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Review Article

Conscious Sedation in Pediatric Dentistry: One Step forward

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Abstract

Early childhood are usually associated with dental pain and anxiety among pediatric patients that is often carried into adulthood. Dental treatment of these patients are often challenging and also require adequate cooperation. Such patients can be managed using pharmacological methods. A thorough knowledge of the basic agents used for sedation is necessary. This article thus has reviewed on basic pharmacological agents used in the procedural sedation in children briefing its pharmacological properties.

Keywords: Conscious Sedation; Children; Pediatric Dentistry; Inhalational Sedation Agents; Intravenous Sedation Agents

Abbreviations

CNS: Central Nervous System; FDA: The Food and Drug Administration, MRD: Maximum Recommended Dose; GI: Gastrointestinal; IM: Intramuscular; IV: Intravenous; IN: Intranasal; SM: Submucosal; SC: Subcutaneous; IO: Intraosseous; ASA: American Society of Anesthesiologists; MAC: Minimum Alveolar Concentration; GABA: Gamma-aminobutyric Acid

Introduction

Pain and fear are the two most frightening enemies of human psyche and an exaggerated perception of pain and anxious behavior is more closely related to dental treatment than any other type of health care. Because of the pain and fear associated with dental treatment, a number of patients try to avoid it until the pathology becomes very severe and there are no effective home remedies. Some retrospective studies have shown the adult dental fear to unpleasant treatment received at an early age [1]. Dental treatment of pediatric patients with behavioral problems is a very difficult task. Behavior management only through psychological techniques are not sufficient for inspecting the patients' cooperation. Therefore, there is a definite need for pharmacological treatment for the problem. Various oral sedative agents have been used for managing uncooperative young dental patients [2].

Conscious sedation is a technique in which the use of a drug or drugs produces a state of depression of the central nervous system (CNS) enabling treatment to be carried out, but during which verbal contact with the patient is maintained throughout the period of

sedation [3]. It is a drug-induced depression of consciousness during which the patient responds purposefully to verbal commands, either alone or with light tactile stimulation. No interventions are required to maintain patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained [4].

The definitions for administration of minimal sedation are as follows [5]:

- **Maximum recommended dose (MRD)**: Maximum FDA-recommended dosages of a drug, as printed in FDA-approved labeling for unmonitored home use.
- **Incremental dosing**: Administration of multiple dosages of a drug until a desired maximum recommended dose is obtained (MRD).
- **Supplemental dosing**: It is a single additional dose of the initial dose of the initial drug that may be necessary for prolonged procedures. The supplemental dose should not exceed one-half of the initial doses and should not be administered until the dentist has determined the clinical half-life of the initial dosing has passed. The total aggregate dose must not exceed 1.5x the MRD on the day of treatment.
- **Conscious sedation/moderate sedation:** A drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain the patency of airway if adequate ventilation is present. The functioning of Cardiovascular system is usually maintained.

Routes of administration in conscious sedation [6]

- **Enteral**: Any technique of administration in which the agent is absorbed through the gastrointestinal (GI) tract or oral mucosa [i.e. oral, rectal, sublingual].
- **Parenteral:** A way of administration in which the drug bypasses the gastrointestinal (GI) tract [i.e. intramuscular (IM), intravenous (IV), intranasal (IN), submucosal (SM), subcutaneous (SC), intraosseous (IO)].
- **Transdermal**: A way of administration in which the drug is administered by patch or iontophoresis through skin.
- **Transmucosal:** A method of administration in which the drug is administered into the mucosa such as intranasal, sublingual, or rectal.
- **Inhalation:** A method of introducing a gaseous or volatile agent into the lungs and whose primary effect is due to absorption through the gas/blood interface.

American society of anesthesiologists (ASA): Patient Physical Status Classification (last modified in 1961) [6]

- ASA I - A normal healthy patient.
- ASA II - A patient with mild systemic disease.
- ASA III - A patient with severe systemic disease.
- ASA IV - A patient with severe systemic disease that is a constant threat to life.
- ASA V - A moribund patient who is not expected to survive without the operation.
- ASA VI - A declared brain-dead patient whose organs are being removed for donor purposes.
- E - Emergency operation of any variety (used to modify one of the above classifications, i.e., ASA III-E).

Objectives of conscious sedation

Bennett (1978) listed the understanding of the objectives as the most important factor for success. Conscious sedation has several objectives [5]:

- Altering of the patient's mood is the main objective. The use of any pharmacologic agent will reduce the child's apprehension and reaction to painful stimuli. The use of a mood-altering drug will render the child more receptive to dental procedures. Hence, future dosages of drugs may be reduced.
- The child should remain conscious, the patient should be responsive even if the child's response to verbal stimuli may seem sluggish.
- The child should be highly cooperative. The dental care needed is completed more quickly and productively to the advantage of both the patient and the dentist.
- All protective reflexes are intact and active. The normal physiological reflexes are in a functioning state. The airway is active, the respiratory mechanism is reflexive, the cardiovascular system is well within normal functioning limits.
- The vital signs must remain stable and normal. If the patient is conscious with all reflexes intact, vital signs should be normal.
- The child's pain threshold should be elevated. Even though local anesthesia is used as an adjunct to conscious sedation, an additional drug can be added to reduce pain at the level of the central nervous system.
- Amnesia should occur. Amnesia is not a major objective, but certain drugs will eliminate the awareness of the procedure, that is, the administration of local anesthesia.

Indications

Conscious sedation is indicated when both patient and dental indications are present.

Patient indications:

- Patients with inadequate cooperation.
- Patients with high dental fear/anxiety/odontophobia.
- Need for reduction of patient's pain perception (prevent fear induced pain), if pain threshold is low.

Dental indications

- Oral examination and treatment of moderate extent and complexity (invasive treatment need should done under general anesthesia)
- Emergency treatment (e.g. Extractions and emergency treatment of dental trauma).

It is the combined assessment of these two types of indications that indicates whether a certain type of oral examination or treatment should be done conventionally or under sedation or general anesthesia. Children with low coping ability (e.g. immature children) or high dental anxiety, and with extensive or complicated treatment needs, should be treated under deep sedation or general anesthesia. This is more appropriate from the perspective of the child, parents, and dental staff, as it is cost effective and also the majority of the treatment may be done in one session.

Contraindications

- For the pre-operative assessment of the patient particularly whether there are any Contraindications for the use of sedation, the ASA classification should be used. The Dentist should consult the physician or anesthesiologist for classes III and IV.
- Sedation of children under 2 years of age is connected with extreme risks and should be done in collaboration with an anesthetist.
- Upper airway problems, trauma, sleep apnea and snoring.
- Uncontrolled seizures.
- Psychotic patients.
- Untreated, acute narrow angle glaucoma.
- Biomycin chemotherapy.
- Cerebral palsy, neck instability, hemodynamic instability.
- Allergy to any drugs, neuromuscular diseases and if any interaction with other medicines is suspected.
- Emergency treatment (e.g. extractions and emergency treatment of trauma).

When dealing with pediatric population it is important not to envision the child as a small adult. Treating a child as a small adult may inevitably lead to errors in medication dosage, fluid administration, and resuscitative measures. The pediatric population is identified as:

- Neonates (< than 30 days)
- Infants (1 - 12 months)
- Children (1 - 12 years)
- Adolescents (13 - 19 years).

For the preoperative assessment of the patient, particularly when there are any contraindications for use of sedation, the ASA Classification system of the patient's physical status should be used. The dentist is expected to take the responsibility for treating patients in Classes I and II under conscious sedation, while those under Classes III and IV should be decided after consulting a physician/anesthesiologist.

Types of sedation agents

Various agents are available to provide conscious sedation depending on the invasiveness of treatment, cooperation of child, duration of treatment, facilities for monitoring and resuscitation and expertise of the personnel involved. Several key features from various studies on sedative agents used in children has been collaborated and compared (Table 1).

Authors	Date	Type of Study	No of Patients	Drugs used and Dosage	Route of Administration	Specialty	Conclusions
Oriby., *et al*. [8]	2019	Prospective Doubleblind Randomized	76	Dexmedetomidine 2µg/kg Ketamine at 3 mg/kg or Midazolam 0.2 mg/kg	Intranasal Oral Oral	Anaesthesiology	Premedication with intranasal dexmedetomidine and oral ketamine was rapid and effective compared to Midazolam
Mehran., *et al*. [9]	2018	Crossover Double blind clinical trial	30	Midazolam 0.4 mg/kg + Water Midazolam 0.4 mg/kg + Promethazine 5 mg/kg of	Intranasal	Dentistry	improvement in cooperation level of those receiving midazolam/chloral hydrate combination when com-pared to those receiving midazolam/promethazine combination

Samir., *et al*. [10]	2017	Randomized clinical study	60	30% N_2O and 70% O_2	Intranasal	Dentistry	significant difference in the time taken to achieve ideal sedation by rapid induction which was almost half the time taken with slow induction.
Peerbhay., *et al*. [11]	2016	Prospective Randomized	118	Midazolam0.3 mg/kg Midazolam0.5 mg/kg	Intranasal	Dentistry	All drugs resulted in safe and effective sedation.
Musani., *et al*. [12]	2015	randomised crossover	30	Midazolam (0.2 mg/kg + Nitrous oxide Midazolam (0.1 mg + Nitrous oxide	Oral Intranasal	Dentistry	The intranasal route of midazolam administration has a quick onset of action and a quick recovery of the patient from sedation as compared to the oral route of midazolam administration.
Surendar., *et al*. [13]	2014	Randomized Triple-blind	84	Dexmedetomidine 1µ/kg Dexmedetomidine 1.5µg /kg Midazolam 0.2 mg/kg Ketamine 5 mg/kg	Intranasal	Dentistry	All the drugs are safe and effective in the light sedation of uncooperative patients
Pokharel., *et al*. [14]	2014	Prospective Doubleblind Randomized	80	Alprazolam 0.5 mg + melatonin 3 mg Alprazolam 0.5 mg Melatonin 3 mg Placebo	Oral	Anesthesiology	The combination of alprazolam with melatonin reduces anxiety Level of sedation is similar to the alprazolam groups
Mitra., *et al*. [15]	2014	Prospective Doubleblind Randomized	60	Clonidine 4 µg/kg + Atropine 20 µg/kg Midazolam 0.3 mg/kg	Intranasal Intravenous	Anesthesiology	Midazolam provides a faster onset sedation; both drugs provide adequate anxiolysis after 30 minutes
Mittal., *et al*. [16]	2013	Prospective Doubleblind Randomized	40	Propofol 1-1.5 mg/kg Ketofol 1-1.5 mg/kg + Ketamine 0.25 mg/kg	Intravenous	Dentistry	Propofol is safer but both drugs have similar sedative effects
Tyagi., *et al*. [17]	2013	Prospective Randomized Triple-blind	40	Midazolam 0.5mg/kg Diazepam 0.5 mg/kg Midazolam 0.06 mg/kg Placebo	Oral Oral Intravenous Oral	Dentistry	Midazolam allows for a higher level of sedation, better anxiolysis, and it is safer than diazepam

Chopra., *et al*. [18]	2013	Prospective Randomized	30	Midazolam Midazolam	Aerosol mouth spray Intranasal	Dentistry	Oral midazolam is more effective but not significantly
Fan., *et al*. [19]	2013	Prospective Doubleblind Randomized	60	Midazolam 0.005 mg/kg/min Dexmedetomidine 0.1µg/kg/min	Intravenous Intravenous	Dentistry	Dexmedetomidine is a good alternative to midazolam for achieving adequate levels of sedation
Tyagi., *et al*. [20]	2012	Prospective Randomized Triple-blind	40	Midazolam 0.5 mg/kg Diazepam 0.5 mg/kg Midazolam 0.06 mg/kg Placebo	Oral Oral Intravenous Oral	Dentistry	Midazolam has stronger sedative effects than Diazepam
Horacek., *et al*. [21]	2012	Prospective Doubleblind Randomized	29	Ketamine 5 mg/kg + Clonidine 2 µg/kg + Midazolam 0.3 mg/kg Ketamine 5 mg/kg + Midazolam 0.3 mg/kg	Oral Oral	Dentistry	Oral ketamine and midazolam are safe and effective sedatives
Pandey., *et al*. [22]	2011	Prospective Randomized	34	Ketamine Ketamine	Intranasal spray Intranasal drops	Dentistry	The spray is better tolerated than the intranasal drops, but both are equally effective
Larsson., *et al*. [23]	2012	Prospective Doubleblind Randomized	60	Saline placebo Clonidine 3-4 µg/kg Clonidine 7-8 µg/kg	Intranasal Intranasal	Anesthesiology	Clonidine provides adequate sedation in both groups
Bahetwar., *et al*. [24]	2011	Prospective Randomized	45	Midazolam Ketamine Midazolam + Ketamine	Intranasal Intranasal Intranasal	Dentistry	Both drugs induce Moderate sedation, but ketamine is more effective
Klein., *et al*. [25]	2011	Prospective Randomized	169	Midazolam Midazolam Midazolam	Intranasal Aerosol mouth spray Oral	Facial and orofacial surgery	Midazolam mouth spray is the most effective route of administration
Shabbir., *et al*. [26]	2011	Prospective Randomized	12	Triclofos 70 mg/kg Midazolam 0.5mg/kg	Oral Oral	Dentistry	Oral midazolam is more effective than triclofos

Pandey., *et al*. [27]	2010	Prospective Randomized Triple-blind	23	Fentanyl 0.3 µg/kg + Midazolam 0.5 mg/kg Placebo + Midazolam 0.5 mg/kg	Submucosal Oral	Dentistry	A combination of fentanyl and midalozam improves sedative effects Dangerous (oxygen desaturation), a combination of fentanyl and midazolam improves sedative effects but may cause oxygen desaturation
Damle., *et al*. [28]	2008	Prospective Randomized Doubleblind	20	Midazolam 0.5 mg/kg Ketamine 5 mg/kg	Oral Oral	Dentistry	After 30 minutes, midazolam shows greater sedative effects with less side effects
Da Costa., *et al*. [29]	2007	Prospective Randomized Doubleblind	12	Placebo Chloral hydrate 75 mg/kg Chloral hydrate 50 mg/kg + Hydroxyzine 2 mg/kg	Oral Oral Oral	Dentistry	Chloral hydrate is a viable method of sedation, however hydroxyzine does not lend any additional benefits
Rai., *et al*. [30]	2007	Prospective Randomized	30	Propofol Midazolam Ketamine	Intravenous Intravenous Intravenous	Dentistry	Ketamine proved to be the most effective drug
Bhatnagar., *et al*. [31]	2008	Prospective Randomized	60	Ketamine 6 mg/kg + Midazolam 0.05 mg/kg + Atropine 0.02 mg/kg Ketamine 10 mg/kg + Midazolam 0.2 mg/kg + Atropine 0.05 mg/kg	Intramuscular Oral	Oncology	Both routes of administration are effective. Oral administration is less painful
Kantovitz., *et al*. [32]	2007	Prospective Randomized Doubleblind	20	Chloral hydrate 40 mg/kg Diazepam 5mg	Oral Oral	Dentistry	Diazepam and chloral hydrate do not affect children's behavior
Horiuchi., *et al*. [33]	2005	Prospective Randomized	55	Lollipop with ketamine 50 mg Midazolam oral syrup 0.5 mg/kg	Oral submucosal Oral	Anesthesiology	Ketamine administered transmucosally in the oral cavity does not appear to have any advantages over oral midazolam

Table 1: A comparative evaluation of various sedative agents and their studies.

Nitrous oxide

Nitrous oxide is a colorless and odourless gas that act as mild sedation agent producing both a depressant and euphoric effect on the CNS with little effect on respiratory system. It is also a potent analgesic. A 50% inhaled concentration of nitrous oxide equals to that of parenteral morphine injection at a standard dose (10mg per 70kg of adult). It can be used in patients who are reluctant to use local analgesia as it decreases the pain of injections in those who require additional local anaesthesia. The effects of the nitrous oxide depends on: The pattern of exposure, tissue sensitivity, vitamin B12 intake and body stores, extent to which methionine synthetase is deactivated [7].

Sevoflurane

Sevoflurane is a sweet-smelling, non-flammable, volatile anaesthetic agent used for the induction and maintenance of general anaesthesia. It is a potent agent with a MAC value less than 2, leaving it with a narrow margin of safety. anaesthetic agents like halothane and are even more potent drugs than sevoflurane, with low MAC values (the MAC of halothane is 0.76) thus reducing the margin of safety making the induction of general anaesthesia more likely [7]. The use of low concentrations (0.1% - 0.3%) of sevoflurane in combination with 40% nitrous oxide in oxygen showed that the margin of safety was wide enough to render loss of consciousness unlikely [35].

Oxygen

Oxygen is not a sedative agent, however, inhalational agents are always delivered in an oxygen-rich mixture which consists of atleast 30% oxygen by volume. Oxygen is stored as a gas in black cylinders with white shoulders, (initial pressure of 2000 pounds per square inch). In conventional slow induction, - initially, 100% O_2 is administered to about 4 - 5 L/min in children to determine the minute volume followed by increments in the N_2O concentration of 5% - 10% for every 1 - 3 min [10]. Therefore it is mainly used as a supplement along with other sedative agents.

Diazepam

Diazepam was the first benzodiazepine to be used in intravenous sedation practice (See figure 1). It is insoluble in water hence it is dissolved in an organic solvent, propylene glycol. Diazepam is metabolised in the liver and eliminated through the kidneys. It has a long elimination half-life (T1/2β) of 43 hours (+/−13 hours) while its distribution half-life (T1/2α) is around 40 minutes. An active metabolite, n-desmethyldiazepam, is produced, which can cause rebound sedation of up to 72 hours after the initial administration of diazepam [7]. In children aged 3 - 8 years old the mean half-life of diazepam has been reported to be 18 hours. A 30-hour half-life was reported in full term infants, with an average half-life of 54 hours in premature infants of 28 - 34 weeks gestational age and 8 - 81 days postpartum.

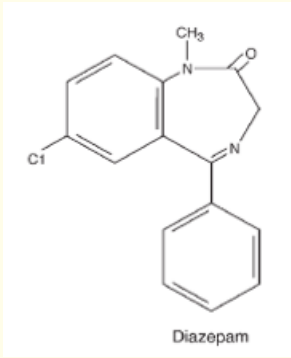

Figure 1: Chemical structure of diazepam, showing a benzene ring structure attached to the diazepine part of the molecule.

It is a reliable hypnosedative which should be given slowly, titrating the dose against the response obtained. The standard dose ranges between 0.1 - 0.2 mg/kg. However, longer period of its recovery and rebound potential makes it inadequate for short dental procedures and its use has largely surpassed by recent and more rapidly metabolised midazolam [7].

Midazolam

Midazolam is an imidazobenzodiazepine which is water soluble with a pH of less than 4.0 It does not irritate veins, and once injected into the bloodstream, at physiological pH, it becomes lipid soluble and readily penetrates the blood-brain barrier. It has an elimination half-life of 1.9 hours (+/−0.9 hours) so that complete recovery is faster compared to diazepam. Midazolam works faster than midazolam, with least 2.5 times more potency and predictable amnesic properties [7]. It is a gamma-aminobutyric acid (GABA) receptor inhibitor frequently used as premedication in pediatrics due to its sedative, anxiolytic, and amnesic effect [8]. It is rapidly metabolised in the liver along with extra-hepatic metabolism in the intestines. Alpha-hydroxymidazolam is an active metabolite produced by Midazolam. This has a short half-life of 1.25 hours (+/−0.25 hours) which is shorter than that of the parent compound and thus does not produce true rebound sedation.

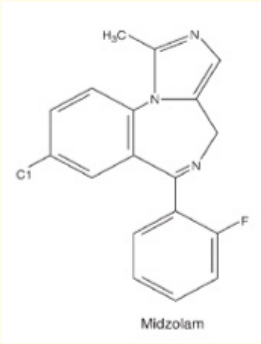

Figure 2: Chemical structure of midazolam, showing a benzene ring structure attached to the diazepine part of the molecule.

The dose of midazolam is titrated according to the patient's response but most patients usually require a dose in the range of 0.07-0.1mg/kg. On the other hand paradoxical reactions, restlessness, and behavioral changes are the side effects observed [8].

Flumazenil (benzodiazepine antagonist)

Flumazenil, a 1,4-imidazobenzodiazepine, is a specific benzodiazepine antagonist which is indicated for use when the effect of a benzodiazepine needs to be attenuated rapidly [36]. It competitively inhibits the activity of benzodiazepine and non-benzodiazepine substances that interact with benzodiazepine receptors site on the GABA/ benzodiazepine receptor complex. It is a true benzodiazepine although it has virtually no intrinsic therapeutic activity (the administration of huge doses of flumazenil may result in very slight epileptiform activity). It is similar to other benzodiazepines in chemical form but does not have the ring structure attached to the diazepine part of the molecule (Figure 3).

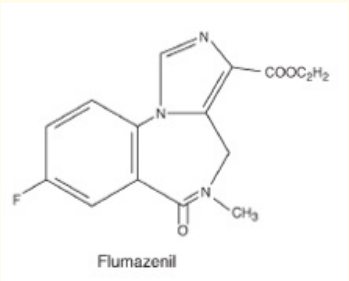

Figure 3: Chemical structure of flumazenil, the benzodiazepine antagonist. The molecule has no benzene ring attached to the diazepine group.

Flumazenil is an effective antagonist as it has a greater affinity for the benzodiazepine receptor compared to other known active drugs. The sedative, cardiovascular and respiratory depressant effects of both diazepam and midazolam can be temporarily reversed by flumazenil. It is currently only recommended for use in emergencies but not to hasten recovery.

Propofol

Propofol (2, 6-diisopropylphenol) is a very short acting sedative, introduced by Kay and Rolly in 1977, and was widely accepted for pediatric sedation regimens due to its minimally reported systemic effects and fast recovery after surgery [30]. It is oil at room temperature and insoluble in aqueous solution with an advantage of undergoing rapid elimination and recovery. It has an elimination half-life of 30-40 minutes and a distribution half-life of 2 - 4 minutes. The clinical effect is of shorter duration because propofol is rapidly distributed into peripheral tissues, and its effects wear off considerably within half an hour of injection. This, together with its rapid effect (within minutes of injection) and the moderate amnesia it induces, makes it an ideal drug for intravenous sedation. Propofol act by enhancing the GABA neurotransmitter system. Propofol is administered as a continuous infusion to maintain general anaesthesia. It may be administered in sub-anaesthetic doses either by a technique using a target-controlled infusion, a patient controlled target infusion or by intermittent bolus administration [7].

Conclusion

Careful patient selection, screening, preparation of prospective patients and prudent administration of the drugs described is the basis for successful use of sedative agents in children. Selected patients should be healthy or have a well-controlled medical condition(s). Safe and adequate administration of sedative and analgesic medications can make painful and anxiety provoking situations tolerable. However, knowledge of medications and the ability to address over sedation and its side effects is essential for safe and effective outpatient procedural sedation [34].

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