anesthesiologist.

**Statistical Analysis**

The sample population was assigned to either the fospropofol or the midazolam treatment group in a 1:1 ratio established by a random number table. All continuous dependent variables were analyzed using Student's t-Test with means, standard deviations, and minimums/maximums, as described. The Satterthwaite method was used to account for unequal variances in a Student’s t-Test. To compare patient satisfaction scores and event recall over the two time periods, repeated measures ANOVA was employed. All binary dependent variables were analyzed using the Fisher's Exact Test with relative frequencies.
and percentages described. Ninety-five percent confidence intervals were reported for all applicable end points. The data gathered from this research was catalogued and stored on an Excel spreadsheet, and analyzed statistically by the SAS program.
Chapter 3 Results

A total of 61 patients were enrolled in the study. The data from two subjects was discarded as they were inappropriately enrolled in the study and did not meet inclusion criteria due to age (51 and 55 year old). Survey results were collected from 50 patients, 11 were not returned. Figures and tables that include an asterisk represent data from our adjusted protocol only; those without an asterisk represent the combined data from our study and that of Dr. Riley’s. The survey data was analyzed using only the results of the returned surveys. Gender and age of the study population found no significant differences between two groups. Both groups showed a greater percentage of female to male participants, 59% for fospropofol and 74% for midazolam.

Table 2. Age and Gender Distribution

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FOSPROPOFOL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>Percent of Total</td>
<td>22.0%</td>
<td>32.2%</td>
</tr>
<tr>
<td>Percent of Drug</td>
<td>40.6%</td>
<td>59.4%</td>
</tr>
<tr>
<td>Percent of Gender</td>
<td>65%</td>
<td>48.7%</td>
</tr>
<tr>
<td><strong>MIDAZOLAM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>-----------</td>
<td>---</td>
<td>----</td>
</tr>
<tr>
<td>Percent of Total</td>
<td>11.8%</td>
<td>33.9%</td>
</tr>
<tr>
<td>Percent of Drug</td>
<td>25.9%</td>
<td>74.1%</td>
</tr>
<tr>
<td>Percent of Gender</td>
<td>35%</td>
<td>51.3%</td>
</tr>
</tbody>
</table>

There was no difference found in the surgery duration times with the mean in the fospropofol group at 41.0 minutes and the midazolam group at 35.5 minutes (p = 0.342). There were seven cases that went beyond the target duration of 40-60 minutes, with the longest duration at 124 minutes. See Figure 2.

The number of supplemental doses required to reach an adequate level of sedation were similar for both groups, and subsequently, the time to onset of sedation were similar as well. Time to onset was calculated using $4 + (4 \times \text{number of supplemental doses})$ since it took at least 4 minutes to evaluate initial sedation, and supplemental doses were administered only in 4 minute increments. The fospropofol group had a mean supplemental dose of 1.97 and the midazolam group was 2.63 (p = 0.101). The mean onset of sedation for fospropofol was 11.9 min and 14.4 minutes for midazolam. See Figures 2 and 3. The slight longer onset was not statistically significant (p = 0.101). The supplemental doses required after 30 minutes in the fospropofol group was slightly greater, but not statistically significant. The fospropofol group mean was 0.81 compared to midazolam with a mean 0.41 (p = 0.13). See Figure 4.
There was no difference found in the time to cognitive recovery with the fospropofol group mean at 7.50 minutes, and the midazolam group mean at 8.81 minutes (p = 0.123). See Figure 5. However, there was a difference in the physical recovery time with the fospropofol group exhibiting a shorter mean recovery time of 11.6 minutes compared to the midazolam group at 18.4 minutes (p = 0.007). See Figure 6.

Surgeon satisfaction scores based off a Visual Analogue Scale were similar for both drug groups, the mean for fospropofol at 85.0 and midazolam at 78.8 (p = 0.336). Surgeon willingness to repeat the sedation was comparable, 93.8% of the fospropofol group and 81.5% in the midazolam group indicated they would repeat the sedation (p = 0.229). See Figure 7.

When adequate sedation could not be achieved or patient comfort for tolerance of the oral surgery procedure could not be obtained, the sedation was deemed a failure and was consequently converted to a deep sedation in order to complete the procedure. This consisted of giving intravenous propofol boluses and/or infusion to the level of deep sedation. The procedures were completed without further complications. This occurred in a total of five patients, one in the fospropofol group and four in the midazolam group (p = 0.167).
Analysis of patient satisfaction scores based on a Visual Analogue Scale found no difference between the fospropofol and midazolam groups. An interaction was found in the responses between time of discharge and one day post operatively for the two study groups. This shows that the means of the change in patient satisfaction from discharge to day one is different for the two drugs. \((p = 0.050)\). Satisfaction levels rose on post operative day one in the midazolam group, but fell in the fospropofol group. See Figure 8. Willingness to repeat at time of discharge was high in both groups. Only one participant in the study was unwilling to repeat the sedation, this participant was in the fospropofol group. When asked on postoperative day one, this same participant noted, however, that they would be willing to repeat the sedation.

Table 3. Adverse Effects

<table>
<thead>
<tr>
<th></th>
<th>Fospropofol</th>
<th>Midazolam</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension</strong></td>
<td>5 (15.6%)</td>
<td>4 (14.8%)</td>
</tr>
<tr>
<td><strong>Hypotension</strong></td>
<td>1 (3.1%)</td>
<td>2 (7.4%)</td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>0 (0%)</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td><strong>Bradycardia</strong></td>
<td>2 (6.3%)</td>
<td>2 (7.4%)</td>
</tr>
<tr>
<td><strong>Tachycardia</strong>*</td>
<td>3 (9.4%)</td>
<td>13 (48.2%)</td>
</tr>
<tr>
<td><strong>Heart Rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>0 (0%)</td>
<td>2 (7.4%)</td>
</tr>
<tr>
<td></td>
<td>Fospropofol</td>
<td>Midazolam</td>
</tr>
<tr>
<td>------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>2 (6.3%)</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>Airway Assistance</td>
<td>0 (0%)</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>Paresthesia**</td>
<td>13 (40.6%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*Significant difference with p=0.017

**Significant difference with p<0.001

Regarding the evaluation of cardiopulmonary stability and incidence of adverse effects, we found a difference in only two main areas – greater incidence of paresthesia in the fospropofol group and the greater incidence of tachycardia in the midazolam group. The data in these categories were analyzed using Fisher’s Exact test and all had values of p>0.05 except for the two categories mentioned. The fospropofol group had a reported incidence of 40.6% and an average duration of 37 seconds (45 to 180 seconds). Paresthesia was characterized as moderate to severe burning, itching, and/or general discomfort of the perianal and perineal region. Others reported the paresthesia located in the legs, buttocks, and abdomen. This was observed immediately after and within five minutes of initial administration of fospropofol, none was observed during supplemental boluses. The midazolam group showed an incidence of tachycardia of 48.2% compared to 9.4% (p = 0.017). Other parameters of cardiovascular stability including hypertension, hypotension, bradycardia, and either blood pressure or heart rate intervention were comparable. Pulmonary stability was also comparable between the two groups when looking at hypoxemia and airway intervention. The incidence of hypoxemia in the
fospropofol group was 6.3%, while it was 11.1% in the midazolam group. Airway intervention did not occur in the fospropofol group and 11.1% in the midazolam group.

Recall was evaluated using three separate tests, examining overall rates of recall throughout the entire process in procedural recall, while specific time points were evaluated in asking about the ability to recall the local anesthetic injections and the ability to recall an image shown to the patient.

We found no difference in the incidence of procedural recall. Ability to recall in the fospropofol group was 90%, midazolam group was 100% (Exact p = 0.265). See Figure 9. Recall in this category included a varied response including remembering the injections, sounds of instruments, pain and pressure localized to both regional areas and temporal relations. There is a significant interaction between the two days. On post operative day one, the number patients who reported recall decreased in the midazolam group, but increased in the fospropofol group (p = 0.021). See Figure 10.

We found no difference in the incidence of image recall. Ability to recall the image was 28.6% with fospropofol and 11.1% with midazolam (Exact p = 0.247). Patients were asked to recall the image but were not shown the image again to elicit recognition. A few patients indicated that they did remember the image shown, but when asked to describe the image, they did not describe the same image that was shown. In these cases, the results were posted as inability to recall image. See Figure 11.
There was a significant difference in the ability to recall the local anesthetic injections. In the fospropofol group the ability to recall was 90.5% compared to 44.4% in the midazolam group (exact p = 0.004). There was a significant difference found in responses taken on post operative day 1 (p = 0.019), as there were fewer patients with local recall in the fospropofol group. See Figure 12.
Chapter 4 Discussion

The selection of the appropriate sedative medication for the patient, procedure, and surgeon is critical to the success of IV moderate sedation, especially with the increase in demand for outpatient dental procedures being performed in dentistry\textsuperscript{12}. The results generated from this study support the use of fospropofol as an alternative to midazolam for IV moderate sedation during dental surgeries. Fospropofol appears to confer some advantages over the traditionally used benzodiazepine, most notably producing faster recovery times. However, there are also some adverse effects and shortcomings that are not as prominent with midazolam; paresthesia and potentially less reliable amnestic qualities. There are differences that exist between any two drugs, and it is important to recognize the limitations and capabilities of any drug so as to select the most appropriate medication to achieve different goals.

The evaluation of recall is an important component to any sedative agent. The basis of patient satisfaction can, in part, be rooted in the subjective experience – the fewer memories that can be used for subjective analysis, the fewer negative and positive experiences that are available to draw upon. Assuming that the overall experience of surgery is a negative one, thus spawning the need for sedation, it can therefore be postulated that the better the amnestic qualities, the better the sedative agent. Midazolam
has long been heralded for its reliable amnestic properties\textsuperscript{13}, and in this study we focused in on determining the amnestic qualities of fospropofol when compared to midazolam.

Midazolam appears to provide slightly more reliable amnesia than fospropofol. Upon discharge, there are fewer patients who recall the local anesthetic injections in the midazolam group. In the fospropofol group the ability to recall the local anesthetic injections was 91\% compared to 50\% in the midazolam group (exact $p = 0.006$). Although there is no statistical difference in the amount of procedural recall between the two drug groups, the combined data from amnestic evaluation results still favor midazolam. Postoperative day one results demonstrated conflicting information. In procedural recall, the midazolam group had fewer patients with recall, while the fospropofol group showed more patients with recall. For postoperative day one results regarding local recall, fewer patients in the fospropofol group had recall, but there was no difference found in the midazolam group (between the two days). Postoperative day one results for image recall showed no interaction between the two days.

The inconsistency in the procedural recall category may be attributed to a variety of factors. Two interesting explanations may include potential differences in the ability of the different sedatives to abolish different types of memory, or to the way the question was posed. “Do you remember anything unpleasant from the surgery”. The open-ended nature of the question allows the patient to respond with a positive response regardless of what was recalled and when it was recalled since it could have been anytime from when
the procedure was started to when the patient was ready for discharge. The design of the question was intended to allow patients to indicate what was unpleasant and not introduce study bias, but the question is leading, which may have prompted higher rates of recall. When asked if anything unpleasant was recalled, patients reported things such as some instances of pain, specific portions of the surgery such as “extraction on the right side, the sound of the drill, some pressure”, etc. Most patients were able to frame these memories in temporal (end or beginning of surgery), and regional (left side, upper jaw) areas.

Creating specific memory points by asking about concrete and chronologic events seems to elicit more useful data. Abolishing the memory of the typically uncomfortable portions of the surgery such as local anesthetic injections would be a useful characteristic of a sedative medication.

A dose dependent model of amnestic qualities may exist with fospropofol, as it does with midazolam\textsuperscript{14}. Although we used manufacturers guidelines for sedation, further studies are needed to investigate the dose dependency of amnesia – our protocol may not have allowed for enough fospropofol to be used to achieve higher levels of amnesia. Alternatively, midazolam may be better at abolishing stimuli that elicit pain, whereas fospropofol may not be as effective. Visual stimuli did not appear to lead to differences in recall as demonstrated by the image recall scores, which would suggest that purely visual stimuli is less likely to produce recall than local anesthetic injections which typically produce a tactile and sometimes painful response. A more sophisticated questionnaire in
determining what was recalled would be needed to extend this discussion. Our results suggest that there may be an increased delay in the onset of the full amnestic properties of drug that may occur after adequate sedation has been achieved according to (MOAAS) evaluation scores and may correlate better with plasma levels of propofol. Separate protocols for each drug may produce more accurate results for each drug has unique drug profiles that should be studied accordingly. Although our protocol allowed ample time for both drugs to work, the optimal actions of the drugs may have been obscured in order to fit a single model.

Those patients that experienced recall still indicated they would repeat the sedation, suggesting that these experiences were acceptable. A more sophisticated study would to bring the same patient back for two procedures (one with midazolam and one with fospropofol) so there was a basis of comparison, but the ethical ramifications and feasibility of such a study would need to be addressed. Additionally, many of the patients have never experienced moderate sedation or any type of sedation, therefore having nothing to draw upon for reference. Therefore, the enjoyment of any improvement over previous dental or surgical experiences may override the relatively subtle differences that would be useful for academic purposes.

The evaluation of recall and amnesia is notoriously difficult to accomplish and future studies would be needed to further investigate the amnestic properties of these two medications. However, with the results from this study, there is preliminary evidence that
fospropofol does not have as reliable amnestic qualities when used in the methods described in the study.

The most commonly reported side effect in the fospropofol group was paresthesia, characterized by perianal or perineal itching or burning. The frequency of paresthesia was similar to other studies of fospropofol. Paresthesia was consistently the most commonly reported side effect, with a rate of occurrence between 49% and 74%. In our study, paresthesia was recorded only when indicated in the survey when the patient was prompted by the question “did you remember anything unpleasant from the surgery”. This indicates that the patient experiences paresthesia before amnestic qualities are achieved, and that the actual incidence of paresthesia is probably much greater. Based upon subjective observation, a substantially higher number of patients in the fospropofol group displayed signs of perianal and perineal discomfort such as fidgeting, scratching and increased overall movement within the first five minutes of fospropofol administration. Future studies may look to examine and define a set of parameters to better evaluate this phenomenon.

Paresthesia in the form of perianal itching or altered sensation is a known side effect of another commonly used IV medications dexamethasone, used for its anti-inflammatory and antiemetic properties. The pharmacologic basis for this phenomenon has yet to be elucidated, but it has been theorized that the phosphate ester groups present on both medications plays a role in mediating this effect. Although patients did not have lower
satisfaction scores compared to the midazolam group, nor did they report any negative issues with this transient paresthesia, methods to minimize or eliminate this side effect need to be studied. Speed of injection or use of other medications may attenuate the severity or incidence of paresthesia.

Overall, the incidence and severity of adverse effects indicates that both drugs are safe to use as a moderate sedation agent. Fospropofol confers an advantage in terms of cardiovascular stability as evaluated by the incidence of hypertension and tachycardia. Although these two parameters were higher in the midazolam, heart rate and blood pressure intervention rates remained similar, suggesting that these effects were transient enough or did not necessarily warrant medical intervention. Bradycardia and hypotension were fairly similar between the two groups. Higher incidences of tachycardia and hypertension have previously been reported with the administration of midazolam\textsuperscript{16}. For the population of patients in our study, this increased incidence of tachycardia and hypertension may not be a major issue, but with patients who have narrower target cardiovascular goals (critically ill patients, cardiovascular disease, etc.), fospropofol may be more useful as a moderate sedation agent.

Pulmonary and airway safety of fospropofol was substantiated by the comparable incidence of hypoxemia and airway intervention between the two drug groups. The rate of hypoxemia and airway intervention in the fospropofol group was 6.3\% and 0\%, again consistent with previous studies on the drug. A rate of 1-12\% has been reported, and most
cases involved patients >75 years of age, and in those undergoing bronchoscopy (compared to colonoscopy, which inherently has a lower chance of airway complications)\textsuperscript{6}. Our study and others have shown that this hypoxemia is relatively transient and reliably treated with supplemental oxygen and standard airway assistance maneuvers. Also, there were no reported incidences of patients falling into deeper than intended levels of sedation. Lusedra is marketed as having a wide margin of safety and although we did not compare directly to propofol, the low incidence of airway problems and unintended over sedation indicates that fospropofol is at least as safe as midazolam when used for moderate sedation. This is certainly an improvement over propofol, which, although can be successfully used for moderate sedation, does not have a wide enough margin of safety to be recommended for providers trained to administer up to the level of moderate sedation.

Mean times to onset of sedation were generally greater than the previously reported times to onset. 4-8 minutes to onset is reported by the Lusedra drug insert\textsuperscript{4}. This could be a reflection of our protocol design, as both drugs exhibited higher than usual times to onset. Nonetheless, there fospropofol did not seem to confer an advantage in this regard, as there was no difference found between the two drug groups. The average supplemental doses to induce was two or greater in the groups, suggesting that higher initial doses may be appropriate. The safety of titration can never be overstressed, but an interesting finding nonetheless.
Although statistically not significant, there was an observed increased incidence of the need to redose fospropofol for procedures that lasted beyond 30 minutes. This may be in part due to the quality of the sedation changing with the initiation of surgical stimulation. Although patients in both drug groups initially met the adequate sedation score (MOAA/S), changes in stimulation may have negatively affected the ability of fospropofol to maintain the adequate level of sedation. Both groups were similar in terms of duration of surgery, and the average duration of surgery fell within the duration of action for both drugs.

The recovery profile of a drug is an important factor when practitioners choose a particular agent – a faster recovery lends itself to a number of potential benefits such as a safer recovery period with fewer complications due to prolonged sedation, reduced time to discharge, and fewer problems with sedation after discharge. Recovery was considered in two dimensions—cognitive and physical—and in this study, fospropofol appears to offer a slight advantage over midazolam. The study results show that physical recovery from fospropofol is faster compared to midazolam (11.6 minutes versus 18.4 minutes), but there was no difference found in the cognitive recovery time (7.5 minutes versus 8.8 minutes). Cognitively, patients were required to exhibit a return to baseline responsiveness on three consecutive tests given two minutes apart, such that the minimum amount of time possible for recovery was 6 minutes. The test for physical recovery examined patient balance and coordination in the form of a 10 second one leg stand, starting five minutes after the end of surgery, and therefore the minimum time to
physical recovery was 5 minutes. Whether any patients were “recovered” prior to the minimums set by the research protocol is unknown; future studies may measure recovery differently, and mean recovery times could be found to be less than 6 minutes. The Lusedra ™ package insert reported a median time to fully alert of 5 minutes, which would not be possible according to our cognitive recovery parameters. Additionally, the method in which we evaluated recovery did not control for the duration of surgery, so recovery times may vary depending on the time of the last medication given and the duration of surgery. Although we were more concerned with a difference in recovery times, it may be prudent to improve the accuracy of this parameter in future studies.

The difference in cognitive and physical recovery in the midazolam group may be in part due to the known muscle relaxant properties of midazolam which is not a feature of propofol or fospropofol. So although both drug groups exhibit early cognitive recovery, midazolam’s muscle relaxing properties may prolong physical recovery. The fospropofol group had an average physical recovery time of 11.6 minutes while the midazolam group had an average of 18.4 minutes. If total recovery is viewed as fully meeting discharge criteria, then fospropofol saves an average of 6.8 minutes in recovery compared to midazolam. Although this is a significant difference, the clinical significance is subject to debate.

The level of sedation throughout the entirety of the procedure is difficult to assess. Continuous evaluation of a MOAA/S score >4 was attempted, with subsequent doses of
anesthetic administered if the sedation was not adequate at the 30 minute mark, but it is difficult to ensure that the patient had a MOAA/S score <4 up until the end of the procedure. This is especially true for procedures that have little stimulation towards the end (suturing). The patient may, in fact, no longer be sedated, leading to a faster recovery time. Future studies can be performed to better assess the quality of the sedation throughout the entire procedure.

We found the rates of sedation failure to be similar in both drug groups given the population of participants which likely reflects the overall limitations of moderate sedation rather than a drug dependent factor. Although the number of failures was similar, the reasons for failure were somewhat different. In both cases cooperation levels fell and it was deemed that the surgery could not be completed. In the fospropofol cases, paresthesia played a central role in the loss of cooperation as the patients were unable to control the urge to resolve the paresthesia through scratching or moving. In the midazolam cases, there was generalized disinhibition and agitation that included talking, movement, and inability to follow commands. These findings reflect well documented instances of paradoxical reactions to benzodiazepines. It must be stressed that the main underlying reason for sedation failure was disinhibition and loss of cooperation and regardless of the reason for sedation failure and neither drug can be implicated in causing more or fewer failures. In addition, the overall incidence of sedation failure was low in both groups.
There was no difference found between the patient satisfaction scores of the two drug groups; both drug groups had fairly high scores. The high satisfaction scores cannot be attributed to any effect of the sedation, such as euphoria or cognitive-impairment, as the grades remained elevated once the sedative agents had worn off. However, it is important to note that patients with no prior experience with moderate sedation will have variable expectations and goals for a successful sedation. Most of the patients in our study never had moderate sedation performed before. Without more information on what exactly leads to higher or lower satisfaction scores, it is not possible to ascertain if one drug is preferable to the other. Further studies to assess what patients prefer during a procedure with sedation could be elucidated by comparing the two drugs in the same patient for the same procedure. Unfortunately, this was not feasible in our study.

When comparing recall scores to satisfaction scores, it appears that patients may not value amnesia to the same degree as anesthesiologists or anesthesia trained providers. Although it makes sense that the fewer memories a patient has regarding a generally unpleasant experience, such as the surgical extraction of a tooth, the better the experience, this may only be true if the patients have had the same procedure done without sedation. It may not hold true at all as patients may simply not care as much about amnesia as they do about overall comfort and any euphoria that can be recalled. There is compelling evidence that more investigation regarding patient satisfaction needs to be completed in order to develop, design, or discover the ideal sedative agent.
Surgeon satisfaction scores were similar. This suggests that fospropofol is equally accepted as a sedative agent based on perceived cooperation and comfort of the patient. To increase the strength of this parameter, we should have designed the protocol to standardize the number of procedures done in the midazolam and fospropofol groups. A major weakness of the study design was the lack of anesthesia provider input and assessment of the case in a general VAS satisfaction score. Although we used several different parameters to assess the sedation, a general satisfaction score from the anesthesia provider or from an independent, blinded anesthesia personnel would be useful in measuring the overall quality of the sedation for the surgeon, patient, and anesthesiologist.

The results of the study need to be interpreted with the knowledge that although this study allowed for patients between the age of 18 and 50, the average age was 26 years old. A younger age group usually indicates a less medically compromised and healthier population that take fewer medications and have greater tolerance for physiologic insults (such as hypoxemia), thus reducing potential drug interactions and proclivity towards adverse events. We should reiterate that our sample size is taken from minor outpatient oral surgery procedures, and thus the results should be interpreted for this population. Additionally, there was a preponderance of female study participants, perhaps due to a sample size that was too small, or perhaps indicating an institutional bias in scheduling or even an underreported phenomenon that exists in the general population of patients undergoing moderate sedation. Regardless of the explanation, these results will tend to
represent the female population more so than the male, since we had a greater number of female participants.
Chapter 5 Conclusion

Moderate sedation is widely used, yet the techniques and drugs used continue to be refined in the perpetual pursuit of improvement. Fospropofol has emerged as a new agent that appears to be a good alternative to midazolam in providing moderate sedation. Compared to midazolam, fospropofol has a faster physical recovery period, fewer cardiovascular side effects, and similar margin of safety when used according to the manufacturer’s guidelines. However, the high incidence of paresthesia, lack of reversal agent, and less reliable amnesia with fospropofol may temper the urge for the wholesale replacement of midazolam.
Appendix A. Study Survey

POST-SEDATION QUESTIONNAIRE

1. Do you remember the local anesthetic injections?
   
   Please circle one: YES  NO

2. Do you remember anything unpleasant during the procedure, prior to being moved to the recovery room? (pain, pressure, any discomfort)
   
   Please circle one: YES  NO

3. Are you able to recall the image that was shown to you during the procedure?
   
   Please circle one: YES  NO

   If YES, please describe the image:

4. How satisfied were you with the sedation?
   
   Please place a single vertical mark on the line below to indicate how satisfied or content you were with the sedation.

   ____________________________________________________________

   Extremely dissatisfied                      Extremely Satisfied

5. Would you be willing to repeat the same type of sedation if you needed another procedure?
   
   Please circle one: YES  NO

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Figure 1. Duration of Surgery
Figure 2. Supplemental Doses to Induce
Figure 3. Onset to Sedation
Figure 4. Supplemental Doses after 30 minutes*
Figure 5. Time to Cognitive Recovery
Figure 6. Time to Physical Recovery
Figure 7. Surgeon Satisfaction
Figure 8. Patient Satisfaction Over Two Days
Figure 9. Incidence of Procedural Recall
Figure 10. Incidence of Procedural Recall
Figure 11. Image Recall Over Two Days*
Figure 12. Local Recall Over Two Days*
Appendix C. Data Tables

Table 4. Age Distribution of Study Population

<table>
<thead>
<tr>
<th></th>
<th>Mean Age (yr)</th>
<th>Minimum to Maximum (yr)</th>
<th>Standard Deviation (yr)</th>
<th>95% Confidence Interval (yr)</th>
</tr>
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<tbody>
<tr>
<td><strong>Fospropofol</strong></td>
<td>26.9</td>
<td>16-49</td>
<td>7.84</td>
<td>24.1 – 29.7</td>
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<tr>
<td><strong>Midazolam</strong></td>
<td>24.9</td>
<td>16-49</td>
<td>7.41</td>
<td>22.0 – 27.9</td>
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</table>

* Significant difference with p=0.015

Table 5. Duration of Surgery

<table>
<thead>
<tr>
<th></th>
<th>Mean Duration of Surgery (min)</th>
<th>Minimum to Maximum (min)</th>
<th>Standard Deviation (min)</th>
<th>95% Confidence Interval (min)</th>
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<tr>
<td><strong>Fospropofol</strong></td>
<td>41.0</td>
<td>6 - 124</td>
<td>22.9</td>
<td>32.7 - 49.3</td>
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<tr>
<td><strong>Midazolam</strong></td>
<td>35.5</td>
<td>10-91</td>
<td>20.9</td>
<td>27.2 - 43.8</td>
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Table 6. Supplemental Doses to Induce

<table>
<thead>
<tr>
<th></th>
<th>Fospropofol</th>
<th>Midazolam</th>
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<tbody>
<tr>
<td><strong>Supplemental Doses</strong> (#)</td>
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<td></td>
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<tr>
<td>Mean</td>
<td>1.97</td>
<td>2.6</td>
</tr>
<tr>
<td>Minimum to Maximum</td>
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<td>0-6</td>
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<tr>
<td>Standard Deviation</td>
<td>1.51</td>
<td>1.52</td>
</tr>
<tr>
<td>95% Confidence Intervals</td>
<td>1.42 - 2.51</td>
<td>2.03 - 3.23</td>
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<tr>
<td><strong>Supplemental Doses</strong> after 30 minutes</td>
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<td></td>
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<tr>
<td>Mean</td>
<td>0.81</td>
<td>0.41</td>
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<tr>
<td>Minimum to Maximum</td>
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<td>0-3</td>
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<tr>
<td>Standard Deviation</td>
<td>1.15</td>
<td>0.80</td>
</tr>
<tr>
<td>95% Confidence Intervals</td>
<td>0.399 - 1.227</td>
<td>0.092 - 0.723</td>
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Table 7. Time to Onset

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<tr>
<th></th>
<th>Mean Time to Onset (min)</th>
<th>Minimum to Maximum (min)</th>
<th>Standard Deviation (min)</th>
<th>95% Confidence Intervals (min)</th>
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</thead>
<tbody>
<tr>
<td><strong>Fospropofol</strong></td>
<td>4.70</td>
<td>4-6</td>
<td>0.949</td>
<td>4.02-5.38</td>
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<tr>
<td><strong>Midazolam</strong></td>
<td>5.80</td>
<td>4-12</td>
<td>2.86</td>
<td>3.75-7.85</td>
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Table 8. Time to Recovery

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<th>Midazolam</th>
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</thead>
<tbody>
<tr>
<td><em><em>Time to Physical Recovery</em> (min)</em>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>11.6</td>
<td>18.4</td>
</tr>
<tr>
<td>Minimum to Maximum</td>
<td>5-29</td>
<td>5-40</td>
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<tr>
<td>Standard Deviation</td>
<td>7.03</td>
<td>10.51</td>
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<tr>
<td><strong>95% Confidence Intervals</strong></td>
<td>9.09 - 14.16</td>
<td>14.25 -22.57</td>
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<tr>
<td><strong>Time to Cognitive Recovery (min)</strong></td>
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<tr>
<td>Mean</td>
<td>7.5</td>
<td>8.8</td>
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<tr>
<td>Minimum to Maximum</td>
<td>6-17</td>
<td>6-20</td>
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<tr>
<td>Standard Deviation</td>
<td>2.79</td>
<td>3.66</td>
</tr>
<tr>
<td><strong>95% Confidence Intervals</strong></td>
<td>6.49 - 8.51</td>
<td>7.37 - 10.26</td>
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*Significant difference with p=0.007
Table 9. Patient and Surgeon Satisfaction Scores

<table>
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<tr>
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<th>Fospropofol</th>
<th>Midazolam</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Satisfaction at Discharge (mm)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>93.2</td>
<td>84.7</td>
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<tr>
<td>Minimum to Maximum</td>
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<tr>
<td>Standard Deviation</td>
<td>13.3</td>
<td>20.8</td>
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<tr>
<td>95% Confidence Intervals</td>
<td>88.4 - 98.0</td>
<td>76.4 - 92.9</td>
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<tr>
<td><strong>Patient Satisfaction at Post-op Day 1</strong> (mm)</td>
<td></td>
<td></td>
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<tr>
<td>Mean</td>
<td>88.2</td>
<td>90.2</td>
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<tr>
<td>Minimum to Maximum</td>
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<tr>
<td>Standard Deviation</td>
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<td>12.0</td>
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<tr>
<td>95% Confidence Intervals</td>
<td>83.6 - 92.8</td>
<td>85.1 - 95.3</td>
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<tr>
<td><strong>Surgeon Satisfaction (mm)</strong></td>
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<tr>
<td>Mean</td>
<td>85.0</td>
<td>78.8</td>
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<td>Minimum to Maximum</td>
<td>22-100</td>
<td>9-100</td>
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<td>Standard Deviation</td>
<td>20.8</td>
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<tr>
<td>95% Confidence Intervals</td>
<td>77.5 - 92.5</td>
<td>67.8 - 89.9</td>
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</table>

*Significant difference with p=0.

**Significant difference with p=0.
References

7 Apfelbaum JL. ASA comments to the Anesthetic and Life Support Drugs Advisory Committee for the May 7, 2008 meeting to discuss the new drug application, fospropropofol disodium injection, for the proposed indication of sedation in adult patients.