A SYSTEMATIC REVIEW ON THE USE OF DEXMEDETOMIDINE AS A SOLE AGENT FOR INTRAVENOUS MODERATE SEDATION

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
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2011

Abstract

Intravenous administration of benzodiazepines can be used for anxiety management in dentistry. The recent approval of Dexmedetomidine in Canada provides an alternative to benzodiazepines for moderate sedation. There is no review comparing Dexmedetomidine and Midazolam as a sole agent for intravenous moderate sedation. This paper determines to fill the void of knowledge. A total of 6 articles out of 117 were identified in Pubmed and Ovid Medline using the key terms “Dexmedetomidine” and “sedation”. The parameters that were evaluated were the need for rescue, patient and surgeon satisfaction, and adverse outcomes. Dexmedetomidine was found to be equal or better than Midazolam in the first three parameters. Hypotension and bradycardia were evident in moderate to high doses, but none needing intervention. Other side effects include headache and dry mouth. Dexmedetomidine is a reasonable and safe alternative to Midazolam, but more research is needed to evaluate Dexmedetomidine for general dentistry.
Acknowledgments

First and foremost thanks be to my Lord and Saviour for the leading me into specialty training and for providing the strength, endurance, and support to pull it off! To my wife Anna I’d like to thank her for her loving, encouraging, supportive patience in the last three years. To Dr. Dan Haas, I’d like to thank him for his example of scholarly excellence and professionalism. I’d also like to thank the anesthesia staff at Toronto East General and the Hospital for Sick Children for their continued efforts to teach and support our program. As well to those in our field who have given up their time to supervise and teach us at the faculty.
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A Systematic Review on the Use of Dexmedetomidine as a Sole Agent for Intravenous Moderate Sedation

Introduction

Anxiety can lead to various psychosocial consequences for a patient. In particular, patients who have anxiety with regard to receiving dental treatment are also associated with higher degrees of depression and anti-social behaviors. They also avoid receiving necessary dental treatment, particularly when their disease can be treated conservatively; delaying treatment until more aggressive measures becomes their only option. Up to 68% of the general population request some form of pharmacologic source of anxiety management, depending on the type of treatment undertaken. There are various modes of pharmacologic management of anxiety. These include inhalational, oral, intramuscular, and intravenous. The most common drug for anxiety management in dentistry is nitrous oxide. This drug has a long history of use dating back to Horace Wells and his demonstration of general anesthesia using nitrous oxide for a dental extraction. Inhalational anesthesia with nitrous oxide has several advantages over other methods of drug administration. This includes a faster onset and offset of action, it is easily titratable, and it is relatively inexpensive. When nitrous oxide is inhaled it diffuses through the lung parenchyma and into the bloodstream. Since it is relatively insoluble in blood the partial pressure of nitrous oxide increases rapidly and elicits its effect quickly. There is very little metabolism by the body and is eliminated primarily by diffusion out of the lungs. This differs from oral administration of sedative agents which must wait for absorption through the digestive mucosa. It is then subjected to the first pass effect whereby liver enzymes metabolize...
and potentially render the drug ineffective. Therefore a significant degree of drug becomes inactivate before it is able to affect its target organ. One of the advantages of oral medication is that it is relatively easy to administer. Typical sedatives that can be administered orally include benzodiazepines. Benzodiazepines were once one of the most widely prescribed medications in the United States. At low doses they provide anxiolysis and increasing doses increase the degree of sedation as well as increase the probability of anterograde amnesia. These properties are good for patients requiring anxiety management for minor outpatient surgical procedures, like dentistry. Benzodiazepines also have a wide therapeutic index validating its safety in the outpatient setting. The disadvantages to oral benzodiazepines are that drug absorption is highly variable due to a high first pass effect and thus cannot be titrated to effect. Drug absorption also delays the time between administration and the peak effect of the drug. Some forms of benzodiazepines can be administered intravenously and thus do not depend on the absorption through the alimentary system and are more predictable allowing for titration of the medication to effect. Intravenous administration of medications requires access to the patients’ circulatory system and thus requires some training and skill of the operator. Yet it offers direct access to the circulatory system and so medications can be given accurately as well as with a fast onset of action and thus allows one to titrate medications. Intramuscular injections are also possible with some benzodiazepines and therefore do not require intravenous access. Absorption is delayed compared to the intravenous route and is not subjected to the first pass effect. It does necessitate the use of a needle, which is the source of some patient’s anxiety. Since the intravenous route of administration provides the
most predictable and direct method of administration of sedative medications it tends to be the route of choice.

Within Ontario, a permit can be obtained by dentists to provide a single sedative agent for administration intravenously. The permit is granted only when the practitioner has taken the necessary training and has demonstrated proficiency in providing the drug of choice for sedation. The typical medication used is Midazolam. Midazolam is a benzodiazepine that provides anxiolysis, sedation, and is known for creating anterograde amnesia. It is preferred to other intravenous benzodiazepines because of its relatively short elimination half-life. Other benzodiazepines like Diazepam are metabolized by the liver and produce multiple metabolites that also have sedative properties, thus prolonging its effects beyond the length of the procedure and even beyond discharge. Potentially patients may become re-sedated after discharge without a trained professional to monitor or provide assistance in case of an emergency. Therefore Diazepam is not typically used in an outpatient setting. Diazepam can cause pain and thrombophlebitis of the vein during injection. This is due to the organic solvents that are used to keep Diazepam in aqueous solution. The problem has been resolved by using a lipid emulsion with diazepam and carries the trade name of Diazemuls™.

Benzodiazepines enhance the inhibitory neurotransmitter system gamma aminobutyric acid (GABA). The GABA\textsubscript{A} receptor is a pentameric protein that forms a chloride selective ion channel. The protein contains a region called the benzodiazepine binding site. When a benzodiazepine binds to this region it exerts a positive allosteric effect by increasing the affinity of the protein to an open configuration when bound by GABA\textsuperscript{4}. Enhancing GABAergic
responses of specific GABA receptor subtypes within the brain may be responsible for the hypnotic and sedative effects of benzodiazepines. Flumazenil is a benzodiazepine antagonist that can be used as a rescue from oversedation with a benzodiazepine. Flumazenil is a competitive antagonist of the benzodiazepine binding site of the GABA_A receptor. Flumazenil is given intravenously and it is titrated to effect.

Regardless of the anesthetic drug of choice, the qualities of a good sedative or anesthetic agent include sedation, anxiolysis, analgesia, and amnesia. Sedation refers to the depression of the level of consciousness. The American Society of Anesthesiologist along with the American Dental Association has dichotomized anesthesia into 4 different levels – minimal, moderate, and deep sedation, and general anesthesia. Minimal sedation, also referred to as anxiolysis, describes a depressed level of consciousness, but allows a patient to respond appropriately to verbal commands and light tactile stimulation. They often seem relaxed, but are fully aware of their surroundings. They also maintain their protective airway reflexes, thus are able to swallow, cough, and breathe without assistance. During moderate sedation the level consciousness is further depressed and patients are less aware of their surroundings than during minimal sedation. Patients may require light tactile stimulation or repeated verbal commands to respond and also be able to maintain their protective airway reflexes and respiration. In deep sedation, patients cannot be easily aroused and may respond purposefully to repeated or painful stimulation. Their ability to protect their airway reflexes and maintain adequate spontaneous ventilation may be impaired. General anesthesia describes a loss of consciousness of the patient who is unable to respond to stimulation including high levels of pain. Their airway and respiratory functions typically require assistance and cardiovascular
functions may be impaired. Intravenous sedation falls under the guidelines for moderate sedation by Royal College of Dental Surgeons of Ontario (RCDSO)\(^6\). Analgesia is the absence of pain. Amnesia is the loss of memory. Anterograde amnesia describes the inability to recall newly formed memories after the point of drug administration, whereas retrograde amnesia refers to loss of previously acquired memories after drug administration.

In September 2010, Dexmedetomidine was approved for use within Canada even though its use for sedation has been reported for almost 20 years. According to Health Canada, Dexmedetomidine has two primary indications\(^7\). The first indication is for sedation of patients initially intubated or mechanically ventilated post-surgically in the intensive care setting. This use is beyond the scope of this review. The second indication is for sedation of non-intubated patients prior to and/or during surgical and other procedures by continuous infusion\(^7\). This includes monitored anesthetic care with the use of local anesthetics such as found in dentistry.

Dexmedetomidine is a unique anesthetic agent. Unlike most anesthetics that affect the GABA receptor, its mechanism of action is to activate the alpha-2 adrenergic receptor. The consequence is a reduction in noradrenergic neurotransmitter release and depression of adrenergic pathways. This occurs because the alpha-2 receptor is predominantly pre-synaptic and activates a member of the guanine nucleotide-binding protein (G-protein) coupled signaling system. Activation of alpha-2 receptors increases the inhibitory G-protein, G\(_i\), and reduces cyclic adenosine monophosphate (cAMP). The reduction in the second messenger cAMP results in sequestration of calcium ions and reduces the synapse from releasing stored neurotransmitters from its vesicles\(^8\). The alpha-2 receptor is not ubiquitous, but is found in certain areas within the brain. An area that is believed to provide the sedative effects of
Dexmedetomidine is known as the Locus Ceruleus. The Locus Ceruleus is located within the brain stem and it receives and transmits multiple innervations to and from many regions within the brain. The Locus Ceruleus has been shown to be involved in circadian wake and sleep cycles as well as a centre for management of stress responses. During wakefulness, the locus ceruleus has a high adrenergic output which decreases during deeper levels of sleep. Therefore, the action of Dexmedetomidine is unique in that it produces sedation in a manner similar to natural sleep. Stress also increases adrenergic outflow within the locus ceruleus.

The pathways for stress response are not clearly understood. There are two mechanisms by which Dexmedetomidine produces analgesia involving activation of presynaptic alpha 2 receptors in the spinal cord. One is by direct activation of the descending inhibitory pain pathway, the other is by inhibiting the release of substance P.

Alpha-2 receptor agonists were originally used to treat hypertension. Clonidine, one of the first alpha-2 receptor agonists developed, was initially used as an anti-hypertensive medication. Patients using Clonidine reported feeling tired and lethargic. It was soon realized that its effect on the alpha-2 receptor also produced sedation. The cardiovascular response appears to be due to the sympatholytic action of alpha-2 agonists. Reduction in sympathetic tone creates an environment where the vagal tone is unopposed. Hypotension and bradycardia can result, but also other vagal-mediated actions can occur. Increase in gastric motility and a decrease in insulin secretion along with reduction in vasopressin and renin secretions from the kidney have been reported in animal studies. The effect on humans appears to be minimal. Cholinergic prejunctional alpha-2 receptors can produce an anticholinergic effect in the bowel as well as in salivary glands. This leads to reduced water secretions into the bowel as well as reducing
salivary secretions, respectively. A paradoxical reaction that can occur during the initial administration of Dexmedetomidine is a transient hypertensive response. This response is mediated by peripheral alpha-2b/c receptors found in the arterial and venous vasculature. These alpha-2b/c receptors are post-junctional and they promote vasoconstriction when activated\textsuperscript{12}. It has also been proposed that these effects may be due to activation of peripheral alpha-1 receptors since Dexmedetomidine has some affinity for that receptor (1620:1 of alpha 2:alpha1)\textsuperscript{13}.

Within Ontario, benzodiazepines have traditionally been the drug of choice as the sole agent for intravenous conscious sedation by dentists. With the recent introduction of Dexmedetomidine into the Canadian market dentists within Ontario may want to employ the use of this drug since it has a different mechanism of action compared with benzodiazepines, it makes it a potential alternative for moderate sedation as a one drug technique. Currently there lacks a cohesive review of the appropriateness of Dexmedetomid as a sole intravenous agent by dentists. Therefore, the goal of this paper is to review the literature on Dexmedetomid as a sole anesthetic agent and evaluate its efficacy, safety, and practicality as compared with benzodiazepines for the general dentist.

**Methods**

The aim of this study is to examine the efficacy and safety of Dexmedetomidine as a sole agent for intravenous moderate sedation as it compares with a single benzodiazepine. To achieve this goal, a systematic review of all peer reviewed literature that compared the use of Dexmedetomidine as a sole sedative agent with a benzodiazepine was performed. Pubmed and
Ovid/Medline were chosen for literature search engines. These search engines allow input for certain inclusion criteria. The inclusion and exclusion criteria were based on what would be potentially useful for dentists wanting to utilize Dexmedetomidine as a sole agent for moderate sedation. The inclusion criteria include all of the following:

- Randomized control trials and clinical trials
- Dexmedetomidine used as a sole anesthetic agent
- Dexmedetomidine should be compared with a benzodiazepine as a sole anesthetic agent.
- American Society of Anesthesiologist’s physical classification of III or less
- Human adult patient population age 18 years and greater
- Administered as an intravenous medication
- Published in the English language

Using the clinical search tool, the key words “Dexmedetomidine” + “sedation” were used.

Using the automated filter program integrated within each search engine, the following criteria were selected: “clinical trials”, “random controlled trials”, “human” studies, articles published in the “English language”, and in “persons 18 years and older”. The list of articles was reviewed at the title, abstract, and article levels and eliminated or included based on the inclusion and exclusion criteria. The exclusion criteria remaining are:

- pediatric population,
- used a second anesthetic agent along with Dexmedetomidine in protocol, and was not the rescue,
• ASA IV and above,
• routes of administration other than intravenous,
• Dexmedetomidine was used only as a premedication prior to the administration of a second anesthetic drug,
• Dexmedetomidine was compared with a general anesthesia or Propofol anesthesia.

Since Dexmedetomidine is also used in the intensive care setting key words, such as “critically ill”, “intensive care”, or “mechanical ventilation” were used to eliminate articles at the title level since they implied ASA IV or greater and not used for moderate sedation. Articles that were unclear as to the intent of the study at the title level were also reviewed at the abstract level. Abstracts were reviewed and eliminated based on the above exclusion criteria. Abstracts that were not complete or did not meet the exclusion criteria were kept for review at the article level. At the article level, each paper was reviewed in depth for exclusion.

In order to evaluate the quality of sedation as compared with a benzodiazepine three outcomes were evaluated. The three outcomes evaluated for quality are: Need for rescue or need for additional anesthetic administration to complete the procedure, patient’s satisfaction, and surgeon’s satisfaction of the sedation. Safety was evaluated by reporting the incidence of complications during and after the administration of the drug. The complications were categorized into three main categories, cardiovascular, respiratory, and others. Cardiovascular complications involved extreme changes in heart rate or blood pressure as reported by the authors. When possible, extremes were defined as a change of greater than 20 percent from baseline. Respiratory complications could involve apnea, hypoventilation, and obstruction that
resulted in significant desaturation as defined by the author. Where possible, we defined desaturation as, SpO$_2$ less than 90%. As well we looked for other respiratory complications including obstruction, loss of protective reflexes, and hyperventilation and tachypnea. All other complications were examined under the other category.

Statistics

Numerical data are reported as means ± standard deviation. Ordinal data are reported as median (Interquartile range). Where possible, the doses and infusion rates were standardized to mcg/kg or mg/kg and mcg/kg/hr, respectively, if reported differently by the authors. Statistical calculations were performed using Microsoft Excel 2003.

Articles were evaluated for internal and external validity based on questions provided by the Oxford Centre for Evidence Based Medicine. With respect to evaluating external validity, the applicability of each article was based on patients in the dental setting since this review is geared towards dentists. The level of evidence of each paper was also viewed with this goal in mind, so that the results provided could be gauged by the strength of evidence from each paper. The categories in the level of evidence provided by the Oxford Centre for Evidence Based Medicine were used as a guideline to assign a grade to each paper. The grading chart and the questionnaire for determining internal and external validity are listed at the end of the review as Appendix 1.
**Results**

**Literature Search**

The initial search of the term “Dexmedetomidine” yielded 323 clinical trials. After applying the other search parameters, “sedation” in human adult populations in the English language, in Pubmed and Ovid a total of 111 and 62 articles were found, respectively. The articles were cross-referenced between the two search engines and it was found that Ovid had 6 additional articles that were not included in the Pubmed search. A total of 6 out of 117 articles satisfied the inclusion/exclusion criteria from a search of “Dexmedetomidine” and “sedation” in Pubmed and Ovid/Medline. Table 1 summarizes the number of articles eliminated and the reason for elimination at various stages of review. Of the 117 articles, 76 were eliminated at the title level. These articles were eliminated because they indicated that they combined other anesthetic agents with either Dexmedetomidine or a benzodiazepine, the study was in critically ill patients, used within the setting of the intensive care unit or during mechanically ventilation, or the drugs were not used as an intravenous agent. The remaining articles (41) were evaluated at the abstract level. 29 articles were eliminated because they did not meet the inclusion criteria. The remaining 12 articles were reviewed thoroughly for their suitability within this review. Six additional articles were eliminated.

The article published by Makary et al\textsuperscript{14} in the Journal of Oral Maxillofacial Surgery describes the use of Dexmedetomidine for office based oral surgical procedures. Although their paper evaluated patient satisfaction, surgeon’s satisfaction, and hemodynamic parameters with the
use of Dexmedetomidine, their paper was a collection of case reports and did not compare their results with a benzodiazepine.

### Table 1. Summary of Reasons Articles were Eliminated

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number of Articles Eliminated</th>
<th>At Title Level</th>
<th>At Abstract</th>
<th>At Article</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA &gt; III</td>
<td></td>
<td>23</td>
<td>11</td>
<td>0</td>
<td>34</td>
</tr>
<tr>
<td>• Mechanical Ventilation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Intensive Care Unit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Critically Ill</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined Anesthetics</td>
<td>17</td>
<td>7</td>
<td>1</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>Age &lt; 18 years</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Not Compared to Benzodiazepine</td>
<td>23</td>
<td>0</td>
<td>5</td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>Non-Intravenous Route</td>
<td>10</td>
<td>4</td>
<td>0</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>No Intervention</td>
<td>2</td>
<td>7</td>
<td>0</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>76</strong></td>
<td><strong>29</strong></td>
<td><strong>6</strong></td>
<td><strong>111</strong></td>
<td></td>
</tr>
</tbody>
</table>

Several articles were eliminated because Dexmedetomidine was compared with a saline placebo. Both Erdurmas et al\textsuperscript{15} and Ayoglu et al\textsuperscript{16} used Dexmedetomidine for sedation during cataract surgery. Patients were subjected to either administration of Dexmedetomidine or saline during the procedure. Erdurmas et al used Propofol as a rescue whereas Ayoglu provided no rescue anesthetic. Unfortunately neither of them provided a comparison with a benzodiazepine and was therefore eliminated from the review. Two other articles also evaluated Dexmedetomidine with a saline placebo. Bergese SD et al\textsuperscript{17} and Candiotti KA et al\textsuperscript{18} both published large multicentre randomized control trials on the use of Dexmedetomidine.
These two articles were also cited by Health Canada as articles that were instrumental in its approval in Canada. Bergese SD et al used Dexmedetomidine for awake fibreoptic intubations and used Midazolam as its rescue. Although over 70% of patients required Midazolam and potentially could have provided some comparison, the data were not clear enough to distinguish patients who received Midazolam and those who did not. Candiotti KA et al looked at Dexmedetomidine for various surgical procedures and also used Midazolam as a rescue. Again, the data were not sufficient to separate those patients who received Midazolam and those who just had saline.

The last article to be eliminated at the article level was Aho et al. They published a comparison of Dexmedetomidine and Midazolam for the legal termination of pregnancies. Unfortunately, all subjects were given Alfentanly as an intravenous premedication prior to the administration of the anesthetic drug. Therefore, this article was eliminated.

Table 2 provides a summary of the articles used in the study. A total of 6 articles were included in the systematic review. Two were for dental extractions, another two for cataract surgeries, one for sedation for placement of a spinal anesthesia for transurethral resectioning of the prostate (TURP), and one for upper endoscopy. The two dental papers evaluated Dexmedetomidine for third molar extractions. Üstün et al designed a prospective, double-blind, crossover, randomized study that included 20 patients undergoing two separate third molar extraction appointments, one sedated with Dexmedetomidine (1 mcg/kg) and the other with Midazolam (0.1 mg/kg). Patients were chosen with bilateral symmetrically identical impacted third molars and were randomly assigned to receive either Dexmedetomidine or
Midazolam during their first appointment. In their article, the test drug was infused over 15 minutes at which time the infusion was stopped, the level of sedation was evaluated, local

**Table 2. Summary of Articles for Review**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Surgical Procedure</th>
<th>N</th>
<th>Dose</th>
<th>1° Outcome</th>
<th>2° Outcome</th>
<th>Level of Evidence *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Üstün Y, et al</td>
<td>Third Molar Surgery</td>
<td>20</td>
<td>4µg/kg/h inf (D) 0.4µg/kg/h (M)</td>
<td>Not stated</td>
<td>Patient Satisfaction Cooperation RSS Recovery Recall Vitals</td>
<td>2b</td>
</tr>
<tr>
<td>Cheung CW</td>
<td>Third Molar Surgery</td>
<td>60</td>
<td>1 µg/kg bolus (D) 5 mg (M)</td>
<td>Patient Satisfaction with numerical rating scale</td>
<td>Amnesia Vitals Surgeon’s satisfaction Pain Pain medication consumption</td>
<td>1b</td>
</tr>
<tr>
<td>Alhashemi JA</td>
<td>Cataract</td>
<td>44</td>
<td>1 µg/kg bolus (D) 0.4µg/kg/h inf. (D) 20 µg/kg (M)</td>
<td>Patient satisfaction using Likert-like scale</td>
<td># needing rescue Surgeon’s satisfaction Vitals Discharge times</td>
<td>2b</td>
</tr>
<tr>
<td>Apan A</td>
<td>Cataract</td>
<td>90</td>
<td>0.25 µg/kg/h (D) 25 µg/kg/h (M) Saline</td>
<td>Change in hemodynamics</td>
<td># needing rescue Verbal Rating Score for pain Vitals Patient satisfaction</td>
<td>2b</td>
</tr>
<tr>
<td>Kaya FN</td>
<td>Spinal for TURP</td>
<td>72</td>
<td>0.5 µg/kg (D) 0.05 mg/kg (M) Saline</td>
<td>Level of sensory blockage</td>
<td>RSS Surgeon and Patient Satisfaction Postoperative pain</td>
<td>2b</td>
</tr>
<tr>
<td>Demiraran Y</td>
<td>Upper Endoscopy</td>
<td>50</td>
<td>1µg/kg bolus (D) 0.2µg/kg/h inf (D) 0.07 mg/kg (M)</td>
<td>VAS for patient: Discomfort Gagging Anxiety Satisfaction VAS for Surgeon: Discomfort Gagging</td>
<td>Time to full recovery Adverse Outcomes</td>
<td>2b</td>
</tr>
</tbody>
</table>
anesthetic was administered, and surgery commenced. Following three weeks, the second operation was performed with the other drug not assigned in the first operation. Üstün measured patient satisfaction and overall pain during the procedure using a visual analog scale (VAS). They also looked at patient cooperation and subjectively compared patient’s personal opinion of which sedation appointment they had preferred. In terms of safety, they evaluated intraoperative vital signs including heart rate, systolic and diastolic blood pressures, and oxygen blood saturation. The methods did not indicate a formal list of complications that they were to observe, but rather reported complications as patients reported them. This article received a 2b level of evidence since they did not provide information on the demographics of the two groups. Therefore the internal validity of this paper is questionable. They also did not provide a primary outcome measure and sample size calculation.

Cheung et al21 also evaluated sedation between Dexmedetomidine and Midazolam for third molar surgery. A total of 60 patients were recruited, 30 received Dexmedetomidine (1 mcg/kg) and 30 received Midazolam (5mg). The drug was administered over 10 minutes by infusion until either the patient reached a specified level of sedation Ramsay Sedation Scale (RSS 4) or until the end of the 10 minute infusion. Their primary outcome was to evaluate patient satisfaction. In addition to evaluating patient satisfaction, they evaluated the surgeon’s satisfaction and subjective patient parameters such as feeling anxious, preference for type of sedation as well as the ability to recall certain events during the procedure. Patient satisfaction was rated using a numerical rating system from 0 to 10, with 10 being most satisfied. They also
reported the number of patients requiring additional Midazolam in order to complete the procedure. Vital signs as well as intraoperative and postoperative complications were recorded. This was a well designed study and received a 1b level of evidence. Their paper was both valid internally and externally.

Like dentistry, cataract surgery can be performed with or without sedation. The two articles for cataract surgery were reported by Alhashemi JA\textsuperscript{22} and Apan A et al\textsuperscript{23}. Alhashemi recruited 44 patients undergoing cataract surgery. They were randomized into two groups receiving either Dexmedetomidine (1 mcg/kg bolus plus 0.1 – 0.7 mcg/kg/hr continuous infusion) or Midazolam (0.25 mg/kg bolus infused over 10 minutes plus 0.5 mg bolus as needed). The primary outcome was patient satisfaction. An elaborate blinding scheme was developed to blind the surgeon and anesthetist from knowing the drug being administered. In brief, the initial bolus of medication was drawn into a 50 ml syringe that contained either Dexmedetomidine or saline. At the end of the bolus, those who received Dexmedetomidine received a 3 ml bolus of saline, while those in the Midazolam group received 0.2 mg/kg of Midazolam in the 3ml syringe. Infusion of Dexmedetomidine was given by a separate syringe and was mimicked by a saline syringe in the Midazolam group. Whenever the infusion was increased a separate bolus of either saline (in the Dexmedetomidine group) or 0.5 mg Midazolam was given to mask the source of the sedative effects. The changes in infusion or additional boluses of Midazolam were given until the RSS reached 3. Alhashemi used a Likert-like rating system, which is similar to a numerical rating system to rate patient satisfaction just prior to discharge (patients having Aldrete score of 10). They also evaluated the surgeons’ level of satisfaction using the same Likert-like scale. They evaluated adverse events such as bradycardia (heart rate < 60), hypotension (Mean
Arterial Pressure or MAP < 60 mmHg), respiratory depression (ventilation frequency ≤ 10), oxygen desaturation (SpO₂ < 92%) or unplanned hospital admission. The article by Alhashemi received a 2b level of evidence since it provided good internal validity. Since this article was not related to dentistry external validity was not high.

Apan A et al²³ also compared Dexmedetomidine and Midazolam for cataract surgery on 90 patients. They divided these patients to receive Dexmedetomidine infusion (0.25 mcg/kg/hr), Midazolam infusion (25 mcg/kg/hr), or control that received Midazolam bolus (7 mcg/kg). Their primary outcome was to measure changes in the hemodynamic and respiratory parameters between the two medications. Patient satisfaction was measured subjectively by evaluating comments made in follow-up. The most common complaint was dryness of the mouth in the Dexmedetomidine group and headache in 2 of each Dexmedetomidine and Midazolam group. Of interest 8 patients in the control group did not require sedation. Their paper received a 2b level of evidence for the same reasons as Alhashemi. In addition, the use of the Bispectral Index (BIS; see below) monitor to evaluate sedation is not universally accepted and the equipment is not ubiquitous in dental offices, therefore the external validity suffered.

Demiraran et al²⁴ published a randomized prospective study comparing Dexmedetomidine and Midazolam sedation for upper endoscopy in 50 patients. Their hypothesis was that Dexmedetomidine is safe and effective as other techniques for upper endoscopy. To this end they compared respiratory and hemodynamic parameters as well as the degree of retching and gagging during the procedure and patient and surgeon satisfaction. The respiratory and hemodynamics were measured every minute at the start of infusion of either 1 mcg/kg
Dexmedetomidine (followed by an infusion rate of 0.2 mcg/kg/hr) or 0.07 mg/kg (to a maximum of 5 mg) of Midazolam. The procedure was started after the patient had reached a RSS of 2. The article received a 2b level of evidence. Surgeons reporting on their satisfaction between the two anesthetics were not blinded to the test drug and therefore the internal validity was poor.

The last article included was by Kaya KN et al\textsuperscript{25}. The primary objective of this article was to evaluate the analgesic properties of Dexmedetomidine during spinal anesthesia for TURP. Seventy-five patients were selected to receive either Dexmedetomidine (0.5 mcg/kg), Midazolam (0.05mg/kg), or physiologic saline. They measured postoperative pain at 4, 8, 12, and 24 hours, time to first analgesic dose. They also evaluated the quality of sedation by having surgeons and anesthesiologist rate the quality of the anesthetic on a 3 point scale (1 = poor, 2 = moderate, 3 = poor). They also inquired the patient as to their preference of anesthetic if they were to have the same procedure done and to ask if the patient recalled the dural puncture for the spinal anesthetic. They also evaluated intraoperative vitals such as heart rate, blood press, respiratory rate, oxygen saturation, and end-tidal carbon dioxide levels. Complications such as nausea, vomiting, headache, bradycardia and hypotension were also evaluated. For the purposes of our study, we only examined the surgeon’s satisfaction, patient preference, and vital parameters and complications. A 2b level of evidence was given for this paper.

Out of the 6 articles a total of 336 patients were studied comparing Dexmedetomidine with Midazolam sedation for 4 different types of surgical procedures.

\textit{Standardization}
In order to determine how Dexmedetomidine sedation compares with Midazolam, three parameters were evaluated. The three parameters are the need for rescue, reported patient satisfaction, and surgeon satisfaction. The need for rescue was evaluated since it provides an indication that the anesthetic is not adequate for the stimulus of the procedure. Rescue is a function of the depth of sedation and by the invasiveness of the procedure. If the depth of sedation is inadequate or the stimulation is excessive, a rescue with deeper anesthesia may be necessary. As described earlier, anesthesia is a spectrum where minimal sedation has the least effect on arousal to general anesthesia where consciousness is abated along with some motor and sensory reflexes. With intravenous sedation, one is assuming a depth of moderate sedation. That is a patient experiences a depressed level of consciousness but is able to respond purposefully to verbal or light tactile stimulation. The depth of sedation can be determined by observation of various patient behaviours when they are sedated. Some of these observable behaviours can be used in a scale to objectively determine the level of sedation a person is experiencing. One such scale is the RSS. This scale is made up of six levels labeled from 1 to 6 and each level associated with an observable behaviour corresponding to the depth of sedation. Appendix 2 provides a table of the rating system for the RSS. A RSS score of 3 or 4 would correspond to moderate sedation. Another means of determining the depth of sedation is monitoring a patient’s encephalogram and using an algorithm to produce a value that corresponds to the depth of anesthesia. This monitor is called the Bispectral Index (BIS) monitor. All of the six articles used some measure to evaluate the depth of sedation created by either Dexmedetomidine or Midazolam. The most widely used in our group of six was the RSS. Cheung CW et al, Üstün Y et al, Kaya FN et al, and Alhashemi JA all used the RSS,
Apan A et al used a Bispectral Analysis, and Demirarn Y et al used a non-validated four-point somnolence scale.

The use of a particular scale allows one to determine the depth of sedation achieved in each study so that each study can be compared with each other. Table 2 outlines the type of sedation scale used and the corresponding dose of Dexmedetomidine and Midazolam used. Cheung CW et al titrated Dexmedetomidine and Midazolam until the RSS reached 4 or until the maximum dose was allowed, that is 1 mcg/kg Dexmedetomidine or 5 mg Midazolam. They found that all thirty patients in the Dexmedetomidine group were able to reach a RSS of 3 or 4 while only 28 patients in the Midazolam group were able to reach the same level. They had one patient with a response similar to a paradoxical reaction to Midazolam and another was fully awake but calm during the procedure (RSS = 2). The median dose of Dexmedetomidine was 0.88 mcg/kg and for Midazolam the median dose was 0.07 mg/kg. Üstün Y et al used a higher dose of Midazolam (0.1 mg/kg) but infused both Dexmedetomidine and Midazolam over a 15 minute period compared with the standard time of 10 minutes. They found no difference in the mean RSS between the groups (RSS = 2.90 ± 1.21 in the Midazolam group and RSS = 2.90 ± 1.19 in the Dexmedetomidine group). Kaya FN et al used a fixed dose of Dexmedetomidine (0.5 mcg/kg) and Midazolam (0.05 mg/kg). In the end, they found that the median RSS scores were lower in the Dexmedetomidine (RSS = 2) than the Midazolam (RSS = 3) group and more patients in the Midazolam (5 vs. 2 patients) group became over-sedated (RSS > 4). Alhashemi JA titrated anesthetics to a RSS of 3 and found the mean dose of 79.5 mcg of Dexmedetomidine (at 1 mcg/kg initial bolus) and 1.5 mg of Midazolam (0.02 mg/kg initial bolus). Apan A et al used a BIS monitor to titrate their anesthetic to a target value of 85. They found that BIS values were
not able to be decreased to the target value despite increases in the rate of infusion in 3 and 4 patients in the Dexmedetomidine and Midazolam groups, respectively. Their dosing was the least amongst the 6 articles reviewed giving 0.25 mcg/kg/hr Dexmedetomidine and 0.25 mg/kg/hr Midazolam. Demiraran Y et al used a four point somnolence score to evaluate the level of sedation. A score of 4 was given to a patient who is fully awake, 3 for patients awake but lethargic, 2 for spontaneous eye closure but responsive to voice, and 1 for patients responsive only to shaking or prodding. The procedure was started when the patient reached a somnolence score of 2. They used a standard dosing of 1 mcg/kg of Dexmedetomidine bolus followed by a 0.2 mcg/kg/hr infusion. The Midazolam dosing was 0.07 mg/kg to a maximum of 5 mg.

Need for Rescue

Once the level of sedation is standardized, the need for rescue can also provide a means of quantifying the quality of sedation by its respective anesthetic. Of the 6 articles, only two papers evaluated need for rescue during Dexmedetomidine and Midazolam sedation. Table 3 summarizes the data. Both papers were for cataract surgery. The first was by Alhashemi in 2006. From a total of 44 patients, 22 received Dexmedetomidine, they used 1 mcg/kg bolus followed by a 0.2 to 0.7 mcg/kg/min infusion and compared that with 20 mcg/kg bolus of Midazolam with 0.5 mg bolus to achieve a Ramsay sedation scale of 3 or greater. The rescue was 300 mcg/kg of propfol as needed. The average total dose of Dexmedetomidine was 79.5 ± 21.7 mcg and the average total dose of Midazolam was 1.5 ± 0.6 mg. There were no patients that required rescue for their procedure.
The second article was by Apan A et al published in 2009. There were three study groups. One to receive Dexmedetomidine at 0.25 mcg/kg/hr, another to receive Midazolam at 0.25 mg/kg/hr and a control group that was to receive the same volume of saline then received 7 mcg/kg bolus of Midazolam after the saline infusion. Infusion of medication was stopped when the BIS values was less than 85. The rescue was 25 mcg of fentanyl. Four patients in the Dexmedetomidine required fentanyl rescue, three in the Midazolam group and four in the control group. The Dexmedetomidine group received the lowest dose, 0.25 mcg/kg/hr out of all the articles examined.

Table 3. Patients Needing Rescue

<table>
<thead>
<tr>
<th>Author</th>
<th>Surgery</th>
<th>Sedation Goal</th>
<th>Dose</th>
<th>Number Needing Rescue</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alhashemi</td>
<td>Cataract</td>
<td>RSS = 3</td>
<td>D: 1 mcg/kg bolus 0.2 to 0.7 mcg/kg infusion M: 20 mcg/kg bolus</td>
<td>0</td>
<td>Not Reported</td>
</tr>
<tr>
<td>Apan A</td>
<td>Cataract</td>
<td>BIS ≤ 85</td>
<td>D: 0.25 mcg/kg/hr M: 0.25 mg/kg/hr C: Saline w/ 7 mcg/kg Midazolam bolus</td>
<td>4 3 4</td>
<td>Not Reported</td>
</tr>
</tbody>
</table>

Dexmedetomidine was similar to Midazolam during cataract surgery in regard to the need for rescue. Both papers show no significant difference between groups requiring rescue anesthetic to complete the surgery while maintaining similar levels of sedation between groups within their respective papers. Although it is not possible to correlate BIS values with RSS, the dose of anesthetic used in Alhashemi AL was greater than that used in Apan A et al and demonstrated that rescue was not necessary at higher doses of anesthetic.
All six articles evaluated patient satisfaction of the overall procedure and sedation. Table 4 summarizes the findings on patient satisfaction. Evaluation of patient satisfaction was done in various ways, typically by simple questionnaires done after recovery from sedation. Only two articles used the standardized visual analog scale. The visual analog scale uses a 100 mm line that represents the two different extremes of patient satisfaction, either satisfied or not, and the subjective variation between the two. This scale allows for quantitative measurement of qualitative data. Patients are asked to mark how they feel about their level of satisfaction and this mark is measured from the 0 mm mark. The average value can be used for statistical analysis and compared between different subject groups. Two articles reported greater proportion of patient satisfaction with Dexmedetomidine over Midazolam. Üstün Y et al reported 65% of their patients preferred sedation by Dexmedetomidine over Midazolam in their double-blinded cross-over study. The reported VAS scores for patient satisfaction were also statistically significant (9.05 ± 1.31 for Midazolam vs 9.70 ± 0.57 for Dexmedetomidine, p = 0.022). Alhashemi JA also noted a significant preference for Dexmedetomidine sedation over Midazolam sedation. Using the 7-point Likert-like verbal rating scale (see Appendix 3) patients receiving Dexmedetomidine for cataract surgery rated a median score of 6, satisfied, with an interquartile range (IQR) of 6 to 7. Patients who received Midazolam also scored a median value of 6, but had an IQR of 4 to 7 (p < 0.05). They stated that although the value was statistically significant, the clinical relevance may be minor. Apan A et al also found favour for
the use of Dexmedetomidine over Midazolam for cataract surgery, but they evaluated patient satisfaction in a subjective manner during a postoperative telephone interview. Patients in the Dexmedetomidine group expressed satisfaction with the sedation and described a painless postoperative recovery, while the Midazolam and control groups had no comment on whether the protocol was comfortable for them. They then concluded that Dexmedetomidine was superior in patient satisfaction compared with Midazolam. The remaining articles found no significant difference between sedation with Dexmedetomidine and Midazolam.

Table 4. Patient Satisfaction

<table>
<thead>
<tr>
<th>Author</th>
<th>Surgery</th>
<th>Sedation Goal</th>
<th>Satisfaction Scale</th>
<th>Result</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Üstün</td>
<td>Third Molar</td>
<td>RSS = 3</td>
<td>VAS</td>
<td>D: 9.7±0.570 M: 9.05±1.31</td>
<td>p = 0.022</td>
</tr>
<tr>
<td>Alhashemi</td>
<td>Cataract</td>
<td>RSS = 3</td>
<td>Likert-Like</td>
<td>D: 6 (6-7) M: 6 (4-7)</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Apan</td>
<td>Cataract</td>
<td>BIS ≤ 85</td>
<td>Yes/No/No Comment</td>
<td>Reported less negative reports in D</td>
<td>No statistics done</td>
</tr>
<tr>
<td>Cheung</td>
<td>Third Molar</td>
<td>RSS = 4</td>
<td>NRS</td>
<td>D: 8 (8-9) M: 8 (8-9)</td>
<td>Not significant p-value not reported</td>
</tr>
<tr>
<td>Demiraran</td>
<td>Upper Endoscopy</td>
<td>4 point somnolence = 2</td>
<td>VAS</td>
<td>D: 90.1±3.0 M: 84.9±4.5</td>
<td>p = 0.72</td>
</tr>
<tr>
<td>Kaya</td>
<td>TURP</td>
<td>RSS = 2/3</td>
<td>Yes/No</td>
<td>D: 100% M: 96% C: 92%</td>
<td>Not significant p-value not reported</td>
</tr>
</tbody>
</table>

In contrast, Cheung CW et al found no significant difference in patient satisfaction between Dexmedetomidine and Midazolam groups for third molar surgery. They used an ordinal numerical rating system to evaluate patient satisfaction (0 being least satisfied and 10 being
most satisfied). Both groups reported a median satisfaction score of 8 with an IQR of 8 – 9. A p-value was not given, but was stated that the values were not statistically significant.

Demiraran Y, et al used a VAS to assess patient satisfaction of Dexmedetomidine or Midazolam for upper endoscopy. They found that there was no significant difference in patient satisfaction including the amount of gagging and discomfort during the procedure (84.9 ± 4.5 for Midazolam, 90.1 ± 3.0 for Dexmedetomidine, p = 0.72). Kaya FN et al found no significant difference in the proportion of patients who would have the same type of anesthetic again for the same TURP procedure. This included no significant difference with the saline group (100%, 96%, and 92% for Dexmedetomidine, Midazolam, and Saline groups).

Based on these articles, patient satisfaction was either better or similar in the Dexmedetomidine group than the Midazolam group.

**Surgeons Satisfaction**

The quality of sedation can also be evaluated by how well the sedation was perceived by the surgeon. Table 5 summarizes the 5 articles that evaluated surgeon satisfaction. Alihasami evaluated surgeon satisfaction for cataract surgery using a 7-point Likert-like rating system. Refer to Appendix 3 for interpretation of the rating system. Surgeons rated their satisfaction as somewhat satisfied, a value of 5 and an IQR range of 4 to 6 for both Dexmedetomidine and Midazolam.

Apan A used a 4 point scale to evaluate the quality of the surgical condition. The four point scale was not validated and ranked as 1: satisfied calm patient, 2: cooperative, mildly anxious, 3: deeply sedated, and 4: unsatisfied, uncooperative. There was no difference between the
different groups in their proportions of each rank, with satisfied and calm patient as the majority.

Cheung CW et al used the same numerical rating system as the one used to measure patient satisfaction. They too found that surgeons were equally satisfied with the sedation during the procedure. The median score for the Dexmedetomidine group was 9 (8 – 10) and 8 (8 – 10) for the Midazolam group.

In the study by Kaya et al, surgeons were asked to rate the quality of the operating conditions during TURP surgery using a 3 point scale (1 = poor, 2 = moderate, 3 = good). There was no significant difference between surgeon’s satisfaction between the Dexmedetomidine, Midazolam and saline groups. The median score and IQR were the same in all three groups, 3 (2-3).

**Table 5 Surgeon Satisfaction**

<table>
<thead>
<tr>
<th>Author</th>
<th>Surgery</th>
<th>Sedation Goal</th>
<th>Satisfaction Scale</th>
<th>Result</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alhashemi</td>
<td>Cataract</td>
<td>RSS = 3</td>
<td>Likert-Like</td>
<td>D: 5(4-6) M:5(4-6)</td>
<td>Not significant p-value not stated</td>
</tr>
<tr>
<td>Apan</td>
<td>Cataract</td>
<td>BIS ≤ 85</td>
<td>Four point rating scale</td>
<td>D:23/6/1/0 M:21/7/2/0 C:24/5/1/0</td>
<td>Not significant p-value not stated</td>
</tr>
<tr>
<td>Cheung</td>
<td>Third Molar</td>
<td>RSS = 4</td>
<td>NRS</td>
<td>D: 9(8-10) M: 8(8-10)</td>
<td>Not significant p-value not stated</td>
</tr>
<tr>
<td>Demiraran</td>
<td>Upper Endoscopy</td>
<td>4 point somnolence scale = 2</td>
<td>VAS</td>
<td>D:88.8±6.5 M:73.5±16.4</td>
<td>p = 0.029</td>
</tr>
<tr>
<td>Kaya</td>
<td>TURP</td>
<td>RSS = 3</td>
<td>3 point rating scale</td>
<td>D:3(2-3) M:3(2-3)</td>
<td>Not significant p-value not stated</td>
</tr>
</tbody>
</table>
The only article to demonstrate a significant difference in surgeon satisfaction between the 2 anesthetic groups was by Demiraran et al. During upper endoscopy, patients demonstrated less retching while sedated with Dexmedetomidine than with Midazolam. Using the VAS to assess surgeon satisfaction, the average VAS score for Dexmedetomidine was 88.8 ± 6.5 while for Midazolam it was 73.5 ± 16.4. This was significantly different with a p-value of 0.029.

Adverse Outcomes

The side effects of anesthetic medications primarily affect the cardiovascular and respiratory systems. Dexmedetomidine boasts its respiratory sparing qualities, but does reduce blood pressure and heart rate. The 6 articles were evaluated for potential complications during moderate sedation.

The lowest dose of Dexmedetomidine was 0.25 mcg/kg/hr administered by Apan for cataract surgery. They found that mean arterial pressure in the Dexmedetomidine group was not significantly different from either the Midazolam or saline control group during the 50 minutes of infusion and also postoperatively. On the other hand, heart rate decreased significantly starting 30 minutes after infusion and continued to be significant in the postoperative period. Demiraran Y et al showed no difference in heart rate, mean arterial pressure and respiratory rate despite using a much higher dose of Dexmedetomidine. They did not measure the changes in these parameters from baseline. The duration of endoscopy was less than 10 minutes in both groups and thus less total drug administered than in other articles. This may explain why no difference in vials was seen between groups.
Higher doses and longer duration of infusion of anesthetics resulted in significant reduction in heart rate and mean arterial pressure. Cheung, Üstün, and Alhashemi demonstrated that heart rate and MAP decrease significantly with Dexmedetomidine. Heart rate was typically reduced within 5 minutes of infusion while MAP decreased over time, typically after 15 minutes of infusion. At most, vitals decreased approximately 20% from baseline, but none of the patients required intervention for severe bradycardia or hypotension.

Kaya FN reported no significant difference in vitals between groups, each group having significant reduction in baseline vitals. Groups with saline control sedation also demonstrated a reduction in vitals from baseline and not different from the Dexmedetomidine group. As well, 2 patients in the Dexmedetomidine group required treatment for bradycardia and hypotension and 4 patients in the saline group was treated for hypotension and one for bradycardia. Since both treatment groups and saline control groups had significant changes in hemodynamic parameters, the cause may be due to the administration of spinal anesthesia rather than from the intravenous anesthetic itself. Therefore, the hemodynamic parameters within the study by Kaya FN were ignored in this review.

For the most part, respiratory complications were similar in both groups. Üstün, Alhashemi, Kaya, and Apan all noted no changes in respiratory rate or respiratory complications (such as oxygen desaturation, apnea, or increase end tidal carbon dioxide) with Dexmedetomidine or Midazolam. Cheung CW et al found that 6 patients had a decrease in oxygen saturation below 90% in patients receiving Dexmedetomidine while only 4 patients had similar events with Midazolam. All patients responded to prompting to take deep breathes while instituting
supplemental oxygen by nasal cannulae. Apnea was noted by Demiraran et al during upper endoscopy with one patient in the Midazolam group. Two patients had decreased SpO₂, but they did not report the threshold that constituted as significant. Patients in the Dexmedetomidine group did not have any adverse respiratory events during endoscopy. The differences between these studies may be due to their methodology. For the most part, the authors provided supplemental oxygen to all of their patients prior to the start of anesthetic administration except for patients in the study by Cheung et al. Supplemental oxygen was only administered after a respiratory complication and it was found that patients in both groups were susceptible to oxygen desaturation. Another reason is that some surgical procedures were in a shared airway. Demiraran et al was a study on upper endoscopy, where a scope is placed into the upper airway and advanced into the stomach. They noted that gagging and retching were complications of the procedure. The act of retching or gagging potentially could compromise the airway or cause atelectasis by increase in abdominal muscle usage and thus affecting oxygenation. This may have contributed to the desaturation seen in the Midazolam group since more retching was observed in this group.

Aside from cardiovascular and respiratory complications, the most common adverse outcomes were headache and dry mouth. Apan A et al, Alhashemi JA, Cheng CW et al all reported headaches postoperatively in patients receiving either Dexmedetomidine or Midazolam. In these cases the surgical field was in the head region and all received local anesthesia. Although the source of the headaches was not evaluated, one cannot rule out that the source may be related to the operation. Dry mouth is fairly common in sedation with Dexmedetomidine. Apan A reported 57% of patients reporting dry mouth in the Dexmedetomidine group.
Although not an adverse event, Alhashemi JA reported prolonged discharge after administration of Dexmedetomidine when compared to Midazolam. The mean anesthetic time was 63 ± 24 minutes and 64 ± 15 minutes for Dexmedetomidine and Midazolam, respectively. Mean time to readiness to discharge, as determined by an Aldrete score of 10, was significantly prolonged (21 [10 – 32] vs 45 [36 – 54] minutes, p < 0.01). This is unlikely due to oversedation with Dexmedetomidine since administration of the anesthetic was titrated to a RSS of 3, therefore both the Dexmedetomidine and Midazolam groups received equipotent doses. Practitioners using Dexmedetomidine must realize that patients require a greater length of time to recover from a Midazolam anesthetic.

**Discussion**

The potential for an anesthetic with a different mechanism of action from a benzodiazepine may prove to be beneficial for dentists. The different mechanism of action of Dexmedetomidine from Midazolam may help reduce some of the adverse side effects seen with Midazolam. For example, a commonly known adverse side effect of midazolam is a paradoxical reaction which includes increased talkativeness, emotional release, excitement, excessive movements and even violent behaviour. The paradoxical reaction creates a situation where the surgeon now faces an increasingly difficult condition to perform the operation. Although the mechanism by which this occurs is not fully understood, the risk factors for paradoxical reaction include children and in the elderly and in patients with a history of alcohol abuse and aggressive/anger behaviours. The incidence of this phenomenon has been reported between less than 1% to over 10% of patients. In this present review, one incidence of
excessive movement and restlessness after the administration of midazolam was reported by Chang et al. Although they did not call the incident a paradoxical reaction, their description of the event is consistent with paradoxical reactions. This one incident represents less than 1% of all the patients in our review who received midazolam, although this may have been underreported since it is difficult to diagnose. As well some studies used Propofol and/or Fentanyl as a rescue and thus did not allow any agitation to continue. This is in comparison to Dexmedetomidine which had no reports of agitation after administration. It demonstrates that Dexmedetomidine may be beneficial in certain cases where patients present the risk factors for this paradoxical reaction, although further studies are needed.

**Inclusion/Exclusion Criteria**

In order to evaluate Dexmedetomidine as a potential substitute for Midazolam a systematic review of articles was performed that evaluated these two drugs as sole agents for intravenous moderate conscious sedation. Six out of 117 articles were identified as appropriate for this review. The small number of articles that qualified for our systematic review may indicate that these drugs typically have not been used as sole agents for sedation, but combined with other agents such as a narcotic or with Propofol. This appears to be the case as 24 articles were eliminated because Dexmedetomidine was combined with other anesthetic agents. Another factor for a small number of articles is the fact that Dexmedetomidine is also used within the intensive care unit. In this scenario, patients require sedation to tolerate intubation and are typically in critical condition such that only minimal anesthetic is necessary. These articles were excluded because it does not portray the environment that dentists would typically face within
their practice. One criticism may be that our search was limited to Pubmed and Ovid Medline and did not utilize other search engines such as the Cochrane Central Register for Clinical Trials. As well the combination of “Dexmedetomidine” and “Sedation” may have limited the search results. This does not seem to be the case as articles retrieved from the Cochrane Central Register for Clinical Trials and from PubMed and Ovid Medline using the key term “Dexmedetomidine” alone were cross referenced with our original search and there were no new articles added to our systematic review.

Another criticism for such a small number of articles may be due to the strict inclusion and exclusion criteria used in this review. The inclusion and exclusion criteria were designed in such a way that it would be representative of the typical population that is seen in a dental practice and who would receive intravenous moderate sedation. For example, dentists within Ontario are permitted to use only one anesthetic medication for intravenous moderate sedation. This necessitated that each study evaluated would compare each anesthetic as a sole agent. One may argue that Ontario dentists are only a small proportion of dentists in North America and that such a focus limits the usefulness of this review. The fact that Ontario dentists are a small proportion of dentists in North America is true, but the study, despite that it focuses only as single agents, provide a basis for its use in dentistry. By evaluating each agent individually allows one to evaluate the quality of sedation without it being masked by combining other agents. If a dentist is permitted to combine other anesthetic agents during moderate sedation, this review would give a basis for how it would work if they were to substitute a benzodiazepine with Dexmedetomidine.
Using adult patients 18 years and older may also pose a problem for some critics. It is true that it would be hard to distinguish the difference between a 16 year old and an 18 year old patient physiologically which is why we included one article that had a 17 year old within their study population. To use children much younger would not be suitable in this study because it is less likely that a child would be able to tolerate the placement of an intravenous cannula and receive only moderate sedation. This may be more traumatic than the dentistry itself. Patients that tend to receive dental treatment are typically ASA I – III. ASA I indicates a perfectly healthy individual while ASA III indicates a patient who has a disease that limits or modifies their lifestyle, but not at a threat to life. ASA IV patients are patients with a disease that is a constant threat to life. These patients would not be the typical patient to receive elective treatment in the dental office, but rather be seen in a facility that can also manage their disease if it were to become significant.

**Protocol**

The initial bolus of Dexmedetomidine is given as an infusion over 10 minutes to avoid a paradoxical hypertension and bradycardia. In order to maintain blinding of the surgeons and anesthetists, many of the authors choose to infuse the Midazolam bolus over the same 10 minute period. This can potentially change the pharmacokinetics of Midazolam as there would not be a large peak effect seen with a bolus. The difference between a bolus and a 10 minute infusion on the pharmacokinetics and patient effect may be minimal. Greenblatt DJ et al examined the pharmacokinetics and effects of 0.1 mg/kg Midazolam by a bolus or continuous infusion over 1 and 3 hours. They found that continuous infusion of up to 3 hours did not
change the pharmacokinetic parameters, distribution half life (t1/2α), elimination half life (t1/2β), volume of distribution, and the effective concentration at 50% of max effect (EC50), compared with a 1 minute bolus. Thus infusing the initial bolus of Midazolam over 10 minutes in these studies may not be a contributing factor in observed sedation and complication. Indeed all the studies infusing Midazolam were able to achieve a RSS of at least 3. As well, Alhashemi JA devised an elaborate blinding scheme to disguise the administration of either Dexmedetomidine or Midazolam. Even with this protocol patients in the Midazolam group were able to reach a RSS of 3 or greater and their results comparing Dexmedetomidine and Midazolam were similar to other studies. Therefore the method of dosing Midazolam by rapid bolus and that by continuous infusion did not change the outcomes.

*Dexmedetomidine in Dentistry*

Of the six articles, two compared the use of Dexmedetomidine with Midazolam during oral surgical procedures. Within the 117 articles initially found, 6 articles were related to dentistry. Kawaai H, et al28 and Makary L, et al14 both were a collection of case reports and compared Dexmedetomidine to baseline hemodynamic results. Two others were involved with oral surgery and combined Dexmedetomidine with other anesthetic agents. The two remaining articles by Üstün and Cheung therefore provide the only articles that compared Dexmedetomidine with Midazolam for extraction of wisdom teeth.

*Quality of Sedation*

In the articles reviewed, there appears to be consensus that Dexmedetomidine is a suitable substitute for Midazolam for intravenous moderate sedation. All of the articles reported the
ability of Dexmedetomidine to achieve adequate sedation levels similar to Midazolam. Three variables were evaluated to help determine the quality of sedation, the need for rescue, patient satisfaction, as well as surgeon satisfaction. Both articles that evaluated the need for rescue, whether it was propofol or fentanyl, did not find any difference between Dexmedetomidine and Midazolam. Apan A et al found that similar numbers of patients in the saline, Dexmedetomidine and Midazolam groups required rescue for cataract surgery, whereas Cheung et al did not require rescue for any of their dental patients. This may be due to the fact that Apan et al used a very small dose of Dexmedetomidine and Midazolam. The standard regimen for Dexmedetomidine administration requires a 0.2 – 1 mcg/kg bolus given over 10 minutes and a continuous infusion at 0.2 – 0.7 mcg/kg/hr. Apan et al chose to administer 0.25 mcg/kg/hr, which is in the low range of this recommendation. The reasoning was that their patient population was much older than in other studies and a high loading dose predisposed patients to hypotension and bradycardia. Yet by administering Dexmedetomidine in this fashion, they found that 6 patients in the Dexmedetomidine and 10 patients in the Midazolam groups required intraoperative changes in dosing. Despite increases in anesthetic dosing, they found that 3 patients in the Dexmedetomidine and 4 in the Midazolam groups could not reach a BIS value of 85 or less. Alhashemi also evaluated Dexmedetomidine and Midazolam for cataract surgery. Their average patient age was slightly younger (61 years old vs 65 years old), but they used an initial loading dose of 1 mcg/kg of Dexmedetomidine and titrated the continuous infusion starting at 0.4 mcg/kg/hr. Although there was a decrease in heart rate and mean arterial pressure compared with Midazolam, none had bradycardia (HR < 60) or hypotension (MAP < 60 mmHg) and no one required intervention. As well, none of the patients
required Propofol as rescue. This indicates that Apan et al in their attempt to reduce cardiovascular changes from the administration of Dexmedetomidine did not provide adequate sedation for their procedure. This is also evident in the number of patients who were not able to reach an appropriate BIS index of 85. The choice of 85 as the target BIS value is higher than what would traditionally be in the moderate sedation range. Within the articles referenced by Apan et al, a target of 70 to 80 would be appropriate for moderate sedation. A paper by Kasuya Y et al\textsuperscript{29} evaluated BIS values for dexmedetomidine sedation compared with an observational sedation assessment scale, Observers Assessment of Alertness and Sedation Scores (OAA/S). They found that an OAA/S score of 4 corresponded to an average of 62 BIS index (range 53.5 – 68.5). BIS values can also be highly variable, both inter-individual as well as intra-individual and may be affected by illness\textsuperscript{30}. Other methods of evaluating the level of sedation include observational scales such as the RSS. This method was employed by Cheung CW et al, Üstün Y et al, Kaya FN et al, and Alhashemi JA. An initial bolus of 1 mcg/kg for 10 minutes was sufficient to sedate a patient to a RSS value of 3 or 4. This was similar to a 0.02 mg/kg bolus or 5 mg infusion (over 10 minutes) of Midazolam. Patients within these studies were equally satisfied with either Dexmedetomidine or Midazolam with some favouring Dexmedetomidine sedation. Patient satisfaction is completely subjective. A way to objectively quantify patient satisfaction is to have patients describe their experience using an ordinal scale. The Visual Analog Scale, the Numerical Rating Scale and the Likert-Like scales are all ways for patients to quantify their experience\textsuperscript{26}. The three methods for measuring subjective outcomes are commonly used in research. They are also valid and reliable measures and some authors prefer the Likert like system as it typically easy to complete and easy to interpret. Patients tend to prefer
Dexmedetomidine sedation over Midazolam for cataract surgery. Patients who received 1 mcg/kg bolus in Alhashemi’s paper rated their sedation as somewhat satisfied using the likert-like sedation score. Apan et al had a simple, Yes, No, or no comment to the statement: “I would have the same procedure when required”. Although they did not provide statistics for this portion of their study, they concluded in their discussion that patients seemed more satisfied with the Dexmedetomidine sedation. The best indication for patient satisfaction was reported by Üstün et al. Üstün et al designed a cross-over randomized control trial for the removal of third molars. In this study, study participants were able to experience both Midazolam and Dexmedetomidine sedation and then reported their satisfaction using the VAS. They found a statistical significance in the VAS, but to clinically qualify it, they found that a greater proportion of patients would choose the Dexmedetomidine sedation over the Midazolam sedation if they were to have the same procedure done again. The lack of difference seen in other papers may be due to the fact that patients were not able to base their decision on experience both types of sedation.

The analgesic effect of Dexmedetomidine is not one of the key outcomes that was evaluated, but it deserves some mention. Üstün et al reported that 75% of patients sedated by Midazolam demonstrated a reaction to pain during intraoral injection while only 30% reacted when sedated by Dexmedetomidine. This is in contrast to Cheung et al who reported no difference between groups in response to local anesthesia injection, pain in the postoperative ward and three days after discharge. The time to request the first analgesic and analgesic consumption was similar between groups. An explanation for this discrepancy may have to do with the sample size and sensitivity of their pain rating system. Their study was focused on patient
satisfaction using the Numerical rating system and not pain. Their pain scores had a much larger range and IQR than patient’s satisfaction and so larger number may have found significance. Kaya FN also reports that Dexmedetomidine prolongs the effects of bupivacaine spinal anesthesia as measured by the time to first request analgesics as well as analgesic requirements postoperatively.

Likewise, surgeons found Dexmedetomidine to be equal to Midazolam in providing adequate sedation. Demiraran JA stated that endoscopists rated the Dexmedetomidine sedation higher in satisfaction than Midazolam sedation. As well, they also noted less retching while sedated with Dexmedetomidine. Unfortunately the endoscopists were not blinded to the type of sedation and therefore the results are less reliable than if they were blinded.

Adverse Outcomes

Bradycardia and hypotension were prominent in doses of Dexmedetomidine that produced moderate sedation. A continuous infusion of Dexmedetomidine of 0.25 mcg/kg/hr without an initial bolus produced no significant changes in the cardiovascular parameters, but it also produced only minimal sedation, as demonstrated by Apan et al. Their reasoning for using a small dose of Dexmedetomidine and Midazolam was to reduce potential cardiovascular side effects. This is reasonable for Midazolam since older patients have a greater elimination half life and reduced total clearance of the drug and thus have higher plasma concentrations than younger patients\(^{33}\). There is no similar effect seen with increase age and reduced elimination or clearance of Dexmedetomidine. A dose of 1 mcg/kg Dexmedetomidine was well tolerated even by the elderly as demonstrated by Alhashemi JA. Heart rate and blood pressure was
significantly decreased with this loading dose, but none of the patients required intervention for hypotension or bradycardia. Kaya FN used an intermediate dose of Dexmedetomidine of 0.5 mcg/kg during the placement of spinal anesthesia and during TURP. They found that patients were more likely to have bradycardia (HR < 50, n = 2) and have hypotension (MAP < 20% from baseline or systolic pressure < 90 mmHg, n = 2) compared with patients having Midazolam sedation. Unfortunately, these results are confounded by the fact that patients also received a spinal anesthetic. Spinal anesthesia is known to reduce sympathetic tone and create bradycardia and hypotension without additional anesthetics. Since hypotension and bradycardia were seen in patients receiving saline placebo anesthetic, it supports the fact that the spinal anesthesia contributed to the cardiovascular changes.

The dose of Dexmedetomidine is not the only factor that determines changes to the cardiovascular system. Although Apan et al eliminated the initial bolus dose and kept the dose of the infusion low, they still found significant bradycardia 35 minutes after the start of infusion. This is presumed to indicate that the drug plasma levels had reached a significant level to affect the heart rate.

This can be exemplified in a case report of profound bradycardia with therapeutic doses of Dexmedetomidine. Gerlach AT et al\textsuperscript{31} published a report of a cardiac patient who developed severe bradycardia that lead to pulseless electrical activity (PEA) after 6 hour administration of 0.7 mcg/kg of dexmedetomidine. The patient received 2 minutes of chest compression and 0.4 mg of atropine which subsequently recovered without sequlae. There were several conditions that predisposed this patient to develop PEA. First, this patient was known to have a cardiac
condition. The patient previously had a myocardial infarction 3 days post repair of an aortic aneurysm and was in recovery in the hospital. Dexmedetomidine was instituted at a dose of 0.11 mcg/kg/hr for agitation. As the patient’s agitation progressed, the dose of Dexmedetomidine was increased to 0.7 mcg/kg/hr, at the upper limits of the infusion dose. Six hours after initiation of Dexmedetomidine the patient’s heart rate was 21 beats per minute and went into PEA. This patient had a known cardiac condition and was a critically ill elderly patient who received near the upper limits of Dexmedetomidine for 6 hours. The parameters that lead to this adverse event may not be applicable to the average dental patient, but does warn the practitioner to be careful of potential cardiovascular compromise.

Midazolam is known to cause respiratory depression. Only two articles had significant oxygen desaturation. Cheung et al had similar number patients with desaturation event (SpO2 < 90%) between groups. They explained the desaturating events as a result of airway obstruction rather than respiratory depression. They reasoned that both Dexmedetomidine and Midazolam can decrease muscle tone that lead to airway obstruction. If this were the case, then the desaturating events would be more common among all the articles reviewed. Another hypothesis for airway obstruction is that they were working within the airway and potentially applying pressure to the jaw that may have lead to the airway obstruction. Üstün et al also reported on the use of these drugs for third molar extraction but they did not report any desaturating events. An explanation for the differences seen between the two articles is the fact that Cheung et al did not use oxygen supplementation from the start of their procedure, but only when the saturations dropped below 90%. The use of oxygen supplementation in Üstun’s study may have masked momentary airway obstruction and therefore no adverse
respiratory events were seen. This would be an indication for the use of supplemental oxygen during moderate sedation. The other article that reported adverse respiratory events was Demiraran et al. They compared Dexmedetomidine with Midazolam sedation for upper endoscopy. Again, this procedure was also performed within a shared airway and it also produced gagging and retching during the procedure. One patient became apneic and two others had decrease SpO$_2$ in the Midazolam group. The use of supplemental oxygen was also not reported. Another reason for more desaturation in the Midazolam group is that patients with Dexmedetomidine sedation had less retching and coughing during the procedure. Coughing during anesthesia can cause desaturation through atelectasis. The one apneic patient illustrates the potential for respiratory depression during Midazolam sedation for susceptible patients.

Dexmedetomidine was similar to Midazolam in producing other adverse events. Common postoperative complaints included headaches, dizziness and nausea and vomiting. The incidence of headaches was reported to be between 5% and 10%. Dizziness was reported by Cheung et al to be 23%. Postoperative nausea and vomiting were reported to 4 to 10% and was similar in both Dexmedetomidine and Midazolam groups. Antiemetics were not provided during any of the studies and its use may reduce the incidence of this complication.

Dry mouth was also reported by Demiraran et al. Approximately 57% of patients complained about it. The antisialoguoge is potentially a benefit for dentistry as it would provide a dry field to work with and potentially less contamination with saliva. It has been shown to be beneficial in awake fibreoptic intubations$^{17}$.
Office based anesthesia must also account for the available space and postoperative recovery since most of these procedures are done within a confined area of a non-hospital based office. Discharge time, though not an adverse event may be a consideration to use of one drug over another. Dexmedetomidine was shown to delay the readiness to discharge. Alhashemi JA found that patients reached an Aldrete score of 10 sooner in the Midazolam group than the Dexmedetomidine group (21 [10 – 32] and 45 [36 – 54] minutes, p < 0.01). Demiraran et al also evaluated discharge time, but found no significant difference. The length of their procedure was on average 9 ± 1.2 minutes whereas Alhashemi JA reported an average time of 64 ± 24 minutes. Thus patients in Alhashemi received more drug and had more to eliminate than in Demiraran et al.

One of the benefits of a benzodiazepine is the availability of a reversal agent in case of an overdose. There is an alpha-2 adrenergic receptor antagonist, atipamezole. This drug has been approved by the Food and Drug Administration for use in dogs, but not in humans. A limited number of studies have evaluated atipamezole in humans with success, but has yet to be approved for human use.

**Conclusions**

Dexmedetomidine provides a comparable substitute to Midazolam. It works through the alpha-2 adrenergic receptor system and thus provides a different sedation profile and complications. It provides anxiolytic and sedative properties similar to Midazolam at equipotent doses, but unlike Midazolam it lacks amnesia yet gains some analgesic properties. It may also have an advantage in dentistry with its antiallogogue effects. Respiratory complications, primarily
oxygen desaturation, did not appear to be related to the type of anesthetic administered, but related to the type of surgery (shared airway), and the use of supplemental oxygen during the procedure. Hypotension and bradycardia are the most common cardiovascular effects of Dexmedetomidine and can persist for up to 30 minutes after the stop of the infusion. Therefore, careful consideration must be taken in selecting the appropriate patients for this type of modality. As well, management of adverse cardiovascular events must be within the practitioner’s competence. Non-medical considerations must also be taken into account prior to its use in the dental practice. Boluses of Dexmedetomidine must be administered over a period of 10 minutes in order to avoid paradoxical hypertension and bradycardia. As well, longer infusion periods of Dexmedetomidine may increase the time to discharge. These increased time factors may play a role in the use of Dexmedetomidine in the dental office. Lastly, Dexmedetomidine does not have a commercially available reversal agent. Although atipamezole has been used in human experiments, it is still waiting regulatory approval for human use. This is in contrast to benzodiazepine which has an effective, commercially available reversal agent, flumazenil.

The fact that only two articles were related to dentistry highlights the need for more research in this area. Although sedation is often used in conjunction with wisdom teeth extraction, there is a need for sedation in general dentistry\(^2\). Often general dentistry procedures are longer in duration compared with wisdom teeth extraction. This may demonstrate prolonged discharge times and may potentially illustrate more cardiovascular complications. Studies should also examine the analgesic effects of Dexmedetomidine. As demonstrated by Kaya et al, Dexmedetomidine has the ability to prolong bupivacaine spinal anesthesia. Although Cheung et
al did not find any analgesic benefit compared with Midazolam, their study design was not advantageous for studying the analgesic properties of Dexmedetomidine.

References


28. Kawaai H, Satoh J, Watanabe M, Kan K, Ganzberg S, Yamazaki S. A comparison of intravenous sedation with two doses of dexmedetomidine: 0.2 µg/kg/hr Versus 0.4 µg/kg/hr. *Anesth Prog.* 2010 Fall;57(3):96-103.


Appendix 1  Evidence-Based Medicine – Level of Evidence

Level Therapy/Prevention, Aetiology/Harm
1a  Systematic Review (SR) (with homogeneity) of RCTs
1b  Individual RCT (with narrow Confidence Interval)
1c  All or none
2a  SR (with homogeneity) of cohort studies
2b  Individual cohort study (including low quality RCT; poor external validity)
2c  "Outcomes" Research; Ecological studies
3a  SR (with homogeneity) of case-control studies
3b  Individual Case-Control Study
4  Case-series (and poor quality cohort and case-control studies)
5  Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Internal Validity Questions

• Was the assignment of patients to treatments randomised?
• Were the groups similar at the start of the trial?
• Aside from the allocated treatment, were groups treated equally?
• Were all patients who entered the trial accounted for? – and were they analysed in the groups to which they were randomised?
• Were measures objective or were the patients and clinicians kept “blind” to which treatment was being received?
• How large was the treatment effect?

External Validity Questions

• Is my patient so different to those in the study that the results cannot apply?
• Is the treatment feasible in my setting?

Appendix 2  Ramsay Sedation Scale

1  Patient is anxious and agitated or restless, or both
2  Patient is cooperative, oriented and tranquil
3  Patient responds to commands only
4  Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5  Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6  Patient exhibits no response
Appendix 3  Likert-like verbal rating scale

1  Extremely dissatisfied
2  Dissatisfied
3  Somewhat dissatisfied
4  Undecided
5  Somewhat satisfied
6  Satisfied
7  Extremely satisfied