Dexmedetomidine, Ketamine, and Midazolam for Oral Rehabilitation: A Case Report

Bill W. S. Kim, DMD, MSc,* and Robert M. Peskin, DDS†

*Chief Resident, Dental Anesthesiology Residency Program, and †Director, Dental Anesthesiology Residency Program and Attending, Departments of Anesthesiology and Dental Medicine, Wyckoff Heights Medical Center, Brooklyn, New York

Intravenous sedation is frequently provided by anesthesiologists for phobic patients undergoing elective dental treatment in outpatient settings. Propofol is one of the most commonly used anesthetic agents that can result in apnea and respiratory depression, thereby posing potential difficulties with perioperative airway management. Dexmedetomidine has been utilized successfully in intravenous sedation for a wide variety of procedures and holds potential as an alternative to propofol in outpatient dental settings. However, as a single agent, it may not provide adequate depth of sedation and analgesia for oral rehabilitation. In this case report we demonstrate an effective alternative intravenous deep-sedation technique for an adult phobic patient undergoing oral rehabilitation utilizing 3 agents in combination: dexmedetomidine, ketamine, and midazolam. This combination of agents may be especially useful for those patients with a history of substance abuse, where administration of opioids may be undesirable or contraindicated.

Key Words: Ketamine; Midazolam; Intravenous deep sedation; Outpatient anesthesia; Dentistry.

Dexmedetomidine is a selective alpha-2 receptor agonist that has been demonstrated to have sedative, analgesic, and anxiolytic effects when administered intravenously.[1,2] Its specificity is known to be 8 times greater for the alpha-2 receptor than that of clonidine, and its elimination half-life is 2 hours compared to 8 hours for clonidine.[1] Its mechanism of action has been described to involve the hyperpolarization of noradrenergic neurons in the locus ceruleus, resulting in inhibitory action on the release of both norepinephrine and histamine, leading to a hypnotic state that is similar to that observed in normal sleep.[3,4] Unlike opioids, benzodiazepines, and propofol, dexmedetomidine has been shown not to depress respiration.[2,5] Dexmedetomidine has also been associated with reduced overall requirement for opioids, benzodiazepines, and propofol during intravenous sedation.[5] In addition, dexmedetomidine has been shown to potentiate opioids and reduce postoperative shivering.[6,7]

Dexmedetomidine was initially recognized as an effective sedative in the intensive care unit for intubated patients. Since then its clinical application has expanded to include neurosurgery, pediatric procedural sedation, awake fiber-optic intubation, cardiac surgery, bariatric surgery, and dental procedures.[5,8–14] Its use as a single agent during dental procedures under intravenous sedation has been reported in several studies. Dexmedetomidine has been shown to be comparable to or better than midazolam as a single agent in third-molar extractions[15,16]; however, it does not produce consistent amnestic effects.[16] More recently, a case report described the use of intravenous dexmedetomidine and ketamine for dental extraction in children with cyanotic heart disease with positive results.[17]

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Address correspondence to Dr Robert M. Peskin, Director, Dental Anesthesiology Residency Program and Attending, Departments of Anesthesiology and Dental Medicine, Wyckoff Heights Medical Center, 601 Franklin Avenue, Garden City, New York 11530; rmpeskin@cs.com.

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Both midazolam and ketamine are intravenous sedative agents used most commonly in combination with other drugs for dental procedures. Midazolam is a good anxiolytic, amnestic agent but is known to pose difficulties to the operator for longer and more complex dental procedures when used alone.[18] It also poses the risk of respiratory depression at high doses and has minimal analgesic effects,[19,20] limiting its utility as a single agent for longer, more extensive dental procedures. Ketamine is a widely used dissociative anesthetic with analgesic, amnestic, and bronchodilatory effects.[21,22] However, its cardiostimulatory effects and unfavorable side effects including hypersalivation, emergence delirium, and postoperative agitation[21,23] present limitations to its use as a single intravenous agent for dental procedures. Although midazolam may attenuate the emergence delirium and postoperative agitation produced by ketamine,[19] it has not been shown to predictably antagonize the central sympathetic stimulation that causes tachycardia and hypertension.

Combining the beneficial effects of midazolam, ketamine, and dexmedetomidine may be effective during open-airway intravenous deep sedation for relatively longer, more extensive dental procedures in outpatient dental settings. The use of the 3 agents in combination may reduce the total dose of each individual agent required as well as their negative side effects. This combination may also be beneficial for patients with a history of opioid abuse in which administration of opioids may be undesirable or contraindicated. We describe an intravenous sedation technique with dexmedetomidine, ketamine, and midazolam in combination for an adult phobic patient with a history of oxycodone abuse who underwent an elective oral rehabilitation in our outpatient dental clinic.

CASE REPORT

A 39-year-old female presented to the outpatient dental clinic requesting sedation for her dental treatment. The treatment plan included multiple restorations and extractions in all 4 quadrants, for which the treatment time was estimated to be approximately 2 hours. Her past medical history included generalized anxiety disorder, oxycodone abuse, and gastroesophageal reflux disease. She also reported having smoked 5–6 cigarettes per day for 15 years, and she had a history of gastric bypass surgery and intravenous sedation for dental treatment as well as for routine colonoscopy with no known complications. Her current medications included sertraline daily and omeprazole as needed. The patient reported no known drug allergies. Her height was 165.1 cm and her weight was 70.3 kg. Physical examination, including cardiovascular and respiratory, was unremarkable. Extraoral examination was within normal limits including a normal range of motion with mouth opening and lateral movements. Intraoral examination revealed multiple deep carious teeth both posteriorly and anteriorly and poor oral hygiene. Her airway was assessed to be class I on the Mallampati scale and her ASA status was determined to be II.

Schedule of Drug Administration*

Time Point (min)	*Dexmedetomidine (mcg)*	*Ketamine (mg)*	*Midazolam (mg)*
0	20		2
5	20		
8		10	
9		10	
18	20	10	
19		10	
25	10	10	
30	10	10	
90	10	10	2
Total dose	90	70	4

* Time point 0 refers to the time at which administration of intravenous agent was initiated.

On the day of her appointment, the patient met the preoperative fasting requirement (>8 hours) and was medically cleared, and all preoperative laboratory test results, including electrocardiograph, were within normal limits. Her same-day urine pregnancy test was negative. She appeared highly anxious but was reassurable. Once she was seated in the chair, a nasal cannula was secured and 100% oxygen was started at 3 L/min. Monitors included a pulse oximeter, 3-lead electrocardiograph, noninvasive blood pressure (BP), sidestream capnography, and skin temperature (T). Her initial vital signs were as follows: BP 145/92 mm Hg, heart rate (HR) 95 bpm, T 37°C, and peripheral capillary oxygen saturation (SpO_2) 100%. A 22-gauge intravenous catheter was placed with ease in the left antecubital fossa after the skin surface was prepared with ethyl chloride spray and intradermal lidocaine (0.5 mL of 0.5% lidocaine without epinephrine) and an infusion of 0.9% sodium chloride solution was established. Midazolam (2 mg) was administered, immediately followed by dexmedetomidine (20 mcg). Vital signs were recorded every 5 minutes. At the first 5-minute point, her vital signs were as follows: BP 140/84 mm Hg, HR 80 bpm, T 37°C, and SpO_2 100%. Another bolus of dexmedetomidine (20 mcg) was then administered and monitoring of the patient continued. Approximately 8 minutes after the first dose of dexmedetomidine the patient started to appear calm and her HR began to decrease (70–80 bpm). An additional bolus of 20 mg ketamine (10 mg/min for 2 minutes) was administered at this point and the vital signs

were recorded at the next 5-minute point as follows: BP 154/90 mm Hg, HR 70 bpm, T 37°C, and SpO_2 100%. Within these 10 minutes, no changes were seen with respect to respiration as the end-tidal CO_2 tracing remained regular in rate and magnitude. The patient continued exchanging spontaneously with the assistance of a slight upward chin tilt. Subsequently no further assistance was necessary. The patient was still responsive to commands, but her eyes began to close at approximately the 13-minute point. Her HR decreased further to 65 bpm and remained steady. Approximately 15 minutes from the beginning of the sedation, the vital signs were as follows: BP 154/85 mm Hg, HR 65 bpm, T 37°C, and SpO_2 100%. At this point a bite block was placed to maintain mouth opening, and a throat pack was placed in the posterior pharynx, which the patient tolerated well. There were no changes in vital signs during this process, and spontaneous ventilation was maintained at all times without signs of obstruction. At around the 18-minute time point, an additional bolus of dexmedetomidine (20 mcg) and 20 mg ketamine (10 mg/min for 2 minutes) were administered. At around the 20-minute point, local anesthetics were injected in all 4 quadrants of the mouth by infiltration (7.2 mL 2% lidocaine with 1:100,000 epinephrine). The vital signs remained steady, and spontaneous ventilation was maintained with no changes occurring clinically to suggest the need for additional dosing at this point. All restorative procedures were completed with a rubber dam. An additional 10 mcg of dexmedetomidine and 10 mg ketamine were administered at both the 25- and 30-minute time points. Her vital signs at the 25-minute time point were as follows: BP 105/62 mm Hg, HR 63 bpm, T 37°C, and SpO_2 100%. The vital signs remained steady for the remainder of the procedure. No additional drugs were administered for the next 65 minutes, during which time all of the restorative treatment was completed. At approximately the 90-minute point, 5 minutes prior to beginning the extractions, an additional 10 mcg dexmedetomidine, 10 mg ketamine, and 2 mg midazolam were administered. The vital signs remained steady, and the extractions of teeth 14 and 21 were completed without complication. The patient first opened her eyes at approximately the 100-minute point. She remained responsive to commands but opened her eyes only intermittently. An analgesic dose of ketorolac (30 mg) was administered for management of postoperative pain. The procedure end time was approximately 120 minutes after the start of drug administration. The patient remained calm until discharge, which took place approximately 20–25 minutes after the completion of the procedure. She was fully awake and ambulatory at the time of discharge, at which time she was accompanied by a family member. No complications (ie, nausea, vomiting, shivering) were observed in the immediate postoperative period. The only remark the patient made prior to leaving the clinic was that she had a dry mouth. The patient came back the next day for postoperative follow-up and complained of mild soreness and swelling associated with the extraction sites but stated that she was very satisfied with the sedation and did not recall any part of the procedure.

In summary, the total doses of dexmedetomidine, ketamine, and midazolam used for this 2-hour oral rehabilitation (excluding preoperative preparation and recovery times) involving multiple restorations and extractions were 90 mcg, 70 mg, and 4 mg, respectively. The schedule and dosing of the 3 agents are summarized in the Table.

DISCUSSION

Open-airway intravenous deep sedation is widely used in outpatient dental settings for both adult and pediatric oral rehabilitation. A variety of sedative agents, both singly or in combination, have been utilized, depending on the type and length of procedure and the medical profile of the patient. Propofol is the most commonly used anesthetic agent, with rapid onset of unconsciousness (40 seconds) and recovery.[19] It is also a potent respiratory depressant that can produce significant intraoperative apnea that must be recognized and corrected immediately with appropriate airway management, devices, and/or techniques. Propofol also obtunds the cough reflex, which may be beneficial to prevent laryngospasm. However, it may induce apnea and thereby put the patient at higher risk for aspiration should any leakage occur through the rubber dam or the throat pack during the dental procedure, where retention of the cough reflex would otherwise serve as a protective mechanism. Propofol also possesses negative cardiovascular effects, with significant reductions in BP without compensatory tachycardia at higher doses[19,24] that may be required to deepen the sedation should the infusion dose be inadequate. Because of its lack of analgesic effects, propofol is often combined with a short-acting opioid (ie, remifentanil, fentanyl), which may exacerbate an existing respiratory depression that can occur despite cautious titration. Cardiopulmonary stability may become especially challenging to control in open-airway deep-sedation cases, particularly for patients with a difficult airway (ie, obesity with sleep apnea) and for procedures involving the oral cavity, where maintenance of spontaneous ventilation is crucial while achieving an adequate depth of sedation and analgesia. Furthermore, minimizing or even eliminating the use of opioids is an important consideration for patients with a history of

opioid abuse. Therefore, an alternative intravenous deep-sedation technique utilizing multiple agents in combination and excluding propofol and opioids may help overcome these challenges and limitations.

The combination of dexmedetomidine, ketamine, and midazolam possesses many favorable qualities that could be beneficial during an open-airway intravenous sedation for routine dental procedures. Dexmedetomidine is known not to cause respiratory depression, and, when administered as a continuous infusion, it is associated with hemodynamic stability without severe hypotension or bradycardia.[1] It is interesting to note that for this 2-hour-long oral rehabilitation case, we did not administer the recommended loading dose within 10 minutes (1 mcg/kg), which would have been approximately 70 mcg for this patient. Rather, a total of 60 mcg dexmedetomidine was administered within the first 18 minutes of the procedure and the total dose for the entire 2-hour procedure was 90 mcg, divided into 5 smaller doses of 10–20 mcg at a time. The most probable explanation for this is the combined use of dexmedetomidine with ketamine and midazolam for a potential additive effect and allowing an adequate depth of sedation throughout the case. The patient did not react at all during the administration of the local anesthetics, which is usually the most stimulating part of the procedure, most likely owing to the analgesic effects of both dexmedetomidine and ketamine. Achieving good analgesia and sedation under spontaneous ventilation without the use of opioids or propofol appears to be one of the main advantages of this technique. Also, there was no significant hypotension or bradycardia at any point during the procedure, most probably because of the opposite, cardiostimulatory effect of ketamine. This combination effect of ketamine and dexmedetomidine was previously demonstrated in pediatric patients undergoing cardiac catheterization, magnetic resonance imaging scan, upper gastrointestinal endoscopy, adult muscle biopsy, and other nondental procedures.[9,25–28]

The rationale for the addition of midazolam was 3-fold: (a) production of reliable amnestic effects, (b) relatively rapid onset of action compared to dexmedetomidine, and (c) attenuation of postoperative agitation and delirium associated with ketamine. Similar to midazolam, dexmedetomidine has been shown to be effective in preventing emergence phenomena.[29] The patient did not experience any postoperative psychogenic effects, most probably because of the combined use of dexmedetomidine and midazolam and also because of the relatively low total dose of ketamine utilized (60 mg). In addition to the analgesic and sedative effects, the bronchodilatory effect of ketamine may have benefited the patient, who maintained spontaneous ventilation devoid of laryngospasm throughout the case and reported a very satisfactory level of deep sedation for the entire procedure. Hypersalivation, oftentimes associated with ketamine, was not a concern at all for the patient, as she reported having a dry mouth. This is most likely due to the relatively low total dose of ketamine used and possibly the opposite effect (dry mouth) reported with dexmedetomidine.[30] The bronchodilatory and antisialagogue effects are both side effects that could be utilized to the anesthetist's advantage during dental cases under open-airway deep sedation, where a dry field and smooth unobstructed spontaneous ventilation are crucial to success.

Another benefit from dexmedetomidine deep sedation may be its control of postoperative shivering. Similar to clonidine, dexmedetomidine has been shown to reduce postoperative shivering in patients undergoing general anesthesia.[6] Postoperative shivering is one of the most commonly encountered complaints by anesthesiologists, with few alternatives for its management or prevention aside from continuous intraoperative warming. Therefore, dexmedetomidine may be an option for future sedation in patients known to experience excessive postoperative shivering.

Intravenous dexmedetomidine has previously been reported to be useful during dental procedures. It has been shown to be comparable to or better than midazolam in patients undergoing third-molar surgery under local anesthesia.[15,16] It has been a recommended intravenous sedative agent in dental procedures, especially for those patients with high risk for respiratory depression and airway obstruction.[5] Recently, cases combining dexmedetomidine and ketamine for dental extraction in children with cyanotic heart disease were reported. All reports and studies on the use of intravenous dexmedetomidine for dental procedures have involved continuous infusion of dexmedetomidine at variable doses and rates.[5,7,15–17] No study so far has reported the combination of low-dose dexmedetomidine titrated to effect together with ketamine (0.85 mg/kg total dose) and midazolam for an adult phobic patient undergoing oral rehabilitation (one of the most commonly encountered patient profiles in outpatient dental settings).

This 3-agent combination technique also holds promise as an alternative for those adult phobic dental patients with a history of opioid abuse. Our patient had a history of oxycodone abuse and therefore the use of opioids was not desirable. Here we demonstrated that a satisfactory level of sedation and analgesia could be achieved without administering opioids for an adult phobic patient with such a history undergoing multiple dental procedures. Further studies with a large population of patients with substance abuse history would be indicated to elucidate

the effectiveness of this technique for this cohort of patients.

Directions for other future studies include delineation of minimum effective and maximum doses for each of the 3 agents when used in combination; comparison with other common intravenous sedation agents such as propofol, fentanyl, and etomidate; and measurement of other outcomes such as patient satisfaction, operator satisfaction, postoperative shivering, and recovery/discharge times in a large patient population including those with anticipated difficult airway and substance abuse history.

CONCLUSION

Intravenous deep sedation may be effectively administered for patients undergoing oral rehabilitation in an outpatient setting by utilization of 3 agents: dexmedetomidine, ketamine, and midazolam. In combining relatively low doses of the 3 agents, a good depth of deep sedation, analgesia, and cardiopulmonary stability may be achieved. This 3-agent combination may be recommended as an alternative to propofol and opioids for intravenous deep sedation during oral rehabilitation, especially for patients with a history of substance abuse.

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