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# The Use of Midazolam in Paediatric Dentistry: A Review of the Literature

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**Context:** Behaviour management and carrying out dental procedures for very young pre-cooperative, highly anxious or medically disabled children could be a challenging task. Various drugs and methods have been introduced to render treatment for this group of child patients. Midazolam is a benzodiazepine used as an adjunct to behaviour management techniques in the dental treatment of child patients.

**Evidence Acquisition:** To conduct this review of the literature, Pub-Med and Scopus were searched using the following terms: midazolam, oral, transmucosal, intravenous, intramuscular, rectal, premedication, paediatric dentistry, general anaesthesia. Fourty-five published papers relating to the use of midazolam in paediatric dentistry were shortlisted out of an initial 124 publications and assessed according to the "critical appraisal skills programme" criteria. Randomized controlled trials, non- randomized studies, clinical trials and case reports were reviewed with regard to midazolam's indications, contraindications, drug interactions and various administration routes when used as a single sedative agents. Research and reviews based on the single-drug use of midazolam in children with adequate sample size as well as clinical guidelines were included. However, those conducted on adult populations, using poly-pharmacy for sedation and clinical investigations with flaws or non-significant results were excluded.

**Conclusions:** Midazolam could be used as a safe and effective drug for conscious sedation, general anaesthetic premedication and the treatment of seizures during dental treatment. However, further research on paediatric patients would be beneficial.

*Keywords:* Midazolam; Benzodiazepines; Conscious Sedation; Pediatric Dentistry

## 1. Context

Reduction of the pain and anxiety in child dental patients has been an issue for a long time. Although the majority of paediatric dental patients could be managed by conventional behaviour management methods, a fair number of them require pharmacological intervention. Various drugs have been studied in order to overcome this problem. Benzodiazepines are a group of commonly used drugs for this matter. Midazolam is a benzodiazepine which became available in 1983. It is characterized by prompt appearance and short duration of action, exerting an anxiolytic, anticonvulsive, muscular relaxant, and amnesic effect (1).

Its short half-life decreases hangover effects when used as a sedative agent, making midazolam a possible sedative drug for use in paediatric dental patients. Sedative drugs could be administered by a variety of methods. Oral, transmucosal (intranasal, buccal or sublingual), intravenous, intramuscular and rectal routes could be used for administration of midazolam. Its advantageous role in the management of child dental patients will be discussed and reviewed in detail.

Benzodiazepines exert their effect throughout the central nervous system. Specific benzodiazepine receptors are located on neurons in the brain. All benzodiazepine molecules have a common core shape, which could bind to these receptors and in turn, alter an existing physiological filter. Normal passage of information from the peripheral senses to the brain is filtered by GABA (gamma aminobutyric acid) system. GABA is an inhibitory neurotransmitter which is released from the sensory nerve endings as a result of nerve stimuli passing from a neuron to another (2).

GABA attaches to the receptors on cell membrane of the post-synaptic neuron and stabilizes it by increasing the threshold for firing. As a result, the number of sensory messages perceived by the brain is reduced. Benzodiazepines, when administered, prolong the effect of GABA. This reduces the number of stimuli reaching higher centres and results in sedation, muscle relaxation, anxiolysis, amnesia and anticonvulsant effects (2, 3). Benzodiazepines should cross blood-brain barrier in order to reach receptors. Midazolam could reach brain very quickly due to its high lipophilic property (4).

Midazolam is a water soluble, non-irritant benzodiazepine with distribution half-life of 6-15 minutes and elimination half-life of 1.5-2 hours (4). Therefore, it could be a safe and effective medicament in children as its elimination half-life (1.5-2 hours) makes it especially suitable for short-lasting procedures (5-7). It has been shown that children treated under midazolam conscious sedation

will not remember treatment being difficult or unpleasant (8).

The drug is used for two main purposes in a child patient; Conscious sedation and premedication in order to relieve anxiety prior to induction of general anaesthesia. It could also be used as an emergency drug for the control of seizure attacks. In general, the use of midazolam is indicated in children who cannot cope with dental treatment due to high levels of anxiety, young age, learning difficulty or an underlying medical condition.

However, midazolam is contraindicated in children with hypersensitivity to benzodiazepines. It is relatively contra-indicated in patients with acute or chronic pulmonary disease, pulmonary and/or cardiac insufficiency and myasthenia gravis (9).

A major drawback of midazolam sedation is paradoxical reactions. These include disinhibition, hallucinations, agitation, inconsolable crying, restlessness and disorientation especially in younger child patients (4, 9). The incidence of these reactions has been reported to be as low as only 1.4% (10). Certain drugs may interact with midazolam which usually manifests as impeding its metabolism in the liver and increasing or prolonging plasma concentrations. Interacting drugs include erythromycin and clarithromycin, fluconazole and ketoconazole and some antivirals. Midazolam may also enhance the hypotensive effects of calcium channel blockers (9, 11). These should be taken into consideration before administering midazolam to patients.

The main side effect of benzodiazepines which may lead to complications is occasional marked respiratory depression. Therefore, it is vital that oxygen and all required equipment for the management of respiratory depression by positive pressure ventilation are available (9). Decrease in mean arterial pressure, cardiac output, systemic vascular resistance and stroke volume could also be detected which may only exhibit a small fall in arterial blood pressure just after drug administration (3).

Flumazenil is the reversing drug used in order to treat over-sedation, respiratory depression or paradoxical reactions caused by benzodiazepines. No paediatric dose has been recommended by manufacturer and it is not licensed for use in children. Adult dose is 200 micrograms given over 15 seconds and further 100 microgram doses at 60 second intervals if required, up to a maximum of 1 mg. Proportional reduction of dosage in children has been recommended (9). It is worth mentioning that half-life of flumazenil is shorter than that of midazolam. Therefore, re-sedation may occur when patient has already reached home (3).

### *1.1. Conscious Sedation for Dental Treatment*

Conscious sedation has been defined as a technique in which the use of a drug or drugs produces a state of depression of the central nervous system enabling treatment to be carried out, but during which verbal contact with the patient is maintained throughout the period of sedation (12). During conscious sedation no interventions are required to maintain a patent airway, spontaneous ventilation is adequate and cardiovascular function is usually maintained (13, 14). The drugs and techniques used to provide conscious sedation for dental treatment should carry a margin of safety wide enough to render loss of consciousness unlikely (15).

Conscious sedation is used as an adjunct to the behaviour management techniques for treating child patients in the dental setting. It avoids the major risks associated with general anaesthesia and aims for behaviour improvement, apprehension and anxiety reduction and an increase in amnesia (1). In a Cochrane systematic review on conscious sedation in anxious paediatric dental patients, the authors were not able to come to a conclusion on the most effective drug or method of sedation for anxious children (16). However, the use of midazolam is a possible option for conscious sedation in paediatric dentistry.

Children who have to undergo conscious sedation with midazolam should be carefully selected. ASA (American Society of Anesthesiologists) class I or ASA class II patients may be candidates for conscious sedation as outpatients. However, ASA class III and IV patients must have conscious sedation in a hospital setting along with consultation with their medical doctor (12, 13).

As mentioned earlier, various routes of administration could be considered for the use of midazolam in conscious sedation.

Oral route of administration is the most widely used in children. It is easy to administer and has decreased chances of allergic reaction. However, when taken orally, onset and duration of action of midazolam is prolonged, gastric absorption is unpredictable and a stable sedative level is attained 30 minutes following drug intake (17-19).

Midazolam's bio-availability is decreased when it passes portal circulation in order to reach systemic circulation. Therefore, a higher oral dosage (0.3-0.5 mg/kg up to 12 mg maximum) is required (9). Oral route of administration is useful in needle phobic young children who cannot cope with dental treatment as well as patients with learning difficulties or other medical conditions. However, the oral intake of the drug is completely dependent on the compliance of the child patient and determination of the appropriate dosage is difficult as some of the solution may be spat out by patient (9).

There is no oral preparation available. Therefore, the IV solution is mixed with a juice in order to mask the strong bitter taste and improve acceptability in child patients. For optimal sedation, the drug should be administered 10-20 minutes prior to commencement of dental treatment.

One study compared Pepsi cola, 10% sodium citrate, pomegranate juice and grapefruit juice as mixtures with midazolam for oral intake concluding that drug ingestion was simpler and sedation was more effective when

midazolam was added to sodium citrate (20).

Another study on the use of oral midazolam for sedation of child patients reported that the technique was well tolerated by children and their parents. However, some children became upset in recovery due to the numb sensation of their lip caused by local anaesthtics. Oral midazolam sedation was mentioned to be safe and effective although some patients became agitated during or after treatment (21).

Wilson et al. (22) did a randomized, controlled cross-over trial on the effectiveness of 0.5 mg/kg oral midazolam sedation for orthodontic extraction of permanent teeth. They concluded that oral sedation with midazolam was safe and acceptable in 10-16 year old patients. In another study, however, in 5-10 year old children oral midazolam was compared to nitrous oxide inhalation sedation. Oral sedation proved to be safe and effective but it was not the method of choice for all patients (23). This may have been due to the unpleasant taste of the oral solution or paradoxical reactions.

Transmucosal, intranasal route of administration is another effective method in child patients. The sedative effect is observed within five minutes of administration of 0.1-0.2 mg/kg midazolam intranasally. Preparations to be used via the nasal route are made to order and administered with a metered nasal spray.

Studies have shown the rapid onset (5-10 minutes) of intranasal midazolam sedation, as well as short recovery time following administration (17-19, 24). Intranasal midazolam is rapidly absorbed from the nasal mucosa into the circulation and the peak effect occurs sooner when compared to the oral route. Therefore, nasal route could be a better option in children. Despite rapid onset and ease of administration, large volume of the solution can cause coughing, sneezing and expulsion of the drug (9). The use of intranasal midazolam is associated with nasal irritation and unacceptability in a child with nasal discharge (25) and could lead to occasional respiratory depression (26).

Karl et al. (27) compared intranasal and sublingual routes of administration of midazolam in child patients 6 months to 10 years old. Their results showed that sublingual administration of midazolam was as effective as intranasal route. However, the sublingual route was better accepted by child patients. The compliance of the 6 month old patients with sublingual lozenges was not clearly addressed in this study.

Intravenous (IV) route is one of the most common routes of administration of midazolam. The advantages of IV midazolam sedation in general include rapid onset (3-4 minutes), adequate patient cooperation on careful case selection and good amnesia. In paediatric dentistry, however, it may only serve as a possible option in anxious adolescents (28). The fact that cannulation has to be carried out may make it a less favourable route of administration in very young children. The recommended dosage for IV midazolam in children is 0.25-1.5 μg/kg/min. The drug must be administered slowly so that its effects are assessed and overdosage is avoided (4).

Robb et al. (28) reported 18 cases of conscious sedation with IV midazolam in children 11-15 years old. No loss of consciousness or fall in oxygen saturation levels was observed and therefore, indicating the safe use of this drug for conscious sedation.

Intramuscular (IM) route of administration has not been broadly studied in paediatric patients. In children, the disadvantages of this technique outweigh its advantages. A stable level of sedation is attained 30 minutes following drug administration (17-19) and giving IM injection to a child patient is unpleasant and most probably not acceptable.

Rectal administration of midazolam has been demonstrated to be effective and safe for sedating child patients, with an onset of action of as short as five minutes (29, 30). However, interruption of absorption by defecation and lack of patients' and parents' acceptance are major disadvantages of rectal midazolam (24).

Midazolam sedated patients via any of the above mentioned routes of administration should be monitored for vital signs including respiration and blood pressure, especially when midazolam is administered via the oral or IV route. Using pulse oximeter throughout sedation is mandatory in order to take action in case of any complication. Oxygen saturation levels below 90% should be investigated and the cause corrected.

### *1.2. Premedication for Dental General Anaesthesia (GA) Induction*

General anaesthesia induction could be challenging in a highly anxious or a pre-cooperative patient as well as a patient with a medically compromising condition or learning difficulty. Various medications have been advocated in order to ease child separation from parents and allay anxiety during different phases of perioperative period.

The ideal premedication agent for children should have acceptable and atraumatic route of administration, rapid and reliable onset, minimal side effects and rapid elimination (31).

It has been reported that midazolam fulfills the above mentioned criteria and therefore, could be used as a premedication agent in child patients undergoing dental treatment under general anaesthesia (6, 32, 33). Wilton et al. (34) first described the use of intranasal midazolam as premedication for GA. Weber et al. (35), in a prospective randomized double-blind clinical trial, used intranasal route of administration for midazolam and concluded that it was an appropriate premedication in preschool children.

A placebo-controlled trial investigated the reaction time and psycho-motor coordination of children undergoing general anaesthetic before discharge and at 48 hours when premedicated with 0.2 mg/kg buccal midazolam to a maximum dose of 10 mg. One hundred and seventy nine children took part in this study, each one receiving buccal midazolam or placebo prior to GA induction. Results showed that reaction time was significantly slower and

the psycho-motor coordination was also significantly impaired in the midazolam group. Midazolam was also associated with anterograde amnesia before discharge and at 48 hours (36). This indicates that impairment of children's cognitive function and amnesia lasting for up to 48 hours post-GA should be expected when midazolam is used for premedication.

In a more recent study, however, the authors showed that 0.2 mg/kg buccal midazolam reduced anxiety in most patients but did not have an effect on psychological morbidity, induction behaviour and subsequent dental attendance (37).

Kain et al. (38) reported that children premedicated with oral midazolam showed less negative behavioural changes during the first postoperative week in compare to children in the placebo group.

It has been suggested that high levels of trait anxiety could be a contraindication to the use of oral midazolam as a premedication for general anaesthesia. In addition, the use of midazolam prior to GA for a child with low state baseline anxiety is deemed unnecessary (39). With regard to recovery and discharge times, Viitanen et al. (40) showed that the use of oral midazolam as premedication for propofol-induced GA in 1-3 year old children delayed early recovery but did not affect discharge time. The authors also concluded that oral midazolam did not improve the quality of recovery.

A review of literature on randomized controlled trials available on midazolam oral premedication studied the effects of midazolam on separation anxiety, induction anxiety, emergence agitation, recovery times, long term outcomes and dose and timing of the drug. The authors concluded that premedication with oral midazolam reduced anxiety in children at separation from parents and anaesthesia induction. However, there appeared to be no evidence on moderation of emergence agitation, the awakening times were slightly delayed but no serious side effects were reported (41). Last but not least, midazolam could be used as an emergency drug in the dental setting;

### *1.3. Control of Acute Seizures in Epileptic Children in the Dental Setting*

A prolonged convulsive seizure is the most common neurological medical emergency with poor outcome. An ideal anticonvulsant should be easy to administer, effective, and safe as well as having a long lasting effect. IV or rectal benzodiazepines have generally been used as first line drugs. In young children however, gaining IV access on the dental chair and during a seizure attack is difficult if not impossible. Transmucosal midazolam has been recently suggested as a possible drug for the management of seizure attacks on the dental chair and at home (42).

Transmucosal (intranasal and buccal) route of administration has mainly been studied and compared with IV or rectal diazepam. Holsti et al. (43), in a prospective randomized study on 358 patients, compared the use of intranasal midazolam with rectal diazepam at home for the treatment of seizures in children with epilepsy. There was no difference among the two drugs in terms of efficacy as a rescue medication. However, ease of administration and overall satisfaction was higher with intranasal midazolam.

Another recent study with 98 participants compared the use of buccal midazolam with rectal diazepam. Results showed that midazolam was as effective as diazepam. However, midazolam was less time consuming and more parents were satisfied with buccal route of administration (42). The buccal administration dose of 0.3 mg/kg (Epistat) has been recommended and the effects are observed within five minutes (36). A Cochrane review concluded that buccal midazolam was successful in the treatment of seizures in almost double the number of that for rectal diazepam. The authors mentioned that intranasal midazolam was as effective as IV diazepam in the treatment of prolonged febrile convulsions, suggesting that when IV access is unavailable buccal midazolam is the treatment of choice (44). It is worth mentioning that only four studies were included in this systematic review. However, more studies have been carried out since then and the use of midazolam for this matter has been proven to be effective (45).

## 2. Evidence Acquisition

Pub-Med and Scopus were searched using the following terms: Midazolam, oral, transmucosal, intravenous, intramuscular, rectal, premedication, paediatric dentistry, general anaesthesia. Randomized controlled trials, non-randomized studies, clinical trials and case reports were reviewed with regard to midazolam's indications, contraindications, drug interactions and various administration routes when used as a single sedative agents.

## 3. Conclusions

In conclusion, midazolam could be used to help child patients cope with dental treatment and undergo general anaesthetic as well as being a life-saving drug in case of a seizure attack (Table 1). Midazolam, like any other drug, has its own side effects which could lead to very serious complications such as respiratory depression (9). Therefore, clinicians should be familiar with the administration of midazolam and handling its complications in case of an emergency.

Monitoring vital signs at all times during sedation is of great importance as proper action could be taken in order to reverse over-sedation. Midazolam reversing drug, flumazenil, should always be present in the dental setting where midazolam sedation is being carried out. In brief, IV and IM routes of administration could only be applied to adolescents. Oral route is associated with the least predictable results. Buccal or sublingual administration highly relies on patient cooperation. Rectal route have proven to be successful but it is not an acceptable route to most parents and children. However, intranasal route seems to be the most reliable if minor volumes of the drug are given at a time.

**Table 1.** Summary of Midazolam Use in Paediatric Dentistry

| Midazolam Use | Number of Papers Reviewed | Grade of Evidence (46) | Conclusions |
|---|---|---|---|
| **Dental sedation** | 24 | I, II, III | 1) oral, transmucosal and intranasal routes of administrations may be best options for young patients: a) oral sedation depends on stomach uptake; b) transmucosal and intranasal sedation requires an extent of patient cooperation.<br>2) IM and IV routes of administration are options of choice for adolescents.<br>3) rectal route of administration is effective, but may not be acceptable for many patients. |
| **Premedication for general anaesthesia** | 16 | II, III, V | 1) premedication recommended for children with high anxiety level.<br>2) Parents should be forewarned regarding impaired cognitive function until 48 hours post-treatment. |
| **Control of seizures** | 5 | I, II, III | midazolam use recommended for this purpose |

The chances of having paradoxical effects in a child sedated with midazolam are high. Therefore, parents should be forewarned about this matter (21). Premedication for general anaesthetic follows the same rules as conscious sedation in terms of routes of administration, case selection and complications. However, parents should be warned about impaired cognitive function until 48 hours post-treatment (36).

The use of buccal midazolam in treating acute seizures on the dental chair is a great improvement and the benefits of this drug definitely outweigh its disadvantages in this particular case. Midazolam is a drug with various uses in paediatric dentistry and any paediatric dentist, if not confident in using it, should at least be aware of its risks and benefits in order to discuss it as an available option to parents so that referrals could be made.

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