A Comparison of Fospropofol to Midazolam for Moderate Sedation During Outpatient Dental Procedures

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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. Sixty patients were randomly assigned to either the fospropofol or the midazolam group. Each participant received 1 µg/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 regard to (a) onset of sedation, maintenance, and recovery profile; (b) patient and surgeon satisfaction; and (c) hemodynamic stability and adverse effects. 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 ($P = .007$). Cognitive recovery comparison did not find any difference with a mean of 7.5 minutes versus 8.8 minutes between the 2 drug groups ($P = .123$). The fospropofol group had a higher rate of local anesthetic injection recall (90.5 vs 44.4%, $P = .004$). 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%, $P = .001$), and more patients in the fospropofol group experiencing perineal discomfort (40.6 vs 0, $P < .001$). No significant difference was found in any other measures of sedation safety, maintenance, or satisfaction. Fospropofol, when administered intravenously by a dentist anesthesiologist at the indicated dose in this study, appears to be a safe, well-tolerated alternative to midazolam for intravenous moderate sedation during minor oral surgery procedures.

Key Words: Fospropofol; Midazolam; Moderate sedation; Outpatient surgery; IV conscious sedation; Benzodiazepine; Propofol.

Moderate sedation is an anesthetic technique that aims to offer improved comfort and relaxation to patients while remaining safe and readily accessible to

Received December 13, 2012; accepted for publication September 6, 2013

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Anesth Prog 60:162–177 2013

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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

ISSN 0003-3006/13
SSDI 0003-3006(13)

are used reflects the lack of a single ideal technique. Additionally, the need and demand for sedation services is on the rise. 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 compared to existing drugs such as a well-known and widely used agent, midazolam, as an intravenous (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 of 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.^{1,2}

Propofol is a sedative/hypnotic agent known for its rapid onset and short duration of action, as well as its antiemetic, 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.² 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 US 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.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.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.³ Additionally, propofol supports a greater risk of bacterial growth and subsequent risk of infection to the patient. To guard against this, a short time of usage is prescribed after opening 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, the 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.⁷ These pharmacokinetic properties retard the negative side effects of propofol and potentially create a wider margin of safety. Fospropofol is associated with less cardiorespiratory depression than propofol.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.⁴ This slow and steady release of propofol from fospropofol may reduce the risk of oversedation and thus makes the safety profile of fospropofol potentially superior to that of propofol.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.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.⁸ Researchers have demonstrated higher rates of sedation success, less need for supplemental pain medication during sedation, and increased patient and physician satisfaction.^{8–11} Sedation success rates of 87 to 89% for fospropofol have been cited, versus approximately 69% for midazolam.^{5,9} Patient satisfaction was found to be 92.3% with fospropofol compared

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

Responds readily to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly/repeatedly, or light tactile stimulus	3
Responds only after prodding or shaking	2
Does not respond to prodding or shaking	1
Does not respond to deep stimulus	0

to 69.2% with midazolam, and physician satisfaction was almost 3 times higher with fospropofol.^{5,9} To date, published studies have focused on comparing the 2 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 and reported 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 in 2011. The data gathered from the 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. 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.

MATERIALS AND METHODS

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. The 2 drug combinations were evaluated by comparing the 2 study groups with regard to 18 specific aims:

1. Time (minutes) to onset of sedation, as defined by 2 consecutive Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale scores less than 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 5 response levels to stimulation as shown in Table 1.

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 less than 4.
3. Time in minutes to cognitive recovery, as defined by 3 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 less than 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 100-mm 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 100-mm 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 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 the proportion/percentage of patients with heart rate decrease greater than 20% from baseline or less than 50 beats/min and a mean arterial pressure greater than 20% decrease from the preoperative level at any time during the sedation.
14. Tachycardia, defined as the proportion/percentage of patients with heart rate greater than 100 beats/min 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 less than 93% for more than 60 seconds or any SpO₂ less than 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 who have a MOAA/S score less than 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. The research protocol was approved by the institutional review board before the initiation of the study. 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 postoperatively when it was used for evaluation of physical recovery from sedation. Fasting requirements were discussed with the patients: nil per os for 8 hours prior to the procedure, with the exception that any necessary medications may be taken with a small amount of clear liquids up to 2 hours before the sedation.

On the day of surgery, nil per os 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 medications, 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 pretracheal 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 2 study groups. Each group received 1 µg/kg of fentanyl in 2 divided doses 30 seconds apart. Two minutes later, the first group received an initial dose of 6.5 mg/kg of fentanyl. The second group (controls) received 0.05 mg/kg of midazolam. In both groups, the MOAA/S score was determined every 2 minutes for the duration of the procedure. This is a 6-level scale (0–5) that is outlined in Table 1. If the patient was not at a MOAA/S score less than 4 (eg, the patient responded to verbal stimulation in a normal tone) at 4 minutes, supplemental sedative agent was given in a dose of 1.6 mg/kg fentanyl for the fentanyl group or 0.02 mg/kg midazolam for the midazolam group, and in any 4-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 were performed by a qualified dentist anesthesiologist in compliance with the ASA guidelines. Medications, physiologic 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 3 consecutive MOAA/S scores of 5 (measured every 2 minutes) as well as achieve a 10-second one-leg stand (measured every 5 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 1 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's 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 research team. 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 would render further treatment unreason-

able according to the judgment of the dentist anesthesiologist.

Study Population

The target population for this research was patients presenting for outpatient oral and maxillofacial procedures requesting moderate intravenous sedation. The sample population included healthy (ASA 1 and 2), consenting volunteers between the ages of 18 and 50 years 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 study 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:

- (a) Age between 18 and 50 years.
- (b) Provided written informed consent to participate in the study.
- (c) Not pregnant.
- (d) ASA physical status of 1 or 2.
- (e) 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:

- (a) Limited decision-making capacity and/or lacking the ability to consent.
- (b) Non-English speaker.
- (c) History of allergic/hypersensitivity reaction to benzodiazepines, fospropofol, fentanyl, or local anesthetic.
- (d) Pregnant and/or breastfeeding.
- (e) Violation of the 8-hour fasting policy.
- (f) Involvement with a clinical trial of an investigational drug within 30 days of enrollment into this study.
- (g) Anticipated difficult intubation according to the judgment of the dentist anesthesiologist.

Statistical Analysis

The sample population was assigned to either the fospropofol or the midazolam treatment group in a 1 : 1

Table 2. Age and Gender Distribution

	Male	Female
Fospropofol		
Frequency	13	19
Percent of total	22.0	32.2
Percent of drug	40.6	59.4
Percent of gender	65	48.7
Midazolam		
Frequency	7	20
Percent of total	11.8	33.9
Percent of drug	25.9	74.1
Percent of gender	35	51.3

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 2 time periods, repeated measures analysis of variance (ANOVA) was employed. All binary dependent variables were analyzed using the Fisher exact test with relative frequencies and percentages described. Ninety-five percent confidence intervals were reported for all applicable

Figure 1. Duration of surgery.

Figure 2. Supplemental doses to induce.

endpoints. The data gathered from this research was catalogued and stored on an Excel spreadsheet and analyzed statistically by the SAS program.

RESULTS

A total of 61 patients were enrolled in the study. The data from 2 subjects were discarded because they were inappropriately enrolled in the study and did not meet inclusion criteria due to age (51 and 55 years 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. ****s. The survey data were analyzed using only the results of the returned surveys. Gender and age of the study population found no significant differences between the 2 groups. Both groups showed a greater percentage of female to male participants, 59% for fospropofol and 74% for midazolam (Table 2).

Figure 3. Onset to sedation.

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 ($P = .342$). There were 7 cases that went beyond the target duration of 40–60 minutes, with the longest duration at 124 minutes (Figure 1).

The number of supplemental doses required to reach an adequate level of sedation was similar for both groups, and subsequently, the time to onset of sedation was similar as well. Time to onset was calculated using $4 + (4 \times \text{the number of supplemental doses})$ 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 ($P = .101$). The mean onset of sedation was 11.9 minutes for fospropofol and 14.4 minutes for midazolam (Figures 2 and 3). The slightly longer onset was not statistically significant ($P = .101$). 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 the midazolam group mean of 0.41 ($P = .13$) (Figure 4).

Figure 4. Supplemental doses after 30 minutes.

Figure 5. Time to cognitive recovery.

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 ($P = .123$) (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 ($P = .007$) (Figure 6).

Surgeon satisfaction scores based on the VAS were similar for both drug groups, with the mean for fospropofol at 85.0 and the mean for midazolam at 78.8 ($P = .336$). Surgeon willingness to repeat the sedation was comparable; 93.8% of the fospropofol group and 81.5% of the midazolam group indicated they would repeat the sedation ($P = .229$) (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 5 patients—1 in the fospropofol group and 4 in the midazolam group ($P = .167$).

Analysis of patient satisfaction scores based on the VAS found no difference between the fospropofol and midazolam groups. An interaction was found in the responses between time of discharge and 1 day postoperatively for the 2 study groups. This shows that the mean of the change in patient satisfaction from discharge to day 1 is different for the 2 drugs ($P = .050$). Satisfaction levels rose on postoperative day 1 in the midazolam group, but fell in the fospropofol group (Figure 8). Willingness to repeat at the time of discharge was high in both groups. Only 1 participant in the study was unwilling to repeat the sedation; this participant was in the fospropofol group. When asked on postoperative day 1, this same participant noted, however, willingness to repeat the sedation.

Regarding the evaluation of cardiopulmonary stability and incidence of adverse effects, we found a difference in only 2 main areas—greater incidence of perineal discomfort in the fospropofol group and the greater incidence of tachycardia in the midazolam group (Table 3). The data in these categories were analyzed using

Figure 6. Time to physical recovery.

Fisher exact test, and all had values of $P > .05$ except for the 2 categories mentioned. The fospropofol group had a reported incidence of 40.6% and an average duration of 37 seconds (45–180 seconds). Perineal discomfort was characterized as moderate to severe burning, itching, and/or general discomfort of the perianal and perineal region. Others reported the discomfort located in the legs, buttocks, and abdomen. This was observed immediately after and within 5 minutes of initial administration of fospropofol, but was not observed during supplemental boluses. The midazolam group showed an incidence of tachycardia of 48.2% compared to 9.4% ($P = .017$). Other parameters of cardiovascular stability including hypertension, hypotension, bradycardia, and either blood pressure or heart rate intervention were comparable. Respiratory stability was also comparable between the 2 groups with respect to 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 was 11.1% in the midazolam group.

Recall was evaluated using 3 separate tests, examining overall rates of recall throughout the entire process in

Figure 7. Surgeon satisfaction.

Figure 8. Patient satisfaction over 2 days.

Table 3. Adverse Effects

	Fospropofol	Midazolam
Hypertension	5 (15.6%)	4 (14.8%)
Hypotension	1 (3.1%)	2 (7.4%)
Blood pressure intervention	0 (0%)	1 (3.7%)
Bradycardia	2 (6.3%)	2 (7.4%)
Tachycardia*	3 (9.4%)	13 (48.2%)
Heart rate intervention	0 (0%)	2 (7.4%)
Hypoxemia	2 (6.3%)	3 (11.1%)
Airway assistance	0 (0%)	3 (11.1%)
Perineal discomfort**	13 (40.6%)	0 (0%)

* Significant difference with $P = .017$.

** Significant difference with $P < .001$.

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%, and in the midazolam group it was 100% (exact $P = .265$) (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

Figure 9. Incidence of procedural recall. **Figure 10.** Incidence of procedural recall.

significant interaction between the 2 days. On postoperative day 1, the number of patients who reported recall decreased in the midazolam group but increased in the fospropofol group ($P = .021$) (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 $P = .247$). 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 (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 $P = .004$). There was a significant difference found in responses taken on postoperative day 1 ($P = .019$) because there were fewer patients with local recall in the fospropofol group (Figure 12). Complete summary of results and tables can be found in Appendix B.

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

Figure 11. Image recall over 2 days.

being performed in dentistry.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, when administered by a dentist anesthesiologist, appears to confer some advantages over the traditionally used benzodiazepine, most notably producing a somewhat faster recovery time. However, there are also some adverse effects and shortcomings that are not as prominent with midazolam: perineal discomfort and potentially less reliable amnestic qualities. There are differences that exist between any 2 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 when the amnestic qualities are better, the sedative agent is deemed better. Midazolam has long been heralded for its reliable amnestic properties,¹³ and in this study, we focused on determining the amnestic qualities of fospropofol when compared to midazolam.

Midazolam appears to provide slightly more reliable amnesia than fospropofol at the doses administered. Upon discharge, there are fewer patients who recall the

Figure 12. Local recall over 2 days.

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 $P = .006$). Although there is no statistical difference in the amount of procedural recall between the 2 drug groups, the combined data from amnestic evaluation results still favor midazolam. Postoperative day 1 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 1 results regarding local recall, fewer patients in the fospropofol group had recall, but there was no difference found in the midazolam group (between the 2 days). Postoperative day 1 results for image recall showed no interaction between the 2 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, “Do you remember anything unpleasant from the surgery” was posed. 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 and specific portions of the surgery such as “extraction on the right side, the sound of the drill, some pressure.” 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.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 a drug that may occur after adequate sedation has been achieved according to (MOAA/S) evaluation scores and may correlate better with plasma levels of propofol. Separate protocols for each drug may produce more accurate results because 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 who experienced recall still indicated they would repeat the sedation, suggesting that these experiences were acceptable. A more sophisticated study would be to bring the same patient back for 2 procedures (one with midazolam and one with fospropofol) for 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, they having nothing to draw upon for reference. Thus, 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 2 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 perineal discomfort, characterized by perianal or perineal itching or burning. The frequency of the discomfort was similar to other studies of fospropofol. Perineal discomfort was consistently the most commonly reported side effect, with a rate of occurrence between 49 and 74%.⁶ In our study, this discomfort was recorded only when indicated in the survey when the patient was prompted by the question, “Do you remember anything unpleasant from the surgery.” This indicates that the patient experiences perineal discomfort before amnestic qualities are achieved and that the actual incidence of this discomfort 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 5 minutes of fospropofol administration. Future studies may look to examine and define a set of parameters to better evaluate this phenomenon.

Perineal discomfort in the form of perianal itching or altered sensation is a known side effect of another commonly used IV medication, dexamethasone, used for its anti-inflammatory and antiemetic properties.¹⁵ 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 play a role in mediating this effect.⁶ 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 drug combinations at the administered doses appear to be safe to use as a moderate sedation agent by dentists trained in the administration of deep sedation and general anesthesia. Whether this also holds true for dentists trained to a level for providing moderate sedation would require further investigation. Fospropofol confers an advantage in terms of cardiovascular stability as evaluated by the incidence of hypertension and tachycardia. Although these 2 parameters were higher in the midazolam group, 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 2 groups. Higher incidences of tachycardia and hypertension have been reported previously with the administration of midazolam.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 (eg, critically ill patients, patients with cardiovascular disease), 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 2 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 to 12% has been reported, and most cases involved patients more than 75 years of age and those undergoing bronchoscopy (compared to colonoscopy, which inherently has a lower chance of airway complications).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 oversedation indicates that fospropofol may be at least as safe as midazolam when used for moderate sedation at these doses. This certainly appears to be an improvement over propofol, which, although successfully used for moderate sedation, does not have a wide enough margin of safety to be recommended for providers trained to administer sedatives only to the level of moderate sedation.

Mean times to onset of sedation were generally greater than the previously reported times to onset. The 4 to 8 minutes to onset is reported in the Lusedra drug insert.⁴ This could be a reflection of our protocol design, as both drugs exhibited higher than usual times to onset. Nonetheless, the fospropofol did not seem to confer an advantage in this regard because there was no significant difference found between the 2 drug groups. The average supplemental doses to induce was two or more in the groups, suggesting that higher initial doses may be appropriate. The safety of titration can never be overstressed, but this is 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 due in part to the quality of the sedation changing with the initiation of surgical stimula-

tion. 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 2 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 vs 18.4 minutes), but there was no difference found in the cognitive recovery time (7.5 minutes vs 8.8 minutes). Cognitively, patients were required to exhibit a return to baseline responsiveness on 3 consecutive tests given 2 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 5 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 (Eisai Corp, Woodcliff Lake, NJ) 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 due in part to the known muscle relaxant properties of midazolam, which is not a feature of propofol or fospropofol.¹⁷ 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 greater than 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 less than 4 up until the end of the procedure. This is especially true for procedures that have little stimulation toward 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 fospopofol cases, perineal discomfort played a central role in the loss of cooperation as the patients were unable to control the urge to resolve the discomfort 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.^{18,19} 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, 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 2 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 because 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 2 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 be true only if the patients had the same procedure done without sedation. It may not hold true at all because 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 fospopofol 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 fospopofol 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 independent, blinded anesthesia personnel would be useful in measuring the overall quality of the sedation for the surgeon, patient, and dentist 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. A younger age group usually indicates a less medically compromised and healthier population that takes fewer medications and has 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 because the number of female participants was greater.

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 at these doses with fentanyl according to the manufacturer's guidelines. However, the high incidence of perineal discomfort, lack of reversal agent, and less reliable amnesia with fospropofol may temper the urge for the wholesale replacement of midazolam.

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APPENDIX A. Study Survey

Patient #: _____

Date: _____

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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APPENDIX B. Data Tables

Age Distribution of Study Population

	Mean Age, y	Minimum to Maximum, y	Standard Deviation, y	95% Confidence Interval, y
Fospropofol	26.9	16–49	7.84	24.1–29.7
Midazolam	24.9	16–49	7.41	22.0–27.9

Significant difference with $P = .015$.

Supplemental Doses to Induce

	<i>Fospropofol</i>	<i>Midazolam</i>
Supplemental doses (no.)		
Mean	1.97	2.6
Minimum to maximum	0–6	0–6
Standard deviation	1.51	1.52
95% Confidence intervals	1.42–2.51	2.03–3.23
Supplemental doses after 30 minutes		
Mean	0.81	0.41
Minimum to maximum	0–4	0–3
Standard deviation	1.15	0.80
95% Confidence intervals	0.399–1.227	0.092–0.723

Time to Recovery

	<i>Fospropofol</i>	<i>Midazolam</i>
Time to physical recovery,* min		
Mean	11.6	18.4
Minimum to maximum	5–29	5–40
Standard deviation	7.03	10.51
95% Confidence intervals	9.09–14.16	14.25–22.57
Time to cognitive recovery, min		
Mean	7.5	8.8
Minimum to maximum	6–17	6–20
Standard deviation	2.79	3.66
95% Confidence intervals	6.49–8.51	7.37–10.26

* Significant difference with $P = .007$.

Duration of Surgery

	Mean Duration of Surgery, min	Minimum to Maximum, min	Standard Deviation, min	95% Confidence Interval, min
Fospropofol	41.0	6–124	22.9	32.7–49.3
Midazolam	35.5	10–91	20.9	27.2–43.8

Time to Onset

	Mean Time to Onset, min	Minimum to Maximum, min	Standard Deviation, min	95% Confidence Intervals, min
Fospropofol	4.70	4–6	0.949	4.02–5.38
Midazolam	5.80	4–12	2.86	3.75–7.85

Patient and Surgeon Satisfaction Scores

	<i>Fospropofol</i>	<i>Midazolam</i>
Patient satisfaction at discharge, mm		
Mean	93.2	84.7
Minimum to maximum		
Standard deviation	13.3	20.8
95% Confidence intervals	88.4–98.0	76.4–92.9
Patient satisfaction at postoperative day 1, mm*		
Mean	88.2	90.2
Minimum to maximum		
Standard deviation	10.9	12.0
95% Confidence intervals	83.6–92.8	85.1–95.3
Surgeon satisfaction, mm		
Mean	85.0	78.8
Minimum to maximum	22–100	9–100
Standard deviation	20.8	27.9
95% Confidence intervals	77.5–92.5	67.8–89.9

* Significant difference with $P = 0.50$.