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Dentistry

SEDATION WITH MIDAZOLAM IN PEDIATRIC DENTISTRY: A REVIEW

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ABSTRACT **Research question:** To find out the preferred route of administration and dosage of midazolam for managing uncooperative children in pediatric dental setting?

Search strategy (databases searched, key words): Ebsco host, Google scholar, PubMed

Results: This review discusses various aspects of midazolam sedation which includes advantages of various routes of sedation and range of midazolam dosage, its antagonist and combination with other sedating drugs.

Discussion: In most dental situations, fearful and uncooperative pediatric dental patients can be managed with non pharmacological behavioral management techniques. But whenever these strategies fail, pharmacologic sedation or anesthesia came into play. Midazolam is one of the most commonly used sedating agent in children due to its advantages such as safe to use, rapid onset of action and property of retrograde amnesia. This review also includes adverse effects and contraindications for midazolam sedation.

KEYWORDS : Midazolam, dosage, routes, pediatric dentistry, sedation

1. INTRODUCTION

The major challenge for a pediatric dentist is to overcome the fear and anxiety in the child's mind.[1] To manage such children various behavior modification techniques have been employed which includes both non-pharmacological and pharmacological management techniques. Children who have highly uncooperative behavior are seen to be best managed pharmacologically[1] by general anesthesia, deep sedation and conscious sedation.[2]

General Anesthesia requires more time, needs special training, a high level hospital setup and high cost. Therefore, nowadays conscious sedation is accepted as an alternative because it is more convenient and economical for both the patient and the operator.[3] Short-term sedation in uncooperative children by non-invasive route of drug administration may be beneficial for diagnostic and painful procedures.[2] For safe and effective outpatient procedural sedation, it is essential to have knowledge about medications and their side effects if over sedated.[4]

One of the most common pharmacologic agents used for sedation in dentistry is midazolam. It is an imidazo type, short acting and lipid soluble member of benzodiazepine which has working time of almost 25 minutes.[5] The recommended dose of midazolam for oral administration is 0.25 to 1.0 mg/kg in pediatric patients with maximum of 20 mg.[5] Oral midazolam has its first pass metabolism in the liver by microsomal oxidation reducing its bioavailability to 35-44%.[6] The property of rapid absorption and metabolism due to its lipophilic nature produces rapid onset and recovery.[7]

Midazolam is found to be an ideal agent for sedation in pediatric patients due to its properties of causing anterograde amnesia, anxiolytic, sedative, muscle relaxant, hypnotic and anticonvulsant effect.[6, 7] This agent works by enhancing the effect of GABA (an inhibitory neurotransmitter).[6] It also increases uptake of chloride ions and hence reduces the excitability of neurons.[6] It is also equally effective as diazepam in treating seizures in children and can be used as an optimal choice for patients with status epilepticus.[8]

Trans mucosal routes such as sublingual, rectal and intranasal routes have gained popularity mainly as a preanesthetic medication. The high vascularity of the nasal mucosa and high permeability of the sublingual mucosa coupled with avoidance of first pass metabolism ensures higher systemic drug absorption and bioavailability.[9] When midazolam is administered by intranasal route, a dose ranging from 0.2 to 0.5 mg/kg can be used for conscious sedation.[2] The newer route of administration for midazolam is the buccal aerosolized midazolam with advantage of being more acceptable to patients and ease of administration.[10]

The common side effects of midazolam include nausea and vomiting, dizziness, headache, vertigo, diplopia, enuresis, hyper salivation, cardiac arrest, anaphylaxis, respiratory depression and arrest.[11]

Flumazenil is a pharmacological reversal agent of midazolam. It antagonizes the sedative and hypnotic effects in low dose while in high dose it antagonizes the anxiolytic and anticonvulsant effects of midazolam.[12]

1.1 Historical Background

Midazolam was first synthesized in 1976 by Dr. Armin Walser and Fryer at Hoffmann-LaRoche, Inc. in the United States.[27] Armin Wasler was a Swiss chemist who worked for the Hoffmann-LaRoche pharmaceutical company throughout his long career. He and his coworkers published his work in a series on quinazolines and 1, 4-benzodiazepines in 1978.

The anticonvulsant properties of midazolam were investigated in the late 1970s and it emerged as a safe and effective treatment for status epilepticus in the late 1990s. It became the most commonly used benzodiazepine for anesthesia by 2010.

In 1984, it was approved by the Food and Drug Administration (FDA) as a water soluble injectable sedative. In the United States, midazolam was initially famous by its trade name Versed.

1.2 Properties

Midazolam, a water soluble quick-acting imidazobenzodiazepine drug of benzodiazepine class with no active metabolites.[2] It is a γ-amino-butyric acid (GABA) receptor inhibitor[13], a safe and effective ultrashort acting sedative, amnesic and anxiolytic used for moderate sedation in pediatric dental care in patients who are candidates of general anesthesia.[29]

It has twice the strength and a half-life 10 times shorter than diazepam.[24] It has a reduced half-life of about 1.75 hours, is rapidly absorbed in the gastrointestinal tract, produces its peak effect in about 30-90 minutes[21], has high lipophilicity and a pH of 3.5.[27]

However, due to its high lipophilicity and high metabolic clearance, a short time of activity is required.[31] It causes less pain at the site of injection compared to other benzodiazepine, such as lorazepam and diazepam.

Midazolam is mainly metabolized by the liver, facilitated by microsomal oxidation which involves binding of the CYP450 enzyme to midazolam, carrying it through an electron transport chain, and releasing an oxidized form of the drug, H2O and the CYP450 enzyme.

This oxidized drug is generally hydrophilic, therefore less commonly penetrate cells and is more easily excreted. **CYP3A4** is a member of the CYP450 family and is the mainstay enzyme involved in midazolam metabolism.[27]

Oral midazolam is rapidly absorbed as most patients demonstrated a satisfactory degree of sedation and anxiolysis within 10 minutes of drug administration and it becomes more effective as time increases (11-20 minutes). According to studies by various authors, satisfactory sedation and anxiolysis appear to last for up to 40 to 45 minutes.[23]

1.3 Composition:
Midazolam comes under different trade names like Versed, Hypnovel, and Dormicum.

Each milliliter of midazolam contains:
- 1 mg/ml or 5 mg/ml midazolam hydrochloride
- 0.89% sodium chloride
- 0.019% edetate disodium
- 1% benzyl alcohol as preservative

2. Route of administration of Midazolam:
Several types of drugs and routes of administration (e.g. oral, anal, intravenous, intramuscular and intranasal) have been tested for sedating the pediatric dental patients.[14] Now-a-days, Midazolam is the most common drug to be used as intravenous (IV) sedative agent in dental practice but it can also be used through nasal, mucosal, muscular and oral routes.

2. 1. Oral Route
Oral route of midazolam administration is found to be the most effective, long lasting, fast acting and easiest for sedation in children as perceived non-threatening to them.[26] It is complicated by variable absorption in gastrointestinal tract and also by oral route, it is difficult to titrate the dose of drug to produce desired effects.[21] The ideal oral sedative agent should be easy to deliver, titrable, safe, effective, reversible, have a fast onset and no cardiorespiratory effects but no such agent exist till now.[24]

It is recommended that oral sedation medications should be administered empty stomach and the traditional psychological behavior management techniques should be used before and during oral drug administration to decrease the anxiety levels as it also hampers the gastric emptying. Due to the hepatic first-pass metabolism, only 40-50% of orally administered dose of midazolam reaches the systemic circulation while parenteral routes of drug administration result in higher bioavailability and rapid onset times. Drowsiness has been noticed after 15 minutes of drug ingestion.[21]

2.2 Intramuscular route
Midazolam is also rapidly absorbed after **intramuscular** (IM) injection and does not require refrigeration, therefore, less expensive than lorazepam (drug used for epileptic seizures in children).[8]

2.3 Intranasal route
When the clinical situation requires a faster action, peak and recovery time, the **intranasal route** should be the most preferred choice. Patients who receive oral midazolam showed improved crying and overall behavior early in the appointment compared to those who receive intranasal midazolam.[18] The **intranasal route** of administration of midazolam is preferable among other routes since it obviates the need for intravenous access, easily accessible and increase the general behavior rating of children based on Houpt rating scale.[14] Fukuta showed that children who had previously displayed combative and uncooperative behavior shown a sedative effect when given intranasal dose of midazolam.[18]

The most common side effect during intranasal administration of the midazolam was coughing due to entrance of midazolam solution into nasal foramina.[14] It has a rapid onset of action (4-5 minutes) as previous studies have found that therapeutic levels of midazolam in the cerebrospinal fluid indicate a more rapid rate of absorption through intranasal administration compared to oral route, due to the rich vascular plexus of nasal cavity that communicates with the subarachnoid space with the help of olfactory nerve.[2]

Intranasal method of midazolam administration involves a path which have an immediate absorption into the bloodstream because of rich vascularity of nasal mucosa and therefore increased drug bioavailability without the hepatic first pass metabolism effect. This technique of sedation is simple to use in children and effective which requires minimal cooperation from patient [30] as well as short recovery period.[14] A mucosal atomizer device (MAD) delivers the drug via a fine spray over a broad surface area in the nasal cavity and also reduces the sneezing and coughing compared to other devices.[2]

2.4 Buccal route
Another route of midazolam administration is the **buccal route** (0.5 mg/kg) [8] as drug absorption through buccal mucosa occurs rapidly, because the mucosal surfaces are relatively permeable and rich in blood supply, providing the means for rapid drug transport to the systemic circulation. Also, the stratum corneum layer of epidermis which is the major barrier to absorption of drug across the skin, is absent in buccal mucosa. There is high bioavailability of drug due to lack of the first pass effect of the liver.[28] Buccal midazolam is more successful according to Scott et al in controlling seizures in children.[8] While administrating the drug through the buccal route, area between the primary first and second molars in the buccal vestibule was used to give injection on the side opposite to the site of the local anesthetic injection.[28]

3. Dosages of Midazolam
The Standard Dental Advisory Committee stated that the standard, recommended technique for intravenous sedation is the use of a titrated dose of a single benzodiazepine and the use of fixed or more rigid doses will be unacceptable as success is directly related to titration according to the individual patient's needs. Thus, the dose of midazolam required for conscious sedation will vary between patients due to factors such as age, gender, anxiety, social habits, procedure performed and medical conditions of the patient.[25]

Prior to December 2008, midazolam was routinely supplied as ampules of 10mg/5ml (2mg/ml), usually drawn up into a 5ml syringe. But after the Rapid Response Report published by the National Patient Safety Agency in December 2008, these 'high strength' ampules of midazolam were replaced with a lower concentration of 5mg/5ml.[25] This change in midazolam concentration decreased the average titrated dose of midazolam when used intravenously.

Oral premedication with benzodiazepines such as midazolam is popular in pediatric dental settings to create an optimal working environment for the anxious child and dentist during treatment.[20] A single oral dose of 1mg/kg is found to be effective dose in children with a maximum of 20 mg in total by Klinberg et al.[33] Wilson et al suggested the use of 0.5 mg/kg of oral midazolam for sedation.[20] However, 0.5-0.75 mg/kg was shown to be effective in children to reduce both separation and induction anxiety.[17, 16] Midazolam dose of at least 0.30 mg/ kg was associated with more cooperative behavior as studied by Azevedo et al and a mean dosage of 0.32 mg/kg achieved satisfactory results as stated by Gallardo et al.[24] Oral midazolam is safe and effective in 2 to 4 year old children when given in dosage of 0.2 to 0.4 mg/kg.[24] While, Jing et al stated that dose range of 0.5-0.75mg/kg is safe and effective in children of three years and younger. Oral midazolam successfully sedated children of 11-13 months when it was administered in dosage of 0.5mg/kg.[33]

Day et al found that an effective dose of 0.5-0.7mg/kg can increase the success rate to as high as 91% while this rate drops to 65% when dose is lowered to 0.2-0.3mg/kg with a statistically significant difference.

Midazolam is rapidly absorbed after **intramuscular (IM)** injection (0.2 mg/kg IM).[8] In a study by Lee –Kim, children's general behavior were found to be similar in both intranasal (0.3 mg/kg) and per oral (0.7 mg/kg) sedation but more child movement and less drowsiness were shown in IV sedation.

In a study by Fukuta et al, sedative effect of 0.2 mg/kg of **intranasal** midazolam administration in 4 to 21 year-old uncooperative mentally challenged patients reported significant changes in behavioral patterns of the patients. But in a study by Rakaf et al, the effect of administration of 0.5 mg/kg of intranasal midazolam produced greater sedation and easier acceptance of treatment compared to the other two doses of 0.3 and 0.4 mg/kg. The mean working time for intranasal midazolam was found to be 29.3(±11.6) minutes.[30] INM (Intranasal midazolam) was shown to be effective in doses ranging from 0.2 to 0.5mg/kg.[2] Other authors found that 0.2 mg/kg of midazolam produced more advantageous results than 0.3 mg/kg of midazolam when administered

intranasally.[24]

In a study by Somri et al, greater number of children showed excellent behavior with higher doses of midazolam (0.75, 1mg/kg) compared to 0.5 mg/kg.[20] A thirty minutes interval between administration of drug and start of the treatment is required to produce desired deeper levels of sedation in children.[24]

4. Combination of midazolam with other drugs:

There are different combinations of sedative drugs used for oral premedication. Oral midazolam when used alone reported an efficacy rate from 40% to 75% during procedural sedation of pediatric dental patients.[19] The shorter duration of sedation offered by midazolam in spite of its wide usage, can be a major limiting factor in pediatric dental patients and to resolve this problem, numerous workers have combined midazolam with a wide range of drugs.[19]

One of the combination of oral midazolam with **hydroxyzine** which is used to produce deep and extended sedation. Hydroxyzine is a long acting, antivomiting and anti histaminic agent with no reported complication.[33] Sedative action of midazolam begins 20 minutes after oral administration in children. Combination of hydroxyzine with midazolam help to extend sedation time long enough for conduction of dental procedures[33] and also prevent nausea and vomiting during dental treatment in children.[26]

Nasal administration of **nitrous oxide** and oxygen inhalation along with benzodiazepines in the form of a cocktail was found to boost up the sedative levels during the child's dental visit and also maintains the oxygen levels.[30]

In a study by Chiaretti et al, administering **lidocaine** spray prior to the administration of intranasal midazolam, as previously suggested by Lugo et al, prevented pediatric patients from experiencing unpleasant nasal sensations and bitter taste.[2]

The short-acting opioids such as **fentanyl** and sufentanil are now preferred for medical and surgical procedures over the longer-acting agents, such as morphine, meperidine, and hydromorphone. Fentanyl is a potent opioid analgesic with rapid onset, reversibility, intermediate duration (30–45 minutes) and rapidly absorbed across any biological membrane due to its lipophilic nature. Due to the poor oral absorption of fentanyl, oral transmucosal route of fentanyl citrate (OTFC) administration was considered as preferred option to deliver fentanyl non-invasively in children. In uncooperative children who do not accept trans mucosal route of fentanyl citrate, another viable option will be submucosal route as this route provide rapid onset, technique insensitive and reach plasma levels comparable to that of intravenous sedation. It is due to the rich blood supply of the oral mucosa and bypass of the hepatic first pass metabolism. The result of a study by Pandey et al indicated that the combination of oral midazolam and submucosal fentanyl may be considered as an effective alternative method to provide extended period of sedation in uncooperative and combative pediatric patients requiring dental treatment.[19]

Miller recommended a dose of 6-10 mg/kg is optimal for oral **ketamine** and 5-6 mg/kg optimal for nasal ketamine. A combination of 0.2-0.75 mg/kg midazolam with 3-10 mg/kg oral ketamine is indicated for children.[30] Ketamine and midazolam combinations are not available in the Indian market for oral administration and therefore various syrups were made up of (levulose 40.5%, dextrose 34.02%, sucrose 1.9%, water 17.7%, and gum and dextrin) to bring the volume to 10 ml and mixed with honey to mask the bitter taste of drug.[16]

Remifentanil is another synthetic narcotic agent with a strong analgesic effect which decreases the risk of apnea during recovery, but, it has a short duration of action. Because it results in minor changes in cardiac waves and leads to rapid recovery, therefore, it is a good choice for cardiac and debilitated patients. Combination of remifentanil with midazolam and propofol during intravenous sedation increases forgetfulness and a less recovery time of 9.23±2.77 minutes after the treatment procedure compared to midazolam alone.[32]

5. Antagonist of Midazolam:

Flumazenil is believed to be an antidote of midazolam which controls the adverse reaction of midazolam, reversing the sedative effects and reducing amnesia.[33] Chloral hydrate has no such antidote to control its adverse reactions. Hence, midazolam has advantage of having flumazenil as antagonist.[26]

6. Adverse effects of midazolam:

Most serious adverse event is respiratory compromise in pediatric dental setting. Children became drowsy after drug administration and some fell asleep. Drowsiness and reduction of anxiety both contribute to the effectiveness of midazolam in producing sedation by increasing the child's threshold of response to painful stimulus. However, some of the children became euphoric after the onset of drug action in a study by Mazaheri et al.[14]

Midazolam administration lead to drowsiness combined with restlessness and unwanted behaviors in some children which is known as a paradoxical response (drug-related anxiety as a side-effect).[14]

7. Contraindications

Midazolam is contraindicated in patients who have high risk of airway adverse events, for example, gastroesophageal reflux, snoring, acute reactive airway disease, obesity, stridor, sleep apnea etc. It is avoided in anemic patients and person with altered mental status and with gastrointestinal disorders.[20]

Injectable midazolam hydrochloride is contraindicated in patients with a known hypersensitivity to the drug and in patients with acute narrow-angle glaucoma. It may be used in patients with open-angle glaucoma only if they are receiving appropriate treatment.

Midazolam hydrochloride is not used for intrathecal or epidural administration due to the presence of the preservative benzyl alcohol in the dosage form. Therefore, midazolam hydrochloride is contraindicated for use in premature infants because the formulation contains benzyl alcohol (causes gasping syndrome).

8. CONCLUSION

The performance of painless procedures for children is one of the key factors in establishing a good rapport. Management with medication can be used for children who are lacking cooperative ability. Midazolam is one of the commonly used oral sedative agent in children. The properties such as safety of use, rapid onset and some degree of amnesia make it a desirable sedative agent in children. Buccal midazolam sedation is acceptable route for short dental procedures in a dose of 0.5mg/kg. A thorough knowledge of different types of drugs, dosage, pharmacokinetics and pharmacodynamics can help a dentist render painless treatment to aggressive and fearful child.

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