Dexmedetomidine as an Oral Premedication to Facilitate Mask Induction for General Anesthesia for Pediatric Dentistry

by

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A thesis submitted in conformity with the requirements for the Master of Science Degree in Dental Anaesthesia

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Abstract

Dexmedetomidine is a relatively new alpha-2 agonist sedative agent that has many beneficial properties of a premedication. In this randomized clinical trial, oral dexmedetomidine was compared to oral midazolam for its efficacy in gaining cooperation for mask acceptance for induction of general anesthesia. Study subjects consisted of 28 children aged between 3-8 years and ASA I-II status who demonstrated poor cooperation at a prior dental appointment that were randomized to receive either dexmedetomidine 6µg/kg or midazolam 0.7mg/kg 15 minutes prior to induction of anesthesia. The midazolam group had a significantly greater level of sedation but there was no significant difference in cooperation behavior during induction. No differences were found in time to discharge and there were no cases of hypotension and bradycardia requiring treatment. Under the context used in this study, oral dexmedetomidine can be a viable alternative oral premedication to midazolam prior to induction of GA. »
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1 Introduction

1.1 Premedication for General Anesthesia

General Anesthesia

General anesthesia (GA) is defined by the American Society of Anesthesiologists (ASA) as “a drug-induced depression of consciousness during which the patient is unable to be aroused, even to painful stimuli. The ability to maintain independent ventilator function is often impaired, and assistance is often required in maintaining a patent airway. Positive pressure ventilation may be required due to depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired”.

As such, due diligence by the anesthesia provider is required for any treatment under GA. GA for pediatric dentistry is the highest level of pharmacological behavior management. Typically, children referred for dental treatment under GA have failed non-pharmacologic methods of gaining cooperation or the amount of work is too extensive to expect continuous cooperation throughout the entire treatment plan (Vermeulen et al., 1991) (Sheller et al., 2003).

A recent survey in the United States highlighted a sentiment of increased need for deep sedation and GA services in pediatric dentistry. Hicks et al. surveyed directors of pediatric and dental anesthesia residencies in the United States and found that 64% of pediatric dentistry directors anticipated an increased need (Hicks et al., 2012). In Canada, the Canadian Institute for Health Information in 2013 reported that there are approximately 19,000 cases of in-hospital GA annually to treat early childhood caries in Canada excluding Quebec. This represents 31% of all in-hospital GA performed for preschoolers in Canada. Other common indications for in-hospital GA were myringotomy (19%) and tonsillectomy and/or adenoidectomy (11%).

Paralleling this finding are the views and opinions of parents towards GA for dental rehabilitation. Traditionally, pharmacologic modalities of behavior management were not viewed favorably (Murphy et al., 1984, Lawrence et al., 1991). The study by Murphy et al., 1984 showed GA only being ahead of the papoose board in terms of acceptability. Lawrence et al., 1991 echoed this finding where GA was ranked last in parental acceptability. This is in stark contrast
to more recent findings where GA is viewed much more favorably (Eaton et al., 2005). Eaton et al. evaluated 8 methods of behavior management in pediatric dentistry and found GA was the third most favorable technique. It was still statistically less favorable than tell-show-do technique but was on par with nitrous oxide sedation and active restraint.

Intraoperative anesthetic care can largely be divided into three phases. They are induction, maintenance, and emergence. Induction and emergence are considered the most crucial phases as they represent the periods of highest mortality and morbidity (Arbous et al., 2005). This is particularly true in children who have decreased physiologic reserve compared to an adult. Inhalational induction of GA is a popular method in anesthesia for children, which is most commonly done with sevoflurane, a volatile vapor.

The decision to perform an inhalational induction versus an intravenous induction in children is dependent on the case and the preference of the anesthesiologist (Zielinska et al., 2011). This may be due to conflicting outcomes which indicate both methods have advantages and disadvantages when they are compared. Indeed, children can be antagonistic to the mask used for inhalational induction as intravenous needles (Przybylo et al., 2005). Aguilera et al., 2003 found that children experience greater anxiety during intravenous induction but Cropper et al., 2011 reported the opposite outcome. However, children in the study by Cropper had been exposed to multiple anesthetic experiences as they were comparing induction methods in that particular subset of children.

While sevoflurane is described as a sweet smelling, non-irritating volatile anesthetic, it is in reference to the other volatile agents such as isoflurane and desflurane. As such it still carries an odor that along with the mask can create an unpleasant sensation (Aguilera et al., 2003, Cropper et al., 2011, Zielinska et al., 2011). During inhalational induction of GA, children are given a facemask which covers their nose and mouth to breathe the anesthetic agent until loss of consciousness. During induction, the child goes through a number of physiologic changes. An inhalational anesthetic is classically described by four stages which are analgesia, excitement, surgical anesthesia, and respiratory paralysis. Anesthesia aims to place the patient in the surgical stage where reflexes to a painful stimulus are blunted (Guedel, 1937).
The intraoperative maintenance phase is characterized by stability. With adequate depth of anesthesia and pain control, vital signs show little fluctuation.

The emergence phase, or recovery, begins with discontinuation of anesthetic agents until the patient regains consciousness. The patient goes through the stages of anesthesia in reverse, from surgical to excitement to relaxation to regain of consciousness (Guedel, 1937).

Occasionally during emergence, patients show a state of hyperexcitation and agitation called emergence delirium. Clinical manifestations are varied and there is no single definition to describe this state. Irritable, uncooperative, inconsolable, incoherent, kicking, thrashing, and inability to orient themselves to the surrounding environment are some of the observations that have been reported. Although seen with more frequency in children, adult patients are also susceptible to this poorly understood phenomenon (Lepouse et al., 2006, Vlajkovic and Sindjelic, 2007).

**Development of coping**

Children develop strategies of coping with stressful situations from infancy until late adolescence. There are several phases based on age where these strategies can be generalized. In the Canadian medical literature, a toddler ranges from 1-3 years and preschool from 3-6 years of age (Olstad and McCargar, 2009, Canning et al., 2004). Childhood can be further divided into early, middle, and late corresponding to ages 6-8, 8-10, and 10-12 respectively.

The boundaries of coping abilities have loosely been identified as; infancy to toddlerhood, 5-7 years of age which spans between late preschool age and early childhood, middle childhood to beginning of early adolescence, 12-16, and 16-22 (Skinner and Zimmer-Gembeck, 2007). Although the classifications based on age do not perfectly correlate to development of coping, they provide convenient reference points.

During toddlerhood until 5 years of age or late preschool age, coping based on direct actions are most commonly seen and voluntary coping actions are first seen. Coping through cognition begins to mature at 5-7 years of age and asserts during middle childhood. Generally, there are 4 coping strategies most commonly displayed. These are support-seeking, problem-solving,
distraction, and escape. Regardless of phase of development, the most common method of coping is support or help-seeking. This may present as distress, seeking parental support, and verbal appeals.

Problem-solving as a coping mechanism is not usually seen under the age of 8. It begins to develop during middle childhood and is only increasingly seen during late childhood and early adolescence. With age, the utilization of help-seeking and problem-solving strategies seemed to be inversely correlated. This makes empirical sense as problem-solving is a cognitive development. This suggests that until the development of increased cognitive capabilities, coping with situations of stress will be through primary action or support-seeking from a caregiver (Skinner and Zimmer-Gembeck, 2007).

Distraction can be divided into behavioral and cognitive. Examples of behavioral distraction are playing games, watching television, and listening to a story. This method of coping has been observed from infancy to adolescents. Increased use of behavioral distraction is seen during infancy to toddler, stagnates during preschool years between 4-6, and then increases again from early childhood to early adolescence. Cognitive distraction is often described as diversionary thinking and is increasingly seen beginning in late childhood to beginning of early adolescence. Examples of cognitive distraction would be thinking about a pleasant experience or efforts to forget about the stressor (Skinner and Zimmer-Gembeck, 2007).

Escape is an attempt to flee the stressing environment or choosing passivity over direct action. This is rarely observed before the 5-7 year age range (Skinner and Zimmer-Gembeck, 2007).

Summarizing these findings, the most effective management for children between ages 1 and 6 may be reassurance to satisfy their help-seeking mechanism and behavioral distraction. Then from middle to late childhood with increases in cognitive capability and self-regulation, cognitive distraction and providing procedural information for problem-solving may become effective.

Anxiety
Up to 50% of children have significant stress and anxiety before surgery (Kain et al., 1996c). This can be attributed to the procedure of induction itself and patient factors. From the child’s perspective, they are placed in an unfamiliar environment with strangers, possibly be separated from their caregivers before introduction of a facemask or an intravenous catheter, and have uncertainties about the surgical procedure itself. For example, anxiety to the dental procedure has been associated with poor behavior at inhalational induction of GA (Hosey et al., 2006).

Significant patient factors that are associated with high anxiety are; labile emotion, shy personality, high parental anxiety, previous hospitalization, and poor prior experience. At 1-3 years of age, children experience significant separation anxiety and cannot understand explanations but are amenable to distraction and comforting measures as the ability to distinguish fantasy from reality is not mature. From 4 to 6, the need for explanations and feeling in control of situations become important. Then from 7 to 12, they begin to be involved in decision making. However, the process of anesthesia and surgery may impose too much stress for their limited coping skills (McCann and Kain, 2001). Indeed, it has been shown that induction of GA which may involve parental separation and introduction of a facemask is the period of highest perioperative anxiety (Kain et al., 1996c, Kain et al., 2004b).

Successful management of anxiety decreases the chances of an uncooperative patient and a non-ideal induction of crying, general struggling, and requirement of physical restraint. This situation of a non-ideal induction creates increased secretions in the airway which poses a risk of laryngospasm and a catecholamine surge that causes increased metabolism and in turn, a higher oxygen consumption. Consistent with adverse effects during induction, preoperatively unmanaged anxiety has been shown to increase chances of experiencing post-operative emergence delirium and new onset maladaptive behaviors at home. The maladaptive behaviors that can occur at home after induction of GA with unmanaged anxiety post-discharge are general anxiety, nighttime crying, and temper tantrums.

Physiological parameters are also affected as failure to manage anxiety causes children to experience more pain from surgery, consume more analgesics, and have more problems eating and sleeping post-operatively. Thus, minimizing psychological trauma to both parent and child
improves satisfaction and benefits the GA process from the pre-operative phase until complete recovery at home.

The link between a non-ideal induction of GA and maladaptive behaviors were first described by Eckenhoff in 1958 where he retrospectively surveyed the parents of over 600 children. Later, Kain et al., 1999 showed in their randomized prospective clinical trial that indeed children with unmanaged anxiety had significantly higher chance of showing maladaptive behaviors at home after discharge from the hospital. They selected 86 children aged between 2-7 years and of ASA I and II status scheduled for elective surgery. The subjects were randomly divided to receive 0.5mg/kg of midazolam with acetaminophen or acetaminophen alone. The authors found that midazolam intervention significantly decreased anxiety prior to parental separation and GA induction and significantly decreased incidences of maladaptive behaviors at home. The finding of unmanaged anxiety being a factor in at home maladaptive behavior was repeated in a retrospective study by Kain et al., 2004 in their review of 791 ASA I and II patients undergoing elective surgery who were not premedicated. It was shown that anxiety was significantly associated with new-onset maladaptive behaviors.

The association between pre-operative anxiety and post-operative pain and analgesic use was demonstrated by Kain et al., 2006. They prospectively recruited 241 ASA I and II children aged between 5-12 years scheduled for elective tonsillectomy and adenoidectomy. Children with high anxiety had significantly higher level of pain compared to children with lower anxiety. This was consistent in both parental and self-report. Related to this finding was that high anxiety children consumed significantly more narcotic and non-narcotic analgesics at home. Echoing the findings of earlier studies, it also reported that emergence and home behavior and were significantly poorer in the high anxiety group. However, it is difficult to infer from this study whether successful management of children with high anxiety would decrease pain and analgesic use (Kain et al., 2006, Kain et al., 1999, Kain et al., 2004b, Kogan et al., 2002, McCann and Kain, 2001, Rosenbaum et al., 2009, Ensinger et al., 1993) (Eckenhoff, 1953).

Post-operative pain and delirium is a factor for increased nursing requirement and possible delayed discharge from hospital as patients cannot be safely discharged before being orientated enough to respond purposefully to simple commands. Neither post-operative delirium nor
delayed discharge is desirable in a hospital setting where such resources are available (Vlajkovic and Sindjelic, 2007). In the outpatient environment where resources are relatively limited compared to a hospital, preventing such occurrences becomes even more important.

**Non-pharmacologic management of anxiety**

There are multiple techniques to allay fear and anxiety pre-operatively. These include Parental Presence during Induction of Anesthesia (PPIA), preparation visits prior to treatment with child life specialists, role playing, child-friendly environments, distraction by operators, and pharmacologic agents (McCann and Kain, 2001).

The perceived benefits of PPIA are avoiding the issue of parental separation and eliminating the need for premedication. This method does not work across all cases as a calm parent is needed to be successful. In addition, it may prolong the induction process and create an extra individual that may possibly need tending to (Kain et al., 1996b) (McCann and Kain, 2001).

It is generally accepted that preparation visits prior to treatment reduces anxiety and gives children a chance to develop or increase their coping ability (Sale et al., 1988). However, the desired outcomes from preparation visits are dependent on multiple factors that must be controlled by the clinician. These factors are age, timing of the visit, and certain individual characteristics. Children older than 6 were less anxious only when the preparation was given at least 5 days in advance and children showing avoidant or escape coping behaviors benefitted less than those with information seeking behaviors. Interestingly, children with previous hospital experience, labile emotions, or aged 2-3 years became more anxious after preparation. However, even when the above factors were optimized, there were no measurable differences in anxiety at parental separation and induction of anesthesia. No differences were found between interventions in the postoperative phase as well (Kain et al., 1996a) (Kain et al., 1998a). In practice, multiple modalities are used in concert as children vary in their level of anxiety and coping mechanisms (Kain et al., 2004a) (Rosenbaum et al., 2009).

**Premedication**

Premedication prior to a GA is a form of advanced behavior and anxiety management by way of pharmacologic intervention. It is frequently used in a pediatric setting where cooperation can be
difficult to obtain (McCann and Kain, 2001). Premedication aims to manage anxiety during this high-anxiety period, thereby benefitting the GA induction process by increasing the chance of gaining cooperation and as part of the perioperative management of anxiety (Kain et al., 2006). Pharmacological means of managing anxiety has been found to be highly efficacious. Kain et al., 1998 compared anxiety between three groups of children through the process of GA induction who received either a sedative premedication, parental presence, or no intervention. The authors found no differences in preoperative anxiety between the groups, but children that received midazolam had significantly less anxiety during the process of induction compared to both control and PPIA. Related to this finding was that the PPIA and the control group had poorer behavior during induction (McCann and Kain, 2001, Kain et al., 1998b).

A premedication can be delivered by a variety of routes of administration. These are by mouth (PO), per rectum (PR), sublingual (SL), transmucosal (TM), intramuscular injection (IM), and intranasal (IN). Of these methods, the oral route has the advantage of being the most familiar method of administering medication in the absence of an intravenous catheter, relatively high patient acceptance, no mucosal or tissue irritation, and the chance to mask the event of drug administration from the child by use of flavoring and sweeteners. Kogan et al., 2002 evaluated 4 routes of midazolam premedication in children which were intranasal, oral, per rectum, and sublingual. There were no significant differences in anxiolysis, sedation, mask acceptance, and time for patient recovery. However, the intranasal group had significantly higher proportion of children who cried and were upset after premedication compared to the other 3 routes. This may due to the unpleasant sensation mucosal irritation and having a fluid filled sinus (Kogan et al., 2002). The disadvantages of the oral route are the slower onset of effect and the potential for rejection by the patient (Giovannitti, 1984) (Kogan et al., 2002) (Almenrader et al., 2007). Nevertheless, various clinical trials of premedication given PO demonstrate adequate depth of sedative effect most often within 30 to 60 minutes and is a very common route of administration (Weldon et al., 1992).

Although the pharmacologic premedication has been shown to be a highly efficacious method of managing anxiety and gaining cooperation, its prevalence in current practice represents a relatively recent shift in anesthetic care. United States data from 1995 showed that the majority of children received neither PPIA nor premedication to manage their anxiety. The report also
showed that when premedication was used, midazolam was the agent of choice (Kain et al., 1997a). A follow up survey from the same authors in 2002 found a significant increase in managing patient anxiety with premedication or PPIA. Midazolam was still the most popular agent (Kain et al., 2004a). Most recently, a French survey of pediatric anesthesia practice in 2010 showed that 72% of practicing anesthesiologists surveyed used premedication in all cases (Constant et al., 2012). Currently, benzodiazepines are the most common premedication agents in the pediatric setting prior to induction of GA, with midazolam being used most frequently (Kain et al., 2004a). Other agents in use are ketamine and clonidine (McCann and Kain, 2001).

**Downsides of premedication**

The pharmacologic behavior management is not always successful. The negative consequences and undesired effects from premedication have also been reported in literature. All drugs are subject to their pharmacokinetics, hence premedication requires time for its intended effect. This waiting time varies from 30-60 minutes and it could have a significant impact in scheduling if premedication is routinely given throughout the day.

One of the discouraging aspects of midazolam, the most popular agent for premedication, is its bitter taste causing reduced acceptance. This is commonly manifested with the patient refusing or spitting out the oral premedication. Ironically, midazolam premedication has also been associated with maladaptive problems at home and paradoxical reactions in the pediatric population (McGraw and Kendrick, 1998, Finley et al., 2006, Isik et al., 2010). Finley et. al. studied how midazolam premedication was affected by emotional reactivity and child temperament. They enrolled children planned for myringotomy under GA and evaluated perioperative anxiety levels. Then the anxiety levels were compared to the emotionality and impulsivity score completed by their parents. The authors found that premedication in children with high emotionality scores significantly decreased anxiety while children with high impulsivity scores did not benefit from premedication. In fact, there was no statistical difference in level of anxiety between placebo and midazolam treatment in children with high impulsivity (Finley et al., 2006). In agreement, the study by Isik et al. found that children with inflexible temperament and psychosomatic abnormalities were more likely to fail midazolam sedation (Isik et al., 2010).
In the study by McGraw and Kendrick, 1998, the authors made an observation that children that received midazolam premedication had a greater incidence of maladaptive behaviors at home. They randomized 70 children to either receive a placebo or 0.5mg/kg of midazolam as a premedication prior to scheduled surgery. While the midazolam group had better behavior and cooperation at induction of GA, they were significantly more likely to have maladaptive behaviors during the first week home. This study must be interpreted with caution as non-validated scales and questionnaires were used but it highlights that midazolam premedication may be effective only in the immediate perioperative period (McGraw and Kendrick, 1998).

What the evidence amounts to is that midazolam premedication will not be effective for a subset of children and the use of an alternative management or agent would be beneficial. Furthermore, the availability midazolam was recently in doubt during 2012 with a North America-wide shortage of this generic injectable drug. An alternative agent clonidine is highly efficacious as a premedication compared to midazolam but this drug requires nearly an hour for its effect. In addition, children remain sleepy for a longer period of time after surgery which can delay discharge. Hence its use in outpatient setting is limited due to logistics and availability of resources (Almenrader et al., 2007).

Next, the question of administering an unnecessary drug to hide procedural deficiencies and unfamiliarity with the proper use of non-pharmacologic management also comes into question. Premedication can substitute for a child-unfriendly environment and the clinician who opts to premedicate regardless of child behavior. It has been shown that “one size fits all” method of preoperative preparation is not an ideal method to teach coping skills and children may be receiving a drug in which the indications were weak at best (Rosenbaum et al., 2009).

*Measuring the effectiveness of premedication*

To evaluate and measure efficacy of premedication, a variety of scales and scoring systems have been developed either to rate anxiety, sedation, or the end point of cooperation. Not including simple global measures designed for individual studies, these scoring systems are the modified Yale Preoperative Anxiety Score (mYPAS), Visual Analogue Score (VAS), State Trait Anxiety Inventory for Children (STAIC), Observers Assessment of Alertness and Sedation (OAA/S), University of Michigan Sedation Scale (UMSS), and the Induction Compliance Checklist (ICC).
The mYPAS is an observational score ranging from 23-100 which rates anxiety by evaluating activity, vocalizations, emotional expressivity, state of arousal, and use of parent. It was developed in the context of inhalational induction of anesthesia in children aged between 5-12 years. It is reliable (intra-rater \( r = 0.91 \), inter-rater \( r = 0.73 \)), easy to score, and usually only 1 minute is needed (Kain et al., 1997b).

The VAS is both an observational and self-reported rating of a subjective state. It is most commonly used in pain and mood states literature. The VAS is a 100mm straight line with each end of this line representing the behavioral extremes. Critical to this 100mm line is that it should be horizontal to increases chances of uniform distribution compared to a vertical VAS line and have right angle stops at each end to signify a boundary that cannot be crossed. A point along this line is marked to represent the subjective phenomenon being examined. This point is measured in millimeters from one end of the scale or a grid with predetermined intervals is superimposed to produce a quantitative translation of a qualitative measure which can be statistically analyzed to a greater extent than a subjective measure. The advantages of the VAS are that it is easy, quick, and can be adapted to measure a variety of subjective states. However, the disadvantage is that the subject must be able to understand what the mark on the 100mm line represents and one end of the extreme does not have an absolute value as it is left to individual interpretation (Wewers and Lowe, 1990) (Kindler et al., 2000).

STAIC is a self-reported measure of situational (state) and baseline (trait) anxiety. It is composed of 40 questions in total designed for use in children between 5-8 years (Spielberger and Edwards, 1973).

The UMSS is an observational 5 point global rating scale for evaluating depth of sedation. It was developed in the context of computed tomography procedural sedation where 32 children aged between 4 months to 5 years received chloral hydrate sedation. It has been shown to be valid when compared to OAA/S and VAS, reliable, and very quick to score (Malviya et al., 2002).

The OAA/S scale was developed to measure alertness and sedation. The criteria measured are responsiveness, speech, facial expression, and eyes. This scale is shown in Appendix A. In
validating this scale, Chernik et. al. compared two end-points of sedation with midazolam, light and heavy, to a placebo and applied the visual analog scale (VAS) and OAA/S scale. Light sedation was defined as “lethargic with mild slowing of speech” and heavy sedation was defined as impaired speech with response only with prodding and shaking. The OAA/S and VAS was scored by two raters blinded to the sedative regimen at 5 and 60 minute points for comparison and validity. Like the VAS, OAA/S scale was able to differentiate the levels of sedation between the placebo, light, and heavy sedation at both 5 and 60 minute marks. The level of differentiation was statistically significant and the correlation to VAS score at 5 and 60 minutes were 0.960 and 0.919 respectively. Inter-rater reliability for the OAA/S scale was also high at both 5 minutes ($r = 0.935$) and 60 minutes ($r = 0.873$) while inter-rater reliability for VAS was 0.908 and 0.769 respectively. These correlation coefficients represented higher inter-rater reliability for the OAA/S than the VAS. In addition, the use of OAA/S is simple, requires minimal training, and scoring typically takes less than 1 minute. The explicit definitions of the scoring system also makes the OAA/S scale easier to interpret than the 100mm VAS (Chernik et al., 1990).

The ICC is an observational scale to describe cooperation and behavior during inhalational induction of anesthesia in children. It evaluates 10 negative behavioral components of mask acceptance. High scores correlate with poor behavioral compliance. A score of 0 indicates a perfect induction, i.e. no negative behaviors, fear, or anxiety during induction. It was developed by an anesthesiologist and a psychologist after examining recordings of 48 cases of children during induction of GA. From these sessions, a checklist of 10 negative behaviors was formed. The checklist was then used by two independent observers to score 36 GA inductions of children from one to 9 years of age. It was found to have a very high interclass correlation within ($r = 0.998, 0.995$) and between observers ($r = 0.978$). In the same study, an ICC score of 6 or greater was classified as a ‘poor’ induction. There was no elaboration why this score was chosen to classify a “poor” or a “good” induction. The ICC is shown in Appendix B (Kain et al., 1998b).

1.2 Agents used for Premedication

1.2.1 Alpha-2 Receptor Agonists

There are 3 subtypes of alpha-2 adrenergic receptors, classified as A, B, and C (Bylund 1988). They are distributed ubiquitously throughout the body including peripheral and central nervous
system, liver, pancreas, kidney, platelets, and the eye. All 3 subtypes of receptors activate guanine-nucleotide proteins (G proteins) which causes activation of second messenger systems. They can inhibit adenylate cyclase which in turn decreases the level of cyclic Adenosine Mono-Phosphate (cAMP). This decrease in cAMP reduces phosphorylation of target proteins that are partly responsible for the effects of alpha-2 receptor stimulation (Cotecchia, Kobilka et al. 1990). The other effects of alpha-2 receptor stimulation are efflux of potassium and inhibition of calcium transport. Efflux of potassium has a hyperpolarizing effect which decreases excitability of membranes and inhibition of calcium leads to decreased secretion of neurotransmitters. Of the three subtypes, subtype A has shown to produce the sedative, analgesic, and anesthetic reduction effect in mice (Lakhani, MacMillan et al. 1997). This receptor is located presynaptically in the autonomic nervous system and regulates norepinephrine and adenosine triphosphate release through negative feedback (Langer 1974). The alpha-2 subtype A receptors are also present in locus ceruleus in the pons in high density where it most likely produces its sedative effect (Nelson, Lu et al. 2003).

Alpha-2 agonists exert their actions by binding to both the pre-synaptic and post-synaptic alpha-2 receptors. They decrease sympathetic nervous system outflow via alpha-2 receptor action in the medullary vasomotor center. The resulting physiologic effects are decreased peripheral vascular resistance, heart rate, cardiac output, and blood pressure (Kamibayashi and Maze, 2000). Paradoxically, the alpha-2 receptors present post-synaptically in peripheral blood vessels cause vasoconstriction. This effect is demonstrated when high plasma concentration of alpha-2 adrenergic agonists are present and is thought to be the underlying mechanism of transient increase in blood pressure when these agents, dexmedetomidine in particular, are intravenously injected as a rapid bolus (Kamibayashi and Maze, 2000) (Potts et al., 2009).

The type of sedation that alpha-2 adrenergics produce has been found to differ from that of gamma-aminobutyric acid (GABA) receptor agonists. Through its actions on the locus ceruleus in the brainstem, alpha-2 agonists create a physiologic sleep state where patients appear sedate but can be easily aroused (Hall et al., 2000, Nelson et al., 2003, Coursin and Maccioli, 2001). The sedative aspect of alpha-2 agonists has been known since the 1960s from their use in veterinary medicine. Veterinarians have been using xylazine, an alpha-2 agonist and analogue of clonidine, for sedation and analgesia in animals with good clinical efficacy (Clarke and Hall,
1969). It has been shown that the sedative effect of alpha-2 agonists are dose dependent and are superior to benzodiazepines in certain settings (Tobias and Berkenbosch, 2004, Bergendahl et al., 2006).

Alpha-2 agonists produce analgesia by activation of alpha-2 receptors in the substantia gelatinosa of the dorsal horn spinal cord. This area of the spinal cord is also the active site of opioids where pain signaling is modulated. Thus, alpha-2 agonists are classified as centrally acting analgesics (Coursin and Maccioli, 2001).

In addition to sedation and analgesia, alpha-2 agonists decrease intraoperative anesthetic requirements, acts as a sympatholytic, improve perioperative hemodynamic control, decrease perioperative oxygen consumption, and decreases the threshold for shivering (Mukhtar et al., 2006) (Taittonen et al., 1997, Talke et al., 1997). The reduction in anesthetic requirements was demonstrated by a decrease in minimal alveolar concentration (MAC) (Aho et al., 1991). The improvement in hemodynamic stability is the result of both analgesia and inhibition of sympathetic outflow in response to a surgical stimulus (Aho et al., 1992). Compared with a benzodiazepine, sedation with an alpha-2 agonist decreased opioid requirements, decreased the need for rescue medications, and produced a greater depth of anesthesia. Alpha-2 agonists have also been shown to decrease reaction to surgical stimuli and laryngoscopy. This was again, attributed to its reduction of sympathetic nervous system outflow, thus maintaining stable cardiovascular parameters (Aho et al., 1992, Maze and Tranquilli, 1991).

**Clonidine**

Clonidine is an imidazoline derivative that is a centrally acting alpha-2 agonist. It classified as a partial agonist that is 220 times more selective for alpha-2 receptors compared with alpha-1 receptors (Bergendahl et al., 2006). The sedative, hypotensive, and bradycardic aspects of clonidine were found during clinical trials in the 1960s as a topical nasal decongestant (Gertler et al., 2001). It exhibits all of the characteristics of an alpha-2 agonist and its use as a sedative agent is off-label. Its current major use is for treatment of hypertension as clonidine increases parasympathetic tone and decreases release of norepinephrine into the plasma (Hoobler and Sagastume, 1971).
Clonidine is most commonly delivered through the oral and transdermal route. After oral administration, 60 to 90 minutes is necessary for peak plasma level. Although the oral bioavailability of clonidine was found to be nearly 100% in adults, bioavailability in children is lower at 55%. It is currently not known why oral bioavailability is lower in children. Although speculative, it may be due to the ingredients in the clonidine elixir. Its elimination half-life ranges from 9 to 12 hours and is excreted through the liver and kidneys (Larsson et al., 2011).

Perioperatively, clonidine affects the cardiorespiratory system, central nervous system, and the autonomic system. Intraoperatively it blunts reflex tachycardia in response to laryngoscopy, improves hemodynamic stability, decreases plasma catecholamine levels, and decreases anesthetic requirements for both inhaled and injected drugs. Postoperatively it enhances analgesia and has been shown to decrease myocardial ischemia, myocardial infarction, and mortality following cardiovascular surgeries (Goyagi and Nishikawa, 1996, Nishina et al., 2002). Cardiac parameters are depressed through its sympatholytic activity. Anxiolysis and sedation are seen through its actions on the central nervous system. Its analgesic effect is a result of its action on the spinal cord.

Clonidine is the most well-known alpha-2 adrenergic agonist today. Although not as commonly used as midazolam, it is an agent available for premedication (Kain et al., 2004a). When used as a premedication to facilitate parental separation and induction of GA, studies are conflicting in their outcomes. While clonidine is more efficacious than diazepam, its effectiveness compared with midazolam is not clear.

Clonidine was superior compared to midazolam in providing adequate sedation for mask acceptance and induction of GA in children (Almenrader et al., 2007). The study population was ASA I and II children aged 2 to 6 and the authors used a non-validated scale to measure anxiety. By contrast, in a study by Fazi et al. clonidine premedication was inferior to midazolam in that children in the clonidine group displayed more anxious behavior and resistance to parental separation and mask acceptance (Fazi et al., 2001). The study population in this study was ASA I and II children from 4 to 12 and the mYPAS was used as the evaluation score. Both studies used a standard premedication dosing and timing schedule of clonidine and midazolam which were 4μg/kg 60-90 minutes before induction and 0.5mg/kg 30 minutes before induction respectively.
It has been demonstrated that preoperative use of clonidine decreases intraoperative propofol requirement, augments analgesia, and attenuates sympathetic responses during surgery (Bergendahl et al., 2006).

Despite its large pharmacodynamic upside, its use as a premedication is usually limited in outpatient settings due to its pharmacokinetics. The onset time of approximately 60 to 90 minutes when given as an oral medication and its long half-life relative to alternate premedication drugs such as midazolam are the major disadvantages to outpatient use where quick onset and recovery is beneficial (Kamibayashi and Maze, 2000, Hayashi and Maze, 1993, Schmidt et al., 2007).

**Dexmedetomidine**

Dexmedetomidine, like clonidine, is an imidazole compound that is an agonist at alpha-2 receptors. However, unlike clonidine which is classified as a partial agonist due to its relatively low selectivity for alpha-2 receptors to alpha-1 receptors (220:1), dexmedetomidine is a full agonist at the alpha-2 receptors displaying high selectivity for alpha-2 receptors (1600:1) (Coursin and Maccioli, 2001). It is the active stereoisomer of medetomidine which it is isolated from.

Dexmedetomidine (Precedex®) has been approved for use by Health Canada. It is indicated for conscious sedation of non-intubated patients undergoing monitored anesthesia care and awake fiberoptic intubation. The pharmacokinetics of dexmedetomidine is well established in adults owing to its approved use. Its pharmacokinetics are not as well described or investigated in children but some information is available. When given intravenously, dexmedetomidine has a redistribution half-life of 7 minutes and an elimination half-life of 2 hours. It is 93% protein bound, and its clearance is 15mL/kg/min (Petroz et al., 2006). Similar values of elimination half-life and clearance are seen in studies with children but it is difficult to make direct comparisons as the sample sizes are small. However, trends seem to show that by 3 years, the elimination half-life and clearance reaches adult parameters (Vilo et al., 2008, Potts et al., 2009). Dexmedetomidine undergoes almost complete hepatic biotransformation in the liver and the metabolites of dexmedetomidine are excreted 95% in urine and 4% in feces (Gertler et al., 2001).
Antilla et al. examined the bioavailability of dexmedetomidine through multiple routes of administration. The authors used 12 healthy adult subjects who were given a single dose of 2μg/kg intravenously, intramuscularly, orally, and transmucosally. Oral dexmedetomidine was given diluted with 150mL of water, minimizing transmucosal delivery. A period of 8 days of rest between dosing was made to ensure complete elimination of drug from the previous route of administration. Blood samples were taken at multiple time points and plotted in a plasma concentration vs time graph. From the graph, the authors determined that the bioavailability of dexmedetomidine was 16% orally, 82% transmucosally, and 104% intramuscularly (Anttila et al., 2003). The low oral bioavailability reflects the large first-pass hepatic effect.

The pharmacodynamic effects of dexmedetomidine are similar to a typical alpha-2 agonist. Its actions are seen in multiple organ systems. These are cardiovascular, respiratory, renal, central nervous system, autonomic nervous system, and thermoregulation. Dexmedetomidine produces sedation and anxiolysis through its actions on the locus ceruleus and analgesia by its actions in the spinal cord (Kamibayashi and Maze, 2000). As stated above, alpha-2 agonists are sympatholytics, therefore it causes a reduction in blood pressure and heart rate.

In the multicenter study of pharmacokinetics and pharmacodynamics by Petroz et al., 2006 three different doses of dexmedetomidine were given intravenously as an infusion at 2, 4, and 6μg/kg/hour for 10 minutes to a heterogeneous sample group from Toronto, Canada and Cape Town, South Africa. The drug effect on vital signs, alertness and sedation, and plasma concentration of dexmedetomidine were measured. Of the three doses, the group which received dexmedetomidine at 6μg/kg/hour showed high efficacy in producing sedation. The decrease in mean arterial pressure showed dose dependence but was not clinically significant. Blood pressure and heart rate remained within age appropriate ranges. All children in the group which received 6μg/kg/hour infusion for 10 minutes for a total dose of 1μg/kg were either drowsy, very sedated, or appropriately asleep at the end of the infusion. This multicenter study also showed that dose-response to dexmedetomidine is consistent across populations of different genetic composition with respect to vital signs and sedation. This was significant due to the potential multicultural nature of the study population and the authors did not report any adverse events attributable to dexmedetomidine (Petroz et al., 2006).
Minute ventilation is minimally affected and respirations remain regular. Transient hypertension can be seen when large doses are rapidly injected intravascularly (Potts et al., 2009). This is thought to be due to its effect on peripheral alpha-1 and post-synaptic alpha-2 receptors (Kamibayashi and Maze, 2000). Dexmedetomidine as a premedication is currently under investigation but not common in anesthetic practice. This may be due to its relatively short time in since Health Canada approval in 2009, the popularity of midazolam, unfamiliarity, economics, and a relatively thin list of trials in the published literature. Dexmedetomidine premedication studies report favorable patient acceptance, good efficacy, and high parent satisfaction compared with the established premedication (Ray and Tobias, 2008) (Yuen et al., 2008) (Sheta et al., 2014). Another study showed that dexmedetomidine, when compared to midazolam, provides a more reliable and a greater level of sedation in patients aged one to 7 years undergoing non-invasive MRI studies less than one hour without differences in vital signs (Heard et al., 2007, Koroglu et al., 2005).

Lastly, use of dexmedetomidine was shown to reduce sympathetic stress activity and provide stable hemodynamics during pediatric cardiac surgery (Mukhtar et al., 2006). This study by Mukhtar et. al., 2006 demonstrates that even in situations where hemodynamics insults are likely during surgery and there is a decreased margin of safety, dexmedetomidine is a safe drug to use in the hands of a trained professional.

The most well described route of dexmedetomidine administration as a premedication currently in literature is intranasal (Sun et al., 2014). Intranasal administration has the pharmacokinetic advantage of rapid systemic absorption and elimination of the first-pass effect as it takes advantage of transmucosal absorption in the nasal mucosa. These properties lend to its reliable and predictable effect after drug administration. In the study by Yuen et al., 2008 intranasal dexmedetomidine was compared to oral midazolam as a premedication. The onset time was set at 60 minutes and the end point was the level of sedation and behavior at parental separation and induction of anesthesia. It was found that dexmedetomidine produced greater sedation than midazolam at both parental separation and induction of anesthesia. Although both drugs were no different in their effectiveness in managing anxiety and gaining cooperation at induction, greater number of children changed from good behavior at parental separation to an unacceptable behavior at GA induction in the dexmedetomidine group. The difference was statistically
significant compared to the midazolam group. The authors then noted findings of paradoxical behavior in the midazolam group whilst none was found in the dexmedetomidine group. Although the onset time of 60 minutes for dexmedetomidine may be considered too long in some settings, this study showed that both midazolam and dexmedetomidine with their advantages and disadvantages can be used as a premedication drug for gaining behavioral cooperation at induction (Yuen et al., 2008). The same author then determined in a separate study, that a intranasal dexmedetomidine dose of 2 μg/kg produced greater sedation than 1μg/kg without affecting the safety profile. In addition, the overall onset time of sedation was 25 minutes which can be accommodated in many contexts without difficulty (Yuen et al., 2012). These findings by Yuen et al., 2012 were repeated by Sheta et al., 2014 which compared IN midazolam at 0.2mg/kg to IN dexmedetomidine at 1μg/kg. The significant aspect of this study was that they selected healthy children receiving GA for dentistry which is comparable to the context in this study. This meant that the indication for GA was due to lack of cooperation in the dental chair which is translatable to the population sample in this study. Interestingly, they reported that there were no cases exhibiting symptoms of mucosal irritation in the dexmedetomidine group. However, there were cases of sedation failure or administration failure in both groups (Sheta et al., 2014). Although neither study used a validated scale to measure sedation or cooperation during induction of GA, the efficacy of IN dexmedetomidine premedication was at least on par or greater than IN or oral midazolam (Sheta et al., 2014, Yuen et al., 2008).

Contrast to the randomized controlled trials of IN use of dexmedetomidine, there are only a few studies reporting or evaluating the oral use of dexmedetomidine (Zub et al., 2005, Ray and Tobias, 2008, Schmidt et al., 2007). The initial impression of oral dexmedetomidine is positive with respect to its pharmacodynamics. Reported cases in the literature showed similar time of onset as intranasal dexmedetomidine for adequate effect to facilitate cooperation in minimally invasive procedures such as IV cannulation or medical imaging (Ray and Tobias, 2008, Zub et al., 2005). A retrospective study by Zub et al., 2005 examined use of dexmedetomidine as an oral premedication to facilitate parental separation, mask acceptance for induction of GA, and/or intravenous cannulation. They found 13 cases where oral dexmedetomidine was used as a premedication. Dexmedetomidine in its undiluted intravenous formulation was given orally in all cases and no vocalizations or complaints were made about its palatability. This is a significant advantage against midazolam as midazolam carries a difficult to mask, intense bitter taste which
is not accepted well by children. They reported that oral dexmedetomidine was successful in providing adequate procedural sedation for all 13 cases. The most interesting aspect of this study was that 9 of the 13 patients had a neurobehavioral diagnosis and in some cases, failed previous attempts of preprocedural sedation with midazolam or chloral hydrate. Following the dexmedetomidine administration, all planned procedures were carried out without issues and there were no reports of adverse events. Although the authors suggested an oral dexmedetomidine dose of 4μg/kg from their review, the drug was given in its undiluted concentration of 100μg/mL. The authors postulated that due to the low volumes used, a portion of the drug was absorbed transmucosally. This makes recreating their results difficult as additional variables such as route of administration, effect of total volume, and the oral environment are introduced (Zub et al., 2005). A second retrospective study by Ray and Tobias, 2008 evaluated preprocedural dexmedetomidine in children with autism and pervasive developmental disorders. They were given oral dexmedetomidine premedication prior to placement of an intravenous catheter. In all cases they reported a successful placement of the intravenous catheter in these difficult to manage patients (Ray and Tobias, 2008). A prospective open-label clinical study by Schmidt et al., 2007 evaluated dexmedetomidine for its anxiolytic and analgesic properties. The authors randomized 60 schoolchildren aged between 7 and 12 to receive oral midazolam, oral clonidine, or transmucosal dexmedetomidine. All children were scored on the STAIC prior to administration of a randomly chosen medication. There were no statistically significant differences in STAIC between the groups at administration of premedication and after the surgery. However, a significant difference was found in the post-operative pain score between midazolam and the alpha-2 agonists. This study demonstrated that anxiolysis by dexmedetomidine is at least on par with midazolam and the addition of its analgesic properties can have a beneficial effect in the post-operative period, potentially benefitting the emergence phase of GA (Schmidt et al., 2007).

Dexmedetomidine as a premedication has several highly desirable properties. The constellation of anxiolysis, lack of bitter taste, and analgesia with limited respiratory depression is particularly desirable (Nelson et al., 2003). As a sedative, patients given dexmedetomidine appear asleep but are readily aroused (Coursin and Maccioli, 2001). In addition, it is thought to have an antisialagogue effect and the ability to reduce postoperative nausea and vomiting (Bergendahl et al., 2006). These effects improve satisfaction and perioperative care as pain, nausea, and
vomiting are some of the most important factors in patient satisfaction surveys (Hocking et al., 2013). The disadvantages compared to midazolam is currently the high cost of the drug and for some practitioners, the lack of anterograde amnesia (Rosenbaum et al., 2009).

Pharmacokinetically, the use of dexmedetomidine as a premedication through the oral route is disadvantageous compared to other routes such as intramuscular or intranasal. The slower onset and poor oral bioavailability owing to the large first pass effect is not optimal for an outpatient practice. These pharmacokinetic disadvantages can be compensated by using a large dose but is not economical as dexmedetomidine is currently on patent to Hospira in Canada as Precedex® and is 20 times more expensive than the generic formulation of midazolam. However, its palatability can be easily masked by a very small amount of diluent, which cannot be done with midazolam. This decreases the amount of cooperation needed and makes it possible to deliver high doses of dexmedetomidine in very low volumes of liquid. Therefore, a significant amount of transmucosal absorption is possible with minimal patient cooperation.

In summary, dexmedetomidine offers the advantage of highly selective alpha-2 agonist action and more rapid onset and offset compared to clonidine which is desirable in an ambulatory outpatient setting. Although direct comparisons cannot be made to dentistry, the oral dexmedetomidine studies all reported favorable efficacy of dexmedetomidine as a premedication compared to midazolam without additional side effects. This was most evident in the studies by Zub et al., 2005 and Ray and Tobias, 2008 where midazolam or a traditional agent failed to produce the cooperation needed for the intended therapeutic procedure while dexmedetomidine gave a successful result (Zub et al., 2005, Ray and Tobias, 2008). Conceptually, dexmedetomidine combines the effects of an alpha-2 agonist with pharmacokinetics similar to that of midazolam. Overall, the pharmacodynamics and pharmacokinetics of dexmedetomidine are favorable to use as a premedication in an outpatient environment.

1.2.2 Benzodiazepines

Benzodiazepines belong to a broad category of drugs that are referred to as gamma-aminobutyric acid (GABA) agonists. GABA is the principal inhibitory neurotransmitter in the central nervous system (CNS). They bind to GABA receptors which causes an influx of chloride ions. This influx causes the post-synaptic nerve to be hyperpolarized, which increases the level of
stimulation required to depolarize the nerve. GABA-A receptor subtypes have been identified, which are alpha-1 and alpha-2. Majority of GABA receptors are alpha-1, being distributed throughout the cerebral cortex, cerebellar cortex, and the thalamus. Alpha-2 GABA receptors are concentrated in the hippocampus and amygdala. It is thought that alpha-1 receptors mediate sedation and alpha-2 receptors are responsible for anxiolysis. Currently available formulations of benzodiazepines are not selective for GABA receptor subtypes (Mohler et al., 2002).

Benzodiazepines act on the benzodiazepine receptor on the GABA receptor complex. This binding increases the GABA receptor’s affinity for its substrate, GABA. This in turn increases the influx of chlorine ions into the cell which hyperpolarizes the cell membrane.

Benzodiazepines are the most commonly used drug for anxiolysis of children prior to induction of GA. Their properties consisting of: anxiolysis, sedation, muscle relaxation, anti-convulsant effect, and anterograde amnesia confer their popularity. The large therapeutic window in combination with minimal respiratory and cardiac depression makes them an excellent choice in the preoperative phase where monitoring is minimal (Kain et al., 2004a).

**Midazolam**

Midazolam is a unique short acting benzodiazepine in that it incorporates an imidazole ring in its structure. This structure is responsible for the water solubility and rapid metabolism. It is approximately two times more potent than diazepam (Gerecke, 1983). Commercial oral formulations are available in the United States and while they have been shown to have a more rapid onset compared to orally administering the intravenous formulation, they are not available in Canada (McMillan et al., 1992).

Midazolam’s distribution half-life after IV administration ranges from 6-15 minutes, clearance range of 6.4-11.1 mL/kg/min, and elimination half-life of 1.7-4 hours. Systemically, midazolam binds to benzodiazepine receptors in the CNS then redistributes into less perfused compartments such as muscle and fat. It is then hepatically metabolized and renally excreted. Due to its high clearance rate, midazolam has a short half-life of approximately 2 hours. The short half-life along with quick absorption lends its popularity as a premedication (Gerecke, 1983) (Reves et al., 1985).
Midazolam, like all benzodiazepines, produce anterograde amnesia, anxiolysis, sedation, anticonvulsant effect, and muscle relaxant activity. It cannot create an isoelectric electroencephalogram (EEG) and is limited in its ability to decrease cerebral metabolic requirement of oxygen. It causes dose-dependent cardiovascular depression, but also shows a limit similar to its effect on the CNS. The effect on the respiratory system is minimal for healthy individuals, but it can cause clinically significant respiratory depression for individuals with comorbidities such as chronic obstructive pulmonary disease and sleep apnea (Gerecke, 1983, Reves et al., 1985).

Currently, midazolam is the most frequently used sedative for children who require premedication prior to GA (Kain et al., 2004a). A survey of trends in the United States by Kain, et. al. found that when a premedication was used, 96% of the cases used midazolam. In addition they found a significant increase in the use of premedication for children from 1995 to 2002 (Kain et al., 2004a). Midazolam owes its popularity to its high efficacy in providing sedation, amnesia, and reduction of anxiety (McMillan et al., 1992, Buffett-Jerrott et al., 2003).

Midazolam is well absorbed orally and shows its anxiolytic effect in 30 minutes or less.

McMillan et al., 1992 compared three doses of midazolam mixed in chocolate syrup in its ability for sedation, anxiolysis, parental separation, and mask acceptance in children. Three midazolam groups at doses of 0.5mg/kg, 0.75mg/kg, or 1.0mg/kg were compared to a placebo group. They rated anxiety and sedation on a 4-point scale and found all 3 doses of midazolam to be significant and effective in its intended effect versus a placebo. In clinical practice, a single dose of 0.5mg/kg to 0.7mg/kg provides reliable anxiolysis within 15 minutes for mask acceptance.

1.2.3 N-methyl-D-Aspartate antagonists

This group of drugs includes ketamine, dextromethorphan, and memantine. N-methyl-D-Aspartate (NMDA) receptors are present throughout the central nervous system. Its main ligand is glutamate but it also possesses binding sites for glycine, polyamine, spermine, zinc, and phencyclidine. When activated, it causes excitatory neurotransmission.
Ketamine

Currently, the only intravenous NMDA antagonist used in anesthetic practice is ketamine. Ketamine possesses both anesthetic and analgesic properties which is unique for an induction agent. Ketamine is a phencyclidine derivative that is a non-competitive antagonist at NMDA receptors with a mild GABA receptor action. It is able to produce a unique type of anesthesia known as a dissociative state that is characterized by analgesia, amnesia, and cataleptic appearance. Ketamine causes dissociation of thalamocortical pathways but stimulates the limbic system. The anesthetized patient exhibits slow nystagmus and many reflexes are maintained. These reflexes are corneal, cough, and swallow. Increased amount of secretions is seen as lacrimation and salivation. Ketamine can be used both as an induction and maintenance agent for anesthesia.

The pharmacokinetics of ketamine has been extensively studied and is well known. Intravenously, it shows a large volume of distribution of 3Litres/kg, and high clearance of 890 to 1227mL/min. These two properties are responsible for its relatively large dosing regimen of 3 to 5mg/kg via the oral or intramuscular administration and short elimination half time of 2 to 3 hours. When given as an intravenous bolus, it shows a two-compartment model showing an initial rapid redistribution phase followed by a slower elimination phase where plasma concentrations gradually decrease. Its high lipid solubility facilitates transfer across the brain blood barrier. Ketamine undergoes hepatic metabolism to form norketamine, which is subsequently conjugated and excreted by the kidneys (Clements et al., 1982). Pharmacokinetics of ketamine administered via multiple routes in human volunteers has been evaluated. Oral bioavailability was measured as 16.6% with a mean lag time of 8.0 minutes and mean time to peak concentration was 30 minutes. The low oral bioavailability, similar to dexmedetomidine, reflects the extensive hepatic first pass effect. Its oral elimination half time did not differ from intravenous or intramuscular routes, which measured roughly 2 to 3 hours (Clements et al., 1982).

Ketamine is unique in that it is both an anesthetic and an analgesic. It produces unconsciousness in a dose-dependent manner. Its direct depressant action is masked by the indirect release of norepinephrine, which stimulates the sympathetic nervous system. This indirect sympathomimetic action is responsible for its cardiostability and bronchodilating action provided
that the sympathetic stores are not depleted. Unlike other intravenous anesthetics, ketamine causes an increase in cerebral blood flow, intracranial pressure, and intraocular pressure. Ketamine’s ability to cause hallucinations precludes use as a single agent. A benzodiazepine is usually co-administered to mitigate adverse psychological effects (Funk et al., 2000).

The pharmacokinetics of ketamine underlying its rapid action followed by quick elimination makes it useful as an oral premedication for short outpatient procedures. It produces reliable sedation for mask acceptance without depressing the cardiorespiratory system. It is usually given in combination with midazolam orally or as an intramuscular injection to increase success of anxiolysis, prevent recall of hallucinations, and mitigate sympathomimetic effects. Ketamine premedication can be used to facilitate parental separation, intravenous cannulation, and GA induction (Funk et al., 2000, Ghai et al., 2005, Jain et al., 2010).

2 Rationale for study

The purpose of this project was to evaluate dexmedetomidine as an oral premedication to manage anxiety and improve cooperation to facilitate mask induction of GA in children undergoing dental rehabilitation. This would represent a novel use for this agent in the dental outpatient office environment.

Currently published studies that looked at oral dexmedetomidine use were either retrospective, had small sample sizes, or the oral use of dexmedetomidine was not the original intended area of study. Most importantly, the studies do not report compliance during induction of anesthesia. In addition, the age ranges of the study population in the above studies were older compared to the pre-cooperative or anxious patient population that receives outpatient general anesthesia for dentistry making it difficult to draw direct comparisons.

At the University of Toronto’s Faculty of Dentistry Pediatric Surgicentre, a premedication is used to increase patient cooperation and allay the anxiety of both the child and the parent. The patients treated at the Pediatric Surgicentre at the Faculty of Dentistry represent a group of patients where non-pharmacologic modalities of behavior management have failed for dental treatment or the amount of work planned exceeds their ability to cooperate. As such, for the majority of cases, cooperation is the indication for GA. They often have significant anxiety in
which premedication may be beneficial prior to GA induction. Midazolam is the most common premedication used for this purpose but dexmedetomidine may be a viable alternative.

Despite the upsides mentioned earlier and its high efficacy, there is a paucity of randomized controlled clinical trials of oral dexmedetomidine premedication in current literature. Its use as an oral premedication to gain cooperation, facilitate mask acceptance and induction of general anesthesia after allowing a shorter time of onset is not well explored. This makes it difficult to evaluate its efficacy and predictability as a preprocedural agent used prior to GA in pediatric dentistry. Since the primary goal of premedication in context of the dental outpatient office is to manage anxiety and gain cooperation, but not necessarily sedation, a shorter onset time may be just as efficacious to facilitate inhalational induction of GA. This randomized clinical trial was aimed at exploring the possible use of this useful intravenous drug as an oral premedication in an outpatient office environment.

3 Hypothesis

The hypothesis tested was that oral dexmedetomidine, when used as a premedication would be no different than midazolam in its ability to induce sedation to allow for mask acceptance and induction of GA in children. The potential significance of this study is that if the null hypothesis is rejected, and the result is that dexmedetomidine is superior, either by improved efficacy or cooperation, then this could benefit patient experience and lead to a new indication and important therapeutic role for this agent. If dexmedetomidine is found to be inferior in the context of this study, future efforts can be directed on methods of increasing its efficacy as a preprocedural medication. On the other hand, even if there are no differences between dexmedetomidine and midazolam as premedication to improve mask acceptance, it could demonstrate that dexmedetomidine is a useful alternative agent for premedication.

4 Methods

4.1 Experiment design

Ethics approval was received by University of Toronto, Research Ethics Board. The patients were randomly assigned by computer generated random sequence of 0’s and 1’s to receive either
0.7 mg/kg oral midazolam (positive control group) or 6.0μg/kg oral dexmedetomidine (study group). The randomization was provided by a third party and the principal researcher was blinded to the generation and assignment of the random sequence and group assignment. This random sequence was then given to the senior (third) year dental anesthesia resident who was responsible for choosing which number would represent either the control or study group. This sequence was given to the staff instructor or the nurse when the principal investigator coincided as the senior resident. The random sequence was kept by the senior year dental anesthesia resident and then locked in the drug cabinet when the principal researcher was the senior resident until the conclusion of the study.

To achieve similar palatability and to maintain blinding to the principal researcher, both premedication were then diluted with a pharmacy-mixed raspberry chocolate marshmallow flavored diluent. The cups were then covered with aluminum foil to hide the contents. The principal investigator was called by the senior dental anesthesia resident to be present with the patient at the time of premedication administration. A period of 15 minutes was given for drug effect under observation of the principal investigator. At the conclusion of the 15 minute wait period, the Observers Assessment of Alertness and Sedation scale (OAA/S, Appendix A) was scored. The patient was then brought into the operating chair by a nurse and GA was induced by mask inhalation of nitrous oxide and sevoflurane. At this period of induction, the induction compliance checklist (ICC, Appendix B) was scored. The principal investigator measured and recorded the OAA/S and ICC. The rationale for using the OAA/S scale and ICC with a cutoff of 3 is further explained in the discussion section.

After induction of GA, all aspects of treatment and perioperative care were routine. As per usual protocol, parental presence at the time of induction was allowed upon parental wishes and resident approval. GA was administered consistent with the usual standard of care as described in the Royal College of Dental Surgeons of Ontario (RCDSO) Standards for Sedation and General Anesthesia for Dentistry. The general anesthetic was conducted by a team consisting of a senior graduate dental anesthesia resident, a registered nurse, and a dental anesthesiologist staff instructor with the Discipline of Dental Anesthesia, Faculty of Dentistry, University of Toronto providing direct supervision throughout the procedure. Routine monitoring for GA was carried out in compliance with RCDSO Standards. Specifically, the monitoring consisted of the heart
rate, blood pressure, electrocardiography, respiration, end-tidal carbon dioxide, oxyhemoglobin saturation, temperature, and gas analysis. A summary flowchart is illustrated in figure 1.

![Figure 1. Study method flowchart](image)

### 4.2 Screening and Consent

By clinic protocol, patients are consulted in pediatric dentistry and dental anesthesia prior to their treatment appointment under GA. The consent process involved both the pediatric dentistry consult and anesthesia consult. At the initial consultation conducted by the pediatric dentistry resident, the study was described, and the Information Sheet (see Appendix C) and Consent Form (Appendix D) were handed out to the parent of a child who met the inclusion criteria (Appendix E). Children of ASA status I and II of ages 3-8 with English-speaking parents who were judged to benefit from a premedication prior to inhalational induction of GA were considered for the study. Children of ASA status greater II, a diagnosis of neurobehavioral problem, and contraindications to midazolam or dexmedetomidine were excluded from the study (Appendix F). Additional exclusion criteria are outlined in Appendix F. They then had an anesthetic consultation with the senior dental anesthesia resident as per usual protocol, that provided an opportunity to answer any questions they may have, further explain the rationale of this study, and review the child’s eligibility for the study. The parent was then asked for consent.
to participate in the study by signing the consent form at either the consult appointment or any
time prior to the treatment appointment under GA.

4.3 Sample size

At the pediatric surgicentre at the Faculty of Dentistry, patients who receive 0.7 mg/kg of oral
midazolam are typically able to accept mask induction within 15 - 30 minutes with good
cooperation behavior (unpublished data). A study most similar to our protocols in the study
showed that 85% of children had successful anxiolysis and were calm 15 minutes after oral
midazolam premedication with 0.5mg/kg or 0.75mg/kg (McMillan et al., 1992). Thus, 85% or
0.85 was used as the sample proportion. The sample size calculation is shown below.

\[
N = \frac{(Z_{1-\alpha/2})^2 \times p \times (1 - p)}{\Delta^2}
\]

Where \(N\) is the sample size
\(Z_{1-\alpha/2}\) is the \(1 - \alpha/2\) percentile from a standard normal distribution
\(p\) is the sample proportion
\(\Delta\) is the difference to be detected

\[
N = \frac{(1.96)^2 \times 0.85 \times (1 - 0.85)}{(0.2)^2}
\]

\(N = 13\)

Therefore it was determined that 13 patients per group are appropriate to detect a 20% difference
from the population mean, for a total of 26 patients. In order to account for potential drop-outs,
we aimed to recruit 40 patients.

4.4 Data collection and analysis

The primary outcomes were the cooperation of the child and the level of sedation during
inhalational induction of GA. The principal investigator and patient were blinded to the
medication given. The principal investigator measured and recorded all outcome data. These
outcomes were measured using the ICC and the OAA/S respectively. Observational data were
collected at two points during the study. First point was scoring of OAA/S 15 minutes from the
time of premedication administration for the level of sedation. The second point was scoring of
the ICC at inhalational induction of GA. The time between the two measurements were not
recorded. The OAA/S score would be tallied for a total possible score of 20. High scores
correlate with lower levels of sedation (i.e. increased alertness). The ICC score was tallied for a
total possible score of 10. High scores correlate with poor behavior during induction. A cutoff
score of 4 was chosen to categorize poor or good cooperation. Both OAA/S and ICC score was analyzed quantitatively using ANOVA. There was no specific training in use of the ICC and OAA/S. Additional data, specifically age, sex, time from premedication to induction of anesthesia, duration of surgery, and time to discharge would be recorded and analyzed for significance between group means using ANOVA. P values less than 0.05 were considered statistically significant for all analyses.

5 Results

5.1 Patient recruitment

Patients were screened for eligibility and consent from October 2012 until April 2014 using the aforementioned inclusion and exclusion criteria (Appendix E, F). Over this period, 39 patients were recruited and 28 patients successfully completed the study. There were 11 dropouts in total. 6 patients did not cooperate for the oral premed, two in the dexmedetomidine group and 4 in the midazolam group. IM premedication was chosen at appointment date for one child, the principal researcher could not be present for 3 patients, and one patient was later found to have autism spectrum disorder, which was one of the exclusion criteria. These patients were not included for analysis. Patient disposition summary is shown in figure 2.
5.2 Patient Demographics

15 patients completed the study in the midazolam(M) group whereas 13 patients completed the study in the dexmedetomidine(D) group. There were 5 males and 8 females in the D group while M group had 9 males and 6 females. This did not reach significant statistical difference within the groups with respect to distribution of sex \( (p = 0.27) \). The mean ages of the patients were 4.0 and 4.5 years in group M and D respectively. There were no significant statistical differences between groups with respect to age \( (p = 0.32) \). Time between administration of premedication and induction of anesthesia was 15.3 minutes in group M and 16.6 minutes in group D. This difference was not statistically significant \( (p = 0.10) \). There was no statistical difference in the two groups with respect to treatment time and time to discharge. There were no significant differences in acceptance of oral dexmedetomidine and midazolam in the chocolate raspberry diluent. Incidences of premedication rejection were 4 in group M and 2 in group D.
### Table 1. Patient demographic data

<table>
<thead>
<tr>
<th></th>
<th>Group M (n=15)</th>
<th>Group D (n=13)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>4.0 ± 1.3 [3-7]</td>
<td>4.5 ± 1.6 [3-8]</td>
<td>0.32</td>
</tr>
<tr>
<td>Sex, M:F</td>
<td>9:6</td>
<td>5:8</td>
<td>0.27</td>
</tr>
<tr>
<td>Premed to induction time (min)</td>
<td>15.3 ± 1.5</td>
<td>16.6 ± 2.4</td>
<td>0.10</td>
</tr>
<tr>
<td>Duration of treatment (min)</td>
<td>136.0 ± 30.0</td>
<td>135.4 ± 23.0</td>
<td>0.95</td>
</tr>
<tr>
<td>Time to discharge (min)</td>
<td>48.5 ± 24.0</td>
<td>40.8 ± 20.5</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Age in mean ± SD, range in brackets. All other values in mean ± SD.

### 5.3 Sedation, induction behavior, and observations

The OAA/S score in the M group ranged from 10 to 20 while scores in the D group ranged from 13 to 20. The mean OAA/S score was 15.1 and 18.7 for group M and D respectively (lower scores indicate decreased alertness and increased level of sedation. This difference was statistically significant ($p < 0.05$). Overall, group M patients were significantly more sedated according to the OAA/S criteria at mask induction of GA than group D. ICC ranged from 0 to 5 in the M group and 0 to 6 in the D group. Mean ICC score was 0.9 and 1.7 for group M and D respectively (lower scores indicate better induction behavior). The difference in ICC between the two groups did not reach statistical significance ($p = 0.30$). More patients showed unsatisfactory mask acceptance and inhalational induction of GA in the D group. Three patients in group D showed poor induction behavior (ICC score greater than 3) compared to one patient in group M. However, this difference did not reach statistical significance ($p = 0.23$). There was an observational trend for patients in the dexmedetomidine group to require less anesthetic agents during maintenance phase and their vitals showed less fluctuation compared to the midazolam group. There were no incidences of bradycardia or hypotension requiring treatment in either group throughout the maintenance period and the recovery phase. Neither group received atropine as part of their routine anesthetic care. There did not seem to be a difference in the post-operative phase between the two groups with respect to agitation and shivering. There were no incidences of nausea and vomiting or cases requiring rescue analgesics during recovery in either group.
6 Discussion

The purpose of this study was to examine oral dexmedetomidine in comparison to oral midazolam as a premedication for GA. Specifically being assessed was its sedative ability and gaining cooperation for GA induction in children within an onset time similar to an oral midazolam premedication in an outpatient office. The results show that the induction condition produced by oral dexmedetomidine at a dose of 6μg/kg is no different to oral midazolam at a dose of 0.7mg/kg. Three out of the 13 patients in group D and one out of the 15 patients in group M had a poor induction as judged by an ICC score of greater than 3.

The ICC was chosen in this study due to the context in which it was developed; an observational scale to describe cooperation and behavior during inhalational induction of anesthesia in children aged between 1-9 years. An ICC score cutoff of 3 was used in this study instead of 6 used by the original developers to divide the induction cooperation into two categories: poor and good. This score was chosen after examination of the ICC by the principal researcher. Behaviors of turning head away from mask, requiring mild physical restraint such as hand holding, attempts to place hand on mask, and complete passivity are not uncommon events with a very cooperative child and can be managed with coaching and distraction. In scoring the ICC, it can be argued that certain items in the ICC such as hysterical crying and kicking should be given added weight to the overall score. However an induction with such poor behavior is highly likely to score positively on other items of the ICC. Therefore, the cutoff score was changed to 3 but the scoring method was not changed from the original description given by the developers. With midazolam oral premedication, the majority of cases will result in good induction conditions but there will be a small number of incidences where it will not be efficacious (Isik et al., 2010). Thus it can be expected that oral dexmedetomidine will also be successful most of the time but there will be instances where it too will not be efficacious. Given the proven efficacy of midazolam and its
widespread use, dexmedetomidine can be an option for the purpose of premedication to gain cooperation for mask acceptance and subsequent inhalational induction of GA (Kain et al., 2004a, McMillan et al., 1992).

There was a significant difference in the OAA/S score produced by midazolam and dexmedetomidine (15.1 ± 3.9 vs 18.7 ± 2.4, p < 0.01) even though both groups produced satisfactory induction conditions (p = 0.23). Although the OAA/S was developed by evaluating sedation with midazolam, a GABA agonist, it was chosen in the present study to measure both midazolam and dexmedetomidine sedation. This was due to that all validated scales of sedation were developed in conjunction with a GABA agonist and a separate validated scale for an alpha-2 agonist does not exist. The VAS measures data from the actual sedated subject. Hence, the VAS would be less likely to have varying outcomes regardless of the sedative agent used. The OAA/S scale has been validated with the VAS. Therefore, although developed with GABA agonists, the OAA/S scale would lend itself to be an accurate tool to measure sedation in both groups. Additionally, the OAA/S scale evaluates multiple signs of sedation with a clear objective scoring system which would increase the likelihood of detecting qualitative differences between the two groups (Chernik et al., 1990).

Alpha-2 agonist sedation is different to that of GABA agonists, it was determined that a global rating scale such as the UMSS or VAS although simpler and quicker to observe, would not be the most appropriate tool to evaluate this outcome. The difference in sedation score may be attributable to dexmedetomidine’s mechanism of action which is fundamentally different than midazolam. Dexmedetomidine is thought to simulate a natural sleep state through its action on the locus ceruleus such that patients are sedate but become readily alert when stimulated. In contrast, midazolam produces a hypnotic state where the patients responsiveness is decreased even when stimulated. Similar attributes were found in this study where patients in group M often presented to induction in a semi-hypnotic state where as patients in group D were often alert and orientated. Typically patients in group D presented at induction with a mild level of sedation or none at all. Despite differences in sedation characteristics, most patients in group D allowed placement of monitors and mask without any resistance, negative vocalizations, or physical restraint. This is shown by the low average ICC score of 1.7±2.3.
Overall, the majority patients in the study showed good mask acceptance and inhalational GA induction behavior. The level of anxiety was not specifically measured as the purpose of this study was to examine whether oral dexmedetomidine can facilitate inhalational induction of GA. However, the ICC may act as a surrogate marker for anxiety as children with high unmanaged anxiety are more likely to be uncooperative during GA induction (Kain et al., 1998b, McCann and Kain, 2001).

There were several limitations to this study. Non-pharmacologic methods of managing anxiety at induction were allowed if they were deemed necessary or beneficial. These methods were distraction techniques using cartoons or video games, coaching, reassurance, tell-show-do, and parental presence. Leaning on a single method to manage anxiety and gain cooperation would be unrealistic in clinical practice, therefore the flexibility of using these non-pharmacologic techniques to manage anxiety was allowed. However, since all of the children who required parental presence in addition to premedication resulted in poor induction behavior, it did not confound the primary outcome.

A second limitation of this study was that there were two different senior residents during the length of this study and pre-operative anxiety and traits of the patients were not separately measured prior to the decision regarding premedication use. Thus, there were no formally agreed upon criteria on the decision to use a premedication which could have introduced a confounding variable to the study. However, the majority children referred to the pediatric surgicenter clinic were due to a lack of cooperation that had already been demonstrated and documented at a previous dental appointment. Thus, the two residents treated patients that were from the same population group of likely high anxiety, used similar methods of distraction during induction, and were supervised by the same group of instructors.

A third limitation was that one of the senior residents administering GA was the principal researcher. This may have introduced possible systematic bias into the results. This effect was minimized by consulting the nurse whose presence remained consistent throughout the study regarding which patients would benefit from a sedative premedication, and by conforming to the protocol that the principal researcher be blinded to the group assignment.
The fourth limitation may have been the OAA/S tool used to evaluate alertness and sedation. This tool was originally developed to evaluate patient response after administration of midazolam, a benzodiazepine. Due to the differences in pharmacodynamics between alpha-2 agonists and benzodiazepines, OAA/S may not be the most appropriate tool to evaluate the type of sedation produced by dexmedetomidine. However, OAA/S has been used in prior studies to assess alertness and sedation after administration of dexmedetomidine, and validated scales developed with alpha-2 agonists do not yet exist (Yuen et al., 2008) (Cimen et al., 2013).

Lastly, the type of anesthetic agents used after induction of GA was not controlled but left to the preference of the resident and supervising instructor. This was not a consideration in the original design of the study, as no further data for the primary outcome were to be collected after GA induction.

Although the period between OAA/S and ICC scoring were not separately measured, this time was typically very minimal at the surgicenter where this study took place. The waiting room and the operating room are beside each other and the child was brought in immediately after OAA/S scoring and placed on the dental chair for placement of monitors and induction of GA.

The 6μg/kg oral dose of dexmedetomidine used in this study is significantly higher than the dose of 3-4μg/kg suggested in one retrospective case review (Zub et al., 2005). This dose was adapted from a pharmacokinetic study of dexmedetomidine combined with data from a multicenter study performed at Hospital for Sick Children (SickKids) in Toronto (Anttila et al., 2003, Petroz et al., 2006). As stated before, dexmedetomidine has an oral bioavailability of 16%. Therefore, the 6μg/kg oral dose would correspond to approximately 1μg/kg intravenous dosing which showed high efficacy in producing anxiolysis and sedation without compromising safety.

There were two additional reasons for this oral dose of dexmedetomidine. First, the premedication was diluted with sweet syrup as to maintain blinding between the two groups. The dilution ensured delivery of the drug that is primarily oral and not transmucosal as it increased the volume of the premedicant. Zub et al. did not dilute the intravenous formulation of 100μg/mL. They hypothesized that a portion of the drug was most likely absorbed transmucosally, bypassing the hepatic first pass effect. Second, the onset time limitation of 15
minutes which is more appropriate in an outpatient office environment would require a larger initial loading dose to achieve therapeutic levels.

Pharmacologic premedication has a number of advantages compared to non-pharmacologic methods for very anxious children. It has been shown to have greater predictability and less variability among practitioners (Kain et al., 1998b). Management of anxiety prior to induction of GA is an important component in perioperative care. In the pediatric dental outpatient population, the most common indication for treatment under GA is lack of cooperation and extensive treatment need (Vermeulen et al., 1991, Sheller et al., 2003). Thus, non-pharmacologic methods of gaining cooperation for mask acceptance for inhalational induction of GA may have its limitations more often in dentistry than other procedures where anesthesia is a crucial indication for the surgery itself.

The purpose of managing anxiety and gaining cooperation has many benefits beyond the immediate induction period. Parents show greater satisfaction with the overall process and patients show less maladaptive behavior in the post-operative and post-discharge period (Kain et al., 2004b). Midazolam is currently the most popular oral pharmacologic premedicant due to its high efficacy, quick onset, safety profile, and low cost (Kain et al., 2004a). It reliably produces good induction conditions while maintaining a large therapeutic window. The disadvantages of midazolam are lack of analgesia, its intensely bitter taste, emergence behavior, and occasional paradoxical effect (Isik et al., 2010, Bergendahl et al., 2006, McGraw and Kendrick, 1998). An alternative premedication to address the above properties is clonidine, an α-2 receptor agonist.

Clonidine can be formulated as a palatable chocolate syrup and has a similar mechanism of action as dexmedetomidine. Like midazolam, clonidine is also able to reliably create good induction conditions in children (Bergendahl et al., 2006). A review of literature by Bergendahl et al.(2006) regarding use of clonidine as a children’s premedication revealed many favorable outcomes over midazolam. These were decreased salivation, post-operative nausea and vomiting, post-operative agitation after sevoflurane administration, shivering, pain, and sympathetic response to tracheal intubation. The disadvantages were the slow onset time of 50 minutes and possible prolonged sedation exceeding the duration of the procedure. Both slow onset time and
prolonged sedation discourage the use of clonidine in the outpatient office environments where quick turnarounds are desirable (Bergendahl et al., 2006).

Ketamine as an agent for premedication is often reserved for the mentally challenged, the very uncooperative, or the combative patient. It is highly effective both orally and intramuscularly while supporting the cardiorespiratory system. To mitigate ketamine’s dysphoric and sialagogue effect, midazolam and an anticholinergic are often administered at the same time (Cote, 1999) (Petros, 1991). Oral ketamine combined with midazolam has been shown to provide higher success in parental separation, mask acceptance, and better post-operative behavior. Funk et al., 2000 compared three oral regimens consisting of midazolam and ketamine as a single agent or midazolam in combination with ketamine. The doses used were midazolam 0.5mg/kg, ketamine 6mg/kg, and 0.5mg/kg midazolam with 3mg/kg ketamine. The midazolam and ketamine combination demonstrated superior parental separation, induction conditions, and post-discharge behavior compared to midazolam or ketamine as a single agent. Of note, ketamine monotherapy was not as efficacious as the midazolam monotherapy premedication and incidences of vertigo and emesis were significantly higher (Funk et al., 2000).

Dexmedetomidine as an intranasal premedication has been investigated more extensively than the oral route (Sun et al., 2014). In the study by Yuen et. al., 2012, 2μg/kg intranasal dose of dexmedetomidine produced better induction conditions than a dose of 1μg/kg in the 5-8 year age group while the difference was not statistically significant in the 1-4 year age group. The authors recommended the higher 2μg/kg intranasal dose as it had a greater chance of success while the safety profile was not adversely affected (Yuen et al., 2012). In a meta-analysis of dexmedetomidine premedication 8 randomized clinical trials were analyzed and it was concluded that dexmedetomidine was superior to midazolam in regards to parental separation and mask acceptance. However, this meta-analysis may not be comparable to the field of GA for dentistry for the following reasons. Only two studies were for the purpose of dentistry, the age of the patients ranged from 1-18years, and the route of drug administration was intranasal for the majority of studies (Sun et al., 2014).

Mountain et al. compared the efficacy of oral dexmedetomidine at 4μg/kg to oral midazolam 0.5mg/kg as a premedication given to children 30 minutes prior to induction of GA for the
purpose of dental rehabilitation. The authors did not find a statistical significance in their endpoints of parental separation, mask acceptance, and emergence delirium. They found no incidences of bradycardia or hypotension. They concluded that dexmedetomidine oral premedication is comparable to midazolam but studies using higher doses of dexmedetomidine were needed (Mountain et al., 2011).

Although the intranasal route of dexmedetomidine is more popular in literature, the oral route was selected in the present study to draw direct comparison to oral midazolam, its ease and familiarity of administration by the clinician, ability to mask the procedure to the patient, avoid introducing a relatively unfamiliar procedure to the patient, and to avoid the unpleasant sensation of a fluid filled sinus. It is important to note that alpha-2 agonists have many beneficial properties that are not specifically accounted for in clinical trial comparisons to midazolam. Trials to study such effects such as post-operative shivering and antisialagogue effect would be difficult to design as the outcomes would consist of qualitative properties with multiple variables. Dexmedetomidine’s anti-shivering effect has been clinically demonstrated. However, the results are difficult to interpret as there was no control group, no randomization, and no blinding (Blaine Easley et al., 2007). The mechanism of dexmedetomidine’s antisialagogue property is by its sympatholytic and vagomimetic effect. In the literature, qualitative reports of this action are well documented but there are no published studies specifically examining the antisialagogue effect (Abdelmalak et al., 2007).

In this study, similar results were obtained compared to previous studies in that dexmedetomidine produced induction conditions no different to that of midazolam (Mountain et al., 2011, Yuen et al., 2008). The null hypothesis is accepted in that dexmedetomidine will be no different than midazolam in its ability to gain cooperation for mask acceptance for the induction of GA. However, midazolam was found to be superior with respect to its sedating ability as shown by the lower OAA/S score that was statistically significant.

This study differed in context to the previous studies using dexmedetomidine in that it was not used in a hospital environment. Dexmedetomidine was given orally at a relatively high dose of 6μg/kg and was able to create good induction conditions 15 minutes before induction of GA without causing adverse side effects. In conclusion, the findings from this study suggest that high
oral dose dexmedetomidine is a viable alternative to midazolam for the purposes of using premedication for mask acceptance where quick onset is needed. No significant difference was found with respect to ICC but there was a significant difference in sedation as measured by the OAA/S scale. The patients in group D showed good cooperation behavior at induction which was no different to midazolam without being sedated. It could be argued that the primary end point during GA induction and dentistry is anxiolysis leading to cooperation and that sedation is a side-effect as the dentition is accessible by non-surgical methods with cooperation from the patient. It is difficult to recommend the use of one agent over another as the purpose of a premedication is not identical across all cases. Practitioners should assess the need for pharmacologic anxiolysis and additional properties desired from the premedication, parental expectations, and the goal of the premedication for each case.

**Future Directions**

Further studies should be aimed at measuring the level of anxiety after oral dexmedetomidine premedication, the optimal time for effect after oral administration, patient acceptance of the drug, ease of parental separation, and parental satisfaction. If dexmedetomidine is found to produce a high level of anxiolysis without significant sedation, it could indicate a new clinical use within the practice of dentistry. The interval of 15 minutes for premedication effect in this study was chosen from clinical observations in the University of Toronto, Faculty of Dentistry Pediatric Surgicenter where oral midazolam premedication typically requires 10 to 15 minutes for adequate effect. It could be that the ideal time for dexmedetomidine effect may be longer than 15 minutes but short enough that it can still be viable in a context where rapid turnovers are desirable. One of the main advantages of dexmedetomidine is its near non-existent taste profile, yet this was not examined in this study. At our center, patients often complain or resist oral midazolam in children’s Tylenol® or cherry flavored sweet syrup due to incomplete masking of the bitter taste. Dexmedetomidine could improve patient acceptance of the premedication as it is not known to be bitter in taste. Lastly, the decreased level of sedation compared to midazolam may have had an impact in parental satisfaction as they may feel that their child is no different or “not sleepy” after taking a medication. Parents may perceive midazolam as a superior option due to its sedating property that decreases response even when stimulated.
References


Assessment of Alertness/Sedation Scale: study with intravenous midazolam. *J Clin Psychopharmacol*, 10, 244-51.


Appendices

Appendix A – Observer’s Assessment of Alertness/Sedation scale (OAA/S)

<table>
<thead>
<tr>
<th>Response</th>
<th>Speech</th>
<th>Facial expression</th>
<th>Eyes</th>
<th>Composite score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responds readily to name spoken in normal tone</td>
<td>Normal</td>
<td>Normal</td>
<td>Clear, no ptosis</td>
<td>5</td>
</tr>
<tr>
<td>Lethargic response to name spoken in normal tone</td>
<td>Mild slowing or thickening</td>
<td>Mild relaxation</td>
<td>Glazed or mild ptosis (half the eye or more)</td>
<td>4</td>
</tr>
<tr>
<td>Responds only after name is called loudly or repeatedly</td>
<td>Slurring or prominent slowing</td>
<td>Marked relaxation (slack jaw)</td>
<td>Glazed and marked ptosis (less than half the eye)</td>
<td>3</td>
</tr>
<tr>
<td>Responds only after mild prodding or shaking</td>
<td>Few recognizable words</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Does not respond to mild prodding or shaking</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Does not respond to noxious stimulus</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>
Appendix B – Induction Compliance Checklist (ICC)

1. Crying, tears in eyes
2. Turns head away from mask
3. Verbal refusal, says “no”
4. Verbalization indicating fear or worry, “where's mommy?” or “will it hurt?”
5. Pushes mask away with hands, pushes nurse or anesthesiologist with hands/feet
6. Covers mouth/nose with hands/arms or buries face
7. Hysterical crying, may scream
8. Kicks/flails legs/arms, arches back, and/or general struggling
9. Requires physical restraint
10. Complete passivity, either rigid or limp

Each positive sign is given a score of one for a maximum possible score of 10.
Appendix C

Information Sheet

Title of Study:

DEXMEDETOMIDINE AS AN ORAL PREMEDICATION TO FACILITATE MASK INDUCTION FOR GENERAL ANESTHESIA FOR PEDIATRIC DENTISTRY

September, 2012

My name is Dr. Joonyoung Ji, and I am a dentist studying to become a specialist in dental anesthesia, meaning I am being trained to put patients to sleep for their dentistry. I am currently registered in the Dental Anesthesia Master of Science program at the Faculty of Dentistry, University of Toronto. I am doing a study that looks at a drug for use in young children who are about to undergo dentistry while being asleep under anesthesia. The title of the study is: “Dexmedetomidine as an oral premedication to facilitate mask induction for general anesthesia for pediatric dentistry” (Supervised by Dr. Daniel Haas, Faculty of Dentistry, University of Toronto).

The drug that we are looking at is called dexmedetomidine. It goes by the trade name of Precedex® and was approved by Health Canada in 2009. This is a sedative that has already been used to help anesthesia in children. It helps treat anxiety and improve cooperation, before and after the appointment. In this study, we are collecting information only by observation after your child receives a premedication.

Currently, a drug called midazolam is the most commonly used premedication for this purpose. While that drug is adequate in helping these children receive their anesthetic, sometimes it does have a few drawbacks, such as reactions which are opposite to sedation, and a bitter taste. The benefits of dexmedetomidine over midazolam is that it creates a normal sleep state, decreases pain, reduces fear and anxiety, and may possibly work better than midazolam.

This study will be performed at the time of your child’s treatment in the Pediatric Surgicentre and no further appointments or time commitments are necessary. We are accepting healthy children from ages 3 to 8 who are fit for anesthesia and have not been asleep for any prior surgery. At the anesthesia consultation, you will be notified by the resident anesthetist whether
your child needs a premedication and you and your child’s eligibility for this study. You will also have the opportunity to ask any questions and have them answered.

If you choose to participate, your child will either receive the typical sedative (midazolam) or the relatively new sedative (dexmedetomidine) in a sweet solution to drink on the day of treatment. Then, your child will be monitored and observed for 15 minutes by Dr. Ji until start of anesthesia and dental treatment. Your child’s sleepiness and cooperation will be observed and recorded at the end of the 15 minute waiting time and at the start of anesthesia. No further research related actions will be done after this point or during the dental treatment. **Compared to a non-study participant, the only difference in treatment is that your child’s level of sedation and cooperation will be observed and assessed between the time of taking the medication, and the start of the anesthetic.** You will not know which sedative your child received at the appointment but the treating dental anesthesia resident and supervisor will. At the end of the appointment, you can be informed which sedative was used by the supervising dental anesthetist. For this study, no personal or identifying information will be used, recorded, or published. All information will be kept in a safe, locked, drawer in the dental school until the conclusion of the study. Information such as anesthetic records and treatment will be placed in the chart as per good record keeping policy. It is our intention to publish the results in a scientific journal at the conclusion of the study.

You and your child’s participation in this study is completely voluntary and you have the option of withdrawing at any time. **Your participation status will not affect the care for your child.** These are the dental treatment, the delivery of a safe anesthetic, and the decision to use the regular premedication (midazolam) if deemed beneficial. All treatments regardless of participation will be performed in accordance to the Guidelines set by the Royal College of Dental Surgeons of Ontario.

**Risk and Benefits**

As with any sedative medication used in anesthesia, there is the potential for risks and complications. The most common possibilities include disorientation, fatigue, slow heartbeats, low blood pressure, and reactions opposite to sedation. You and your child should not participate if he or she has had an extended stay in a hospital, is unfit for anesthesia in an office, is taking
psychotic medications, has problem with breathing, has heart problems, has a current infection or illness, or has an allergy to the medications being used.

The possible benefit of this study is identifying the relatively new sedative dexmedetomidine as an effective and safe alternative to midazolam for use as a premedication. Your participation in this study can increase our knowledge about dexmedetomidine and potentially benefit children in the future undergoing anesthesia.

**Privacy and Confidentiality**

You and your child’s personal and health information will remain secure, private and confidential and will be used internally within the dental school in the context of this research project. The protection of your personal health information is governed by law under the Ontario *Personal Health Information Protection Act (PHIPA)*. This Act sets out rules that must be followed when collecting, using or sharing personal health information for research purposes. An identification chart number will be assigned to your child so that his or her information will be nameless. None of the data published will identify your child.

**Anonymous paper and electronic data will be stored for two years after publication of study findings.** Data collected from this study will be analyzed and compiled with the intention of thesis dissertation, presentation at scientific meetings, publication in a scientific journal, and/or teaching in educational and academic settings.

**Contact Information**

The following contacts may be kept for your reference:

- If you have any questions about your rights as participants, you may contact the Office of Research Ethics at [ethics.review@utoronto.ca](mailto:ethics.review@utoronto.ca) or 416-946-3273.

- If you have any questions about the study, you may directly email Joonyoung Ji [joj299@mail.usask.ca](mailto:joj299@mail.usask.ca) or call 416-979-4900 ext. 4324

If you are interested in the results of this study, you may also request a summary of the research findings via my email.
Appendix D

Consent Form

Principal: Dr. Joonyoung Ji, D.M.D., M.Sc. Candidate, Dental Anesthesia, Faculty of Dentistry, University of Toronto

Study title: Dexmedetomidine as an oral premedication to facilitate mask induction for general anesthesia for pediatric dentistry (Supervisor: Dr. Daniel Haas).

Purpose of Research: This study investigates whether dexmedetomidine is better than midazolam as a premedication prior to general anesthesia for dentistry.

I ______________________, the legal guardian and/or parent of __________________________ have listened to the explanations about the purpose of the study and what it entails. I have had an opportunity to discuss any concerns or questions that I may have. I am satisfied with the explanation that I have been given. I understand that the possible complications in participating in this study involving dexmedetomidine are similar to other sedatives given for this same purpose. These include disorientation, fatigue, slow heartbeats, low blood pressure, and reactions opposite to sedation.

I understand and am willing to accept the risks to participate in this study. I understand that I nor my child is obligated to complete the study once it begins and that participation is voluntary and that we may withdraw at any time.

Any information that is acquired about my child during this study will be confidential and neither the name nor any other identifying information will be made available to anyone other than the investigators, nor will such information appear in any publications.

I have read and understood the attached information sheet. I have had an opportunity to ask any questions I may have had, and my questions have been answered to my satisfaction.
Date

Signature of Witness

Print Name

Date

Signature of Parent/legal guardian

Print Name
Appendix E – Inclusion Criteria

1. ASA I, II status
2. Need for premedication prior to induction of general anesthetic
3. Mask inhalational induction planned for an intubated general anesthetic
4. Ages 3 to 8 years, inclusive, at the time of the general anesthetic
5. English speaking parent

Appendix F – Exclusion Criteria

1. ASA III status or higher
2. Previous experience of general anesthesia
3. Congenital heart disease
4. Uncorrected cardiovascular disease
5. Midazolam or dexmedetomidine allergy
6. Acute narrow angle glaucoma
7. Diagnosis of neurobehavioral problems, including Autism and Attention Deficit Hyperactivity Disorder
8. Currently taking anti-psychotics, antidepressants, sedative-hypnotics, or erythromycin
9. History or presence of sleep apnea
10. Active respiratory disease
11. Current infection requiring antibiotics
12. Craniofacial anomalies predicting a difficult airway