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Sedative Agents in Minor Paediatric Oral Surgical Procedures- A Narrative Review

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ABSTRACT

Sedation in pediatric dentistry reduces anxiety during surgical procedures and also helps cope with very stressful events encountered during dental treatment. Various sedative agents like Nitrous oxide, diazepam, midazolam, Ketamine, propofol, fentanyl, and dexmedetomidine have been administered through several sedation routes including oral, nasal, inhalation, intramuscular, and sub-mucosal to attain active sedation. However, it is evident that the sesedative drugs also have the prospective to causelethal complications.

Aim: The present review was carried out to brief the clinical aspects of various sedative agents currently available in pediatric practices based on the existing literature with special emphasis on their role in minor pediatric oral surgical procedures.

Discussion: Nitrous oxide is frequently used in combination with complextime-consuming procedures and dental extractions, particularly for young and anxious patients undergoing orthodontic extractions. Fentanyl decreases pain and anxiety but causes respiratory distress. Oral ketamine is a potent dissociative drug often combined with midazolam produces excellent analgesic and sedative effects. None the less, the most common combinations include

sedatives with ketamine/opioids or dexmedetomidine to maintain the airway reflexes if given in small doses with precautions. Sometimes a combination of inhaled gases especially short-acting sevoflurane along with Diazepam is favored.

Conclusion: Within the limitation, it is evident that a clear understanding of the proper selection of sedative agents, awareness of the intended level of sedation or route of drug administration, and knowledge of adverse responses during and after sedation are essential to achieve appropriate sedation levels during minor oral surgical procedures.

1. INTRODUCTION

Management of oral health care needs in children necessitating minor surgical approaches is a challenging task owing to the excessive prevalence of fear, dental anxiety, and age-specific behavioral patterns among these individuals [1]. Pediatric dentist reduces dental anxiety, minimize physical discomfort, and impart ease of dental procedural controlled behavior among children using several pharmacological and

non-pharmacological behavioral methods thus bringing about effective and efficient oral health care [2]. Over the years with the advancement of techniques and the use of the latest technologies, several pharmacological methods such as pre-medications, deep sedation, conscious sedation, general anesthesia, and anxiolytic or minimal sedation methods have been used frequently in amalgamation with non-pharmacological behavioral modification techniques [3, 4].

Sedation in pediatric dentistry reduces anxiety during surgical procedures and also helps cope with very stressful events encountered during dental treatment [5]. There are different types of sedation, established by the guidelines of the American Academy of Pediatric Dentistry (AAPD), the American Academy of 2 Pediatrics (AAP), and the American Dental Association (ADA). Minimal

sedation produces the lowest depth using oral sedative agents (also called as anxiolytics) where the child can respond normally to verbal commands or stimuli [6]. Moderate sedation is a drug-induced state of consciousness (Conscious sedation) with sustained patent airway, spontaneous ventilation, and cardiovascular function [7]. Deep sedation or Analgesia is a drug-induced depression of consciousness during which the child cannot be easily woken, as there is a transient loss of protective reflexes; however, they respond firmly after repeated verbal or painful stimulation [8]. General anesthesia is a druginduced sedative technique of loss of consciousness through which the child cannot be roused, even by a painful stimulus. The AAPD (American Academy of Pediatric Dentistry) acclaims the use of general anesthesia or conscious sedation techniques in anxious children, complex extensive dental rehabilitation procedures of longer duration situations, extremely uncooperative child behavior, and in case of children with physical or physiological ailments [6-8]. Sedative drugs must induce a state of soothing or relaxation of anticipated depth after administration, with rapid onset of action and recovery. Furthermore, sedative agents or medication must be rapid, fast acting, reversible, and should be safe for the children. Various sedative agents like Nitrous oxide, diazepam, midazolam, Ketamine, propofol, Fentanyl, and dexmedetomidine have been dministered through several sedation routes or techniques such as oral, nasal, inhalation, intramuscular, and sub-mucosal to attain active sedation [9, 10]. Nonetheless, it is evident that these sedative drugs also have the prospective to cause lethal complications. Thus cautious pre-sedation evaluation of respiratory, cardiovascular, and other related systemic diseases, past medical history and drug allergies assessment have to be carried out by thorough understanding of patient selection, evaluation, and training with familiarity towards pharmacodynamics and pharmacokinetics of various sedative agents [11, 12]. Hence the present review 3 was carried out to elaborate on the pharmacological aspects of various sedative agents currently available in pediatric practices based on the existing literature with special emphasis on its role in minor pediatric oral surgical procedures.Methodology:

A structured literature search for articles written in the English language in PubMed/MEDLINE, Cochrane Reviews, Google Scholar, Scopus, Web of Science, and EBSCOhost databases was retrieved by using MeSH terms “Sedation” OR “Sedation in dentistry” AND “Dental Sedatives”, “Pediatric Oral Surgery” AND “Minor surgical procedures” "Sedation, Sedative Agents" OR “Oral Sedation”, “Intravenous Agents”, “Dental anxiety” OR “Dental Conscious Sedation” OR "All Metadata"

Sedative Agents in Pediatric Minor Oral Surgeries:

2. Diazepam and Midazolam:

Diazepam is a long-acting benzodiazepine drug with potent anxiolytic, hypnotic, mild sedative, and muscle relaxant properties deliver through the rapid onset of action due to its high lipid solubility and rapid first passmetabolism. It acts through the GABA-mediated opening of chloride channels. Averley et al [13], Erlandsson AL et al [14], Jensen B [15], Monisha K et al [16], Arya VS et al [17], in their respective studies, observed Oral or sublingual doses of Diazepam produced a significant decrease in blood pressure, reduce anxiety and pain, and minimize discomfort. Midazolam is a short-acting benzodiazepine used as a potent pre-medication drug in children before minor surgical procedures. It can be observed that a higher preference for midazolam over diazepam may be due to its short-acting with potent anxiolytic and anticonvulsant properties over other drugs and also due to its lower incidence of complications like nausea, vomiting, and 4 prolonged discharge time when compared to drugs given orally and/or nasally. Studies by Mazaheri et al [18], Gao F and Wu Y [9] showed the intranasal route of midazolam or Nasal spray administration in minor oral surgeries had better efficiency when compared to the intravenous route. Oral sedation with midazolam does not permit for the equivalent degree of titration as intravenous or parenteral methods, which makes it significant to implement caution when anticipating potential pharmacodynamic interactions with other categories or similar classes of drugs. Mazaheri et al [18] and Shashikiran et al [19] in their respective studies evaluated the efficacy of the intranasal and intramuscular diazepam and midazolam respectively and revealed a slight

increase in pulse rate regardless of the route of midazolam drug administration. One of the advantages of midazolam is that it can be combined with other drugs such as ketamine, which provides moderate dental sedation during minor surgical procedures. The

sedation and anxiolysis observed in patients with intranasal route of midazolam administration had better convenience and compliance when compared to the intravenous route. Flumazenil is used as an antagonist in case of over-dosage to produce reversal effects during surgical procedures [14, 15, 17, 19].

3. Dexmedetomidine (DEX):

Dexmedetomidine (DEX) is a long-acting, highly selective alpha-2 adrenoceptor antagonist with prolonged onset acts by binding with both presynaptic alpha-2 receptor and central alpha-2 postsynaptic receptor that induce analgesia, anxiolytics, and sedation often mimics natural sleep without causing respiratory depression. They decrease sympathetic tone, with attenuation of the neuroendocrine and hemodynamic responses to anaesthesia and surgery; reduce anesthetic and opioid requirements; and cause sedation and analgesia. Oral DEX is often used as a premedication, provides satisfactory

levels of sedation, ease of separation from parents and mask acceptance in 5 children. In addition, it drops unpredicted movements in children during minor dental surgeries compared to other intravenous sedation with Propofol and Midazolam. Studies by Mincer RC et al, Unkel JH et al had also shown intranasal and intravenous DEX in combination with oral medications such as

Ketamine and Fentanyl and/or with nitrous oxide has produced satisfactory premedication and effective milder sedation among uncooperative children [20, 21, 22].

4. Fentanyl and Sufentanil:

Fentanyl is an opioid analgesic administered by parenteral, transdermal, nasal, and oral routes. It is a strongly lipophilic agent readily absorbed from the buccal

mucosa when administered orally with an overall bioavailability of approximately 30–50% [23]. Alfentanil, a synthetic short-acting μ-opioid agonist that has a shorter half-life and quicker recovery time produces minimal adverse reactions such as less respiratory depression and postoperative nausea and vomiting (PONV) with significant clinical advantages during outpatient or

chairside dental anesthesia than fentanyl [24]. ufentanil is a short-acting synthetic opioid analgesic with shorter distribution and postoperative recovery time administered by parenteral, transdermal, nasal, and oral routes similar to Fentanyl to produce analgesia and sedation effect. It is 10 times more potent than fentanyl which presents with a higher incidence of nausea and vomiting and a prolonged discharge time when compared to nasally administered midazolam [2, 5, 6, 9].

5. Hydroxyzine:

Hydroxyzine is a slow-onset, long-acting anti-histaminic drug with a mild sedative, anticholinergic, antispasmodic, and antiemetic properties that is used in combination with midazolam to enhance the sedative effect and reduce systemic complications induced by intranasal midazolam. Hydroxyzine hydrochloride is a diphenylmethane given orally or intramuscularly, either as a 6 single dose or in combination with chloral hydrate. Several studies have utilized doses ranging from 1 to 2 mg/kg when combined with other sedative medications. Wilson et al [25], Song S et al [26] observed the combination of chloral hydrate (CH), hydroxyzine, and N2O inhalation produced intraoperative adverse events such as transient hypoxia and apnoea, prolonged sedation, including excessive sleep and less activity and recommends cautious use of these combinations to prevent the risk of adverse events and adequate dose should be of great apprehension for pediatric minor dental surgery sedation [2,

5, 6, 25, 26]

6. Ketamine:

Ketamine is an N-methyl d-aspartate (NMDA) receptor antagonist, a dissociative drug that produces profound amnesia and moderate sedation with well-sustained respiratory and cardiovascular functions. It is a dose-related cardiovascular stimulant that rarely increases heart rate and mean pulmonary rtery pressure even in CHD children. Heinz et al observed an increase in salivary flow following the administration of ketamine and recommend the use of an anti-sialagogue such as atropine before the surgical procedure [2, 5, 9, 27].

Tucker MR et al used IV ketamine at an induction dosage of 0.6 mg/kg and a maintenance dosage of 0.4 mg/ kg every 10 min to achieve adequate levels of sedation in children [28].

7. Nitrous Oxide and Oxygen Mixture:

Nitrous Oxide is a colorless, odorless gas with a mild sedative, analgesic and anxiolytic properties recommended for pediatric patients with dental phobias, high gag reflexes, intellectual disabilities, and those requiring profound local anesthesia. It is administered through specific vaporizers that convert liquids into gases, and these decrease, or at higher doses elicit the patient's

consciousness. It is a safe, practical, and effective drug with minimal side effects for emergency dental treatment of uncooperative pediatric patients. 50% 7 nitrous with oxygen can produce minimal sedation and 70% nitrous combined with oxygen can produce moderate sedation. Nitrous oxide is frequently used in combination with complex time-consuming procedures and dental extractions,

particularly for young and anxious patients undergoing orthodontic extractions. The use of N2O is contraindicated in patients with cold, tonsillitis, porphyria, pregnancy, and pulmonary diseases like COPD [2, 4-7, 29].

8. Propofol:

Propofol is an intravenous sedative-hypnotic drug that is often used for the induction and maintenance of deep sedation or general anesthesia. It acts by activating central inhibitory neurotransmitters and re-distributes rapidly to facilitate quick offset of anesthetic and hypnotic actions. It has a short duration of action, rapid elimination, and dose-dependent effects leading to changes in

blood pressure and heart rate at higher doses. Lower doses of propofol below the recommended anesthetic dosage used for IV conscious sedation infusion enabled operative dental treatment in anxious and uncooperative children. The most critical adverse effect of propofol is its potent respiratory depression, which may lead to sudden apnoea [9, 17].

9. Sevoflurane:

Sevoflurane is a low soluble, potent volatile, inhalation drug with a low bloodgas partition coefficient used widely as an induction agent before Intravenous agents such as propofol to maintain quick, smooth, and depth of sedation. Additionally, it offers a quick adjustment of anesthetic depth and has a high safety profile concerning the cardiovascular system. One of the major

advantages of using sevoflurane in pediatric patients is the ability to avoid excess anxiety, particularly in children with needle phobia or rational disabilities and it is easy to administer compared to sedation using intravenous drug injection. With sevoflurane, a dose of propofol used is an initial loading 8 dose, (usually 1 mg/kg body weight) and the maintenance dosage needed to achieve satisfactory sedation, ranges from 0.3 to 4 mg/kg/h [2, 9, 13].

Newer drug development

Remimazolam is a rapidly metabolized intravenously administered benzodiazepine sedative that induces sedation with quicker onset and offset of a hypnotic effect than midazolam. The recommended dose of 5mg of remimazolam administered IV over 1min is suggested for inducing procedural sedation. ADV6209, 0.2% aqueous Midazolam formulation of potent pediatric anxiolytic that showed better solubility than midazolam. Cyclopropylmethoxycarbonyl metomidate, also known as ABP-700 had also shown better binding to the GABAA receptor as etomidat is currently being developed for general anesthesia and procedural sedation [9].Techniques for sedation delivery and Multi-drug delivery systems:Most of the literature studies have shown that oral sedatives are easy to administer, avoid needle usage, require less expertise and skill, that provides adequate sedation with minimal or no complications. However, lack of immediate effect as seen in Intravenous or Inhalation sedation and dosage

variation leading to impulsive sedation level should be considered before the procedure to attain the level of relaxation and sedation needed to assist minor surgical procedures such as extraction with the minimum of anxiety and discomfort.

Ideally, combined sedatives produce a mixture of positive effects with reduced complication and speedy post-operative recovery time while minimizing the systemic effects. The most common combinations

include sedatives with ketamine/opioids or dexmedetomidine to maintain the airway reflexes if given in small doses with precautions. Sometimes a combination of inhaled gases 9 especially short-acting sevoflurane along with Diazepam is favored. Studies ave indicated that premedication regimens combining the anxiolytic properties of midazolam with the analgesic properties of ketamine resulted in superior pediatric behavior compared to the administration of these drugs separately.Total intravenous anesthesia (TIVA) is a general anesthesia technique that employs a blend of intravenous anesthetics without the administration of any inhalation anesthetics. In recent times, Target-controlled infusions (TCI) sedation delivery system using TCI devices that delivers a bolus, followed by

exponentially declining infusions to quickly achieve and sustain a stable drug concentration in the plasma or at the site of drug effect was also developed to enhance the efficiency [9].

Summary:

Table showing the sedative effect and Dosages of commonly used Sedative agent for Minor Oral Surgeries in Paediatric practice:

Drug	**Route of administration**	**Sedative effect**	**Dosage**
Diazepam	Oral,sublingual, Intranasal, Intramuscular	Rapid onset,longacting,Mild sedation	IV- 0.5mg to 1mg Oral- 0.125mgto0.25mg
Dexmedetomidine (DEX)	Oral Intranasal Intravenous	Short-acting, Mild sedative	IN 1-4ug/kg (max 100ug) IV1–3ug/kgloadingdose (max 100ug) over 10min, followedby0.5–1ug/kg/h continuous infusion
Fentanyl	Intravenous, Transdermal, OralandNasal	Moderate sedative	1mcg/kg/doseIVbutnot exceeding 4 mcg/kg.
Ketamine	Intramuscular, Intravenous	Rapidonset, shortacting, Dissociative anaesthesia	Intra-muscularat3–4mg/kg Intravenous at 1–2 mg/kg
Midazolam	Oral- Tablets, Syrup, Transmucosal, Intranasal, Rectal,	Rapidonset, shortacting, Moderate sedation	Oral Dose is 0.3–0.5 mg/kg IV0.05–0.1mg/kg(maximum 0.6mg/kg) IM0.1–0.5mg/kg
NitrousOxide	Inhalation	RapidOnset, Moderate sedation	Starting at 100% O2, IncreasingDoseofN2Ois 50%in50%oxygen,upto 70% can be used
Propofol	Intravenous	RapidOnset, Shortacting, Sedative-Hypnotic	1mg/KgBodyweight- Loading dose

Conclusion:

Within the limitation, it is evident that a clear understanding of the proper selectionofsedativeagents,awarenesstowardstheintendedlevelofsedationor route of drug administration, and knowledge of adverse responses during and after sedation followed by physiological monitoring and continuous observation are the essential elements to achieve desirable sedation and analgesic effects. Knowledge of each sedative drug's time of onset, peak response, and durationof action is crucial in determining the recovery outcomes and associated complications.

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