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Conscious Sedation by Midazolam and Ketamine in Pediatric Dentistry – A Review

Sarvesh Kumar J[1], Mahesh Ramakrishnan[2] and Murugaiyan Arun[3]

[1]*Saveetha Dental College and Hospitals Saveetha Institute of Medical and Technical Sciences Saveetha University, Chennai-77, India*

[2]*Reader Department of Pedodontics and Preventive Dentistry Saveetha Dental College and Hospitals Saveetha Institute of Medical and Technical Sciences Saveetha University , Chennai-77, India*

[3]*Senior lecturer Department of Oral and maxillofacial surgery Saveetha Dental College and Hospitals Saveetha Institute of Medical and Technical Sciences Saveetha University, Chennai-77, India*

ABSTRACT

Management of an uncooperative behaviour is important in treating a child in a dental office. Young, uncooperative children needing extensive dental treatment are difficult to manage, for these children, conscious sedation or general anesthesia are the primary treatment options that allow comprehensive restorative dental care. To control the pain and anxiety in pedodontic patients, pharmacologic sedation like anesthesia and analgesia are commonly used. Safe sedation of a pediatric patient requires a thorough knowledge of the pharmacokinetics and pharmacodynamics of the drugs used to sedate the patient and the skills necessary to deal effectively with potential adverse events as a result of the sedation. conscious sedation can be very supportive in allying anxiety, uneasiness, fear and minimizing an uncooperative child's attempt to resist treatment procedures. There are a variety of drugs available that can be used for conscious sedation for dental office procedures. Pediatric sedation technique should ideally be customized for the patient and the procedure to be performed. The present review discusses the various aspects of conscious sedation and its application in pediatric dentistry

INTRODUCTION

Management of children for various dental procedures in dental offices is very challenging. The behavioral problems are commonly seen in children under the age of 6 years due to various elements such as immature reasoning, restricted coping skills and anxiety(Henry and Jerrell, 1990; Swetah and Ramakrishnan, 2019). Conscious sedation is defined as a controlled state of low consciousness that conserves protective and unconditioned reflexes, permits continuance of a patient's airway impartially and allows the patient to communicate appropriately to physical and verbal stimuli(Kauffman et al., 1992).

Procedural conscious sedation includes providing an adequate level/degree of sedation whereas decreasing pain and anxiety, maximizing amnesia, curtailing the potential for adverse drug-related events, monitoring and governing behavior, and sustaining a stable cardiovascular and respiratory status. Sedation drugs can be administered through various routes such as oral, inhalational, nasal, intramuscular, subcutaneous, and intravenous routes(Mistry and Nahata, 2005).

The primary use of pharmacological sedation is to modify or eliminate negative behavior and allow the child to

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cooperate(McComb et al., 2002),improve the patient's behavior, reduce apprehension, minimize the negative psychological response toward treatment by reducing anxiety, and maximize amnesia potential so as to control behavior during dental procedure.(Coté, 2001) Sedative drugs may be administered by oral, inhalation, rectal, submucosal, intramuscular, or intravenous routes. The selection of techniques is often made as a matter of clinical judgment. Oral sedation is regarded by many dentists to be the simplest and most convenient sedation method for managing uncooperative children, since it is easy to administer and there is no need for nasal hood or injection.(Wright and McAulay, 1973).

Our department is passionate about child care, we have published numerous high quality articles in this domain over the past 3 years (Govindaraju et al., 2017a, 2017b; Jeevanandan et al., 2019; Jeevanandan and Govindaraju, 2018; Nair et al., 2018; Panchal et al., 2017; Veerale Panchal et al., 2019; V. Panchal et al., 2019; Ramadurai et al., 2019; Ramakrishnan et al., 2019; Ravikumar et al., 2017, 2018, 2019; Ravindra et al., 2018, 2019; Samuel et al., 2020; Subramanyam et al., 2018; Vignesh et al., 2019; Vishnu Prasad et al., 2018). With this inspiration the present review was conducted to discuss the advantages of conscious sedation by midazolam and ketamine in pediatric dentistry.

Sedative Drugs: The use of sedative drugs alongside local anesthesia is often appropriate to reduce anxiety and fear among patients. There are a number of sedative drugs that can be used for dental procedures, midazolam belongs to benzodiazepine groups that is used as a short and fast acting drug prior to general anesthesia or several other medical diagnostic approaches(Golpayegani et al., 2012). On the other hand, several other studies(Chudnofsky et al., 2000; Karapinar et al., 2006; Sener et al., 2011; Shende et al., 2003; Warner et al., 1995), have looked at the sedative effects of similar drugs used along with midazolam with a synergic effect to reduce the required dose of midazolam. Ketamine and midazolam combination has already been used successfully for the surgical treatment of young fearful and anxious children (Chudnofsky et al., 2000; Golpayegani et al., 2012; Sener et al., 2011).

Midazolam: The resultant effects of midazolam in children under sedation for dental procedures have been studied in a number of projects, and midazolam is now the standard agent for conscious sedation during pedodontic treatments (Erlandsson et al., 2001; Jensen, 2002; Jensen and Matsson, 2002; Lindh-Strömberg, 2001; Yanase et al., 2009). Midazolam is a short-acting benzodiazepine with quick onset, shorter term of activity and negligible symptoms. The intramuscular prescribed amount (used for premedication) is 0.07–0.08 mg/kg; the intravenous measured quantity for tranquility is 0.07–0.1 mg/kg, titrated according to response; the oral amount for tranquility/drowsiness is 0.2 mg/kg. The end point for sedation is drowsiness and slurring of speech – response to commands is maintained (Butler, 2006; Sasada and Smith, 1997). Diazepam and midazolam exhibit similar sedative effects, but the latter provides a better anxiolytic effect as well as a minimally higher level of sedation; therefore, diazepam does not offer any sedative advantage over midazolam(Tyagi et al., 2013).

Midazolam-mode of action: The mode of action of benzodiazepines (midazolam) is thought to act through specific benzodiazepine receptors found all around the central nervous system (CNS) and focal sensory system. Benzodiazepine receptors are completely joined with gamma amino butyric acid (GABA) receptors. GABA receptors open chloride particle channels, which hyperpolarize and produce hypnosis and sedation (Butler, 2006; Sasada and Smith, 1997).

Ketamine: Ketamine is an N-methyl d-aspartate (NMDA) opponent which prompts a daze like sedation with few considerable impacts (Karapinar et al., 2006; Shende et al., 2003; Warner et al., 1995). Ketamine is a dissociative agent that gives sedation, control of pain and amnesia(Rodriguez and Jordan, 2002). Ketamine is used for the induction of anesthesia, especially in high risk patients with hypotension or asthma, for short procedures it is the fundamental technique, for instance; intra-visual examinations, burns dressings and radiological and radiotherapy procedures in children, as an agent for mass casualties in the field, for analgesia both post-operatively and in patients receiving intensive care, for pain relief from chronic pain for patients and for the reversal of severe unresponsive asthma(Sasada and Smith, 1997).

Ketamine-mode of action: Ketamine is a non-competitive antagonist of the N-methyl-d-aspartate (NMDA) receptors Ca^{2+} channel pore and also inhibits NMDA receptor activity by interaction with phencyclidine binding sites. It may also modulate opioid and muscarinic activity. Ketamine causes tachycardia, an increase in the blood pressure, central venous pressure and cardiac output secondary to enhance sympathetic tone. It causes mild stimulation of respiration with relative reservation of airway reflexes. Bronchodilation is a feature of the action of the drug. The state of dissociative anesthesia is produced by ketamine. The cerebral blood flow, cerebral metabolic rate, intraocular pressure increased; amnesia is a marked feature. At high doses, ketamine exhibits local anesthetic properties(Nagdeve et al., 2006; Sasada and Smith, 1997).

Ketamine and Midazolam combination: Ketamine and Midazolam have been utilized independently to encourage the sedation of painful techniques for pediatric patients(Sievers et al., 1991; Tobias et al., 1992). However, benzodiazepine sedation does not give a pain relieving impact and is deficient to anticipate pain emulated by additional combative techniques for example central venous catheter insertion or bone marrow biopsy. It was demonstrated that the combination of ketamine with midazolam gave faster onset of absence of pain and much proficient amnesia, diminishing the obliged dosage of ketamine and the occurrence of illusions(Beebe et al., 1992; Okamoto et al., 1992). when comparing oral midazolam and oral ketamine, while they exhibit similar sedative effects, midazolam is more conducive to anxiolysis, and orally administered ketamine results in a slower recovery period post-sedation(Damle et al., 2008).

Routes of Drug Administration

Intravenous and intramuscular route: Diazepam's absorption after IM injection is slow and erratic and it is often associated with severe pain(Bergman et al., 1988), whereas midazolam is well-absorbed and is less painful via the IM route. When administered intravenously, diazepam may cause phlebitis and local pain, whereas midazolam does not, due to its increased water solubility. The recommended dose for IV administration of midazolam is between 0.05-0.1 mg/kg, depending on the nature of the procedure and whether other drugs are being used(Diament and Stanley, 1988; Tolia et al., 1990, 1991). Intravenous ketamine has been shown to have a powerful sedative effect; some researchers actually preferred ketamine to midazolam due to increased patient cooperativeness and because it carried less side effects. (Rai et al., 2007)

Oral route: Numerous studies of oral midazolam in children have given conflicting results.(Feld et al., 1990; Payne et al., 1991) A single oral dose of 0.2 mg/kg was found to be effective during laceration repair in the emergency room(Hennes et al., 1990). However, most studies indicated that a higher oral dose is needed (Silver, 1992). Only 15-30% of an orally administered dose reaches the systemic circulation in its non metabolized form due to an extensive first pass hepatic effect, Thus, the oral dose should be approximately double or triple the intravenous dose to achieve similar clinical effects(Payne et al., 1989). oral administration of ketamine has also been studied using a lollipop to deliver the drug, and its effectiveness was then compared with oral midazolam without evidence of any greater sedative effects(Horiuchi et al., 2005).

Rectal route: Oral administration requires patient cooperation, whereas the rectal route does not. Children could be told that their temperature is being taken and frequently they will cooperate for the procedure. Most drugs, however, are not as well-absorbed rectally as from the upper intestine(Holroyd et al., 1988). Rectal midazolam has been studied as a preanesthetic medication for children and the optimal sedative dose was determined to be 1.0 mg/kg(Spear et al., 1991).

Nasal Route: Ketamine can be delivered safely and effectively via an intranasal route of administration (Bhatnagar et al., 2008). Ketamine also proves very useful when administered intranasally, inducing a high level of sedation. Children sedated with intranasal midazolam are passive and moderately drowsy but usually do not fall completely asleep. The average time to peak plasma concentrations and maximal effect is 10 min (Latson et al., 1991; Rose et al., 1990) and recovery time is approximately 30 min, with the degree of the sedative effect similar to that obtained with IM administration (de Santos et al., 1991). Intranasal midazolam may be used in combination with other drugs in diagnostic and short surgical procedures in children. One technique involved 0.2 mg/kg intranasal midazolam followed by 9.0 mg/kg ketamine administered rectally(Saint-Maurice et al., 1990).

Adverse Effects: Side effects of midazolam confined to occasional discomfort at the site of injection. Withdrawal phenomena may occur in children after prolonged infusion(Kain et al., 2000). In case of any unwanted event, antidote for midazolam (Flumazenil) can be administered intravenously (0.01 mg/kg/dose).The dose can be repeated for up to four times with an interval of one minute each(Adams and Dervay, 2012; Khalid et al., 2011). Emergence delirium, unpleasant dreams and hallucinations are much notable complications of the use of ketamine(Sasada and Smith, 1997; Webster and Walker, 2006). Transitory depression of breath and apnea can be seen after administration of ketamine either intramuscularly or intravenous(S. M. Green et al., 1998; Steven M. Green et al., 1998; Zsigmond et al., 1976). The benzodiazepine group of drugs is one of the safest presently in use. Midazolam is virtually free of any side effects.

The major risk associated with high doses of midazolam is hypoventilation and associated hypoxemia(Sievers et al., 1991). Respiratory depression has been reported in adults(Lewis and Benjamin, 1990), however, there have been few reports of depression in children. Children receiving midazolam should be monitored for early signs of hypoventilation or apnea. Respiratory depression appears to be dose related(Reves et al., 1985), and dosage regimens should be strictly followed (Sievers et al., 1991).

The increase in muscle tone produced by ketamine makes it unsuitable for operations where muscle relaxation is needed(Kolawole, 2001). The increase in salivation produced by ketamine can be troublesome during dental procedures and premedication with an antisialogogue may be needed (Dundee and Wyant, 1974). Patients have reported disturbing sensations when awakening from ketamine anesthesia. Ketamine can cause an increase in blood pressure and intracranial pressure, or pressure in the brain. Ulcerative cystitis, secondary renal damage and hepatic failure can occur with high doses of oral ketamine (Bell, 2009).

CONCLUSION

Midazolam offers many advantages when compared with diazepam, which are, it is more water soluble, rapid onset, short acting, anticonvulsant, muscle relaxant, relatively high margin of safety, reversal agent available and can be administered intranasally and when given intravenously, it is less irritating and causes fewer adverse local vascular reactions and pain. Its distribution and elimination half-lives are much shorter than with diazepam. Evidences provided strong, positive evidence for the use of ketamine alone or in combination with midazolam to reduce dental anxiety and behavioral non-compliance

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