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Sedation in pediatric dentistry, an overview and current update

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Abstract
Introduction: Conscious sedation is a technique of administering sedatives or dissociative agents with or without analgesics to induce a state that allows the patient to tolerate unpleasant procedures.
Objective: To analyze the literature on the types of sedation and the different drugs that can be used such as midazolam, dexmedetomidine, propofol, and nitrous oxide.
Methodology: A comprehensive search was performed in PubMed, SCOPUS and Google Scholar using keywords such as sedation, pediatric dentistry, midazolam, dexmedetomidine, propofol, nitrous oxide.
Results: The types of sedation are minimal, moderate, and general anesthesia, these are important in order to provide the best option according to the patient's age, condition and level of anxiety. Oral midazolam is usually used as a premedication causing good behavior, patient cooperation and decreased anxiety. Dexmedetomidine has anxiolytic, analgesic effects and little postoperative agitation. Propofol has a fast effect, short duration and fast elimination helping dentists to carry out dental treatments; as well as nitrous oxide, these two are preferred by parents.
Conclusion: The best drug for sedation in pediatric dentistry is nitrous oxide because it is preferred by parents for being safe, effective, with minimal side effects and gives a good working time, it can be used in patients with special needs, with excessive anxiety or behavioral disorders making it a good alternative for sedation.

Keywords: Sedation, pediatric dentistry, propofol, nitrous oxide, midazolam, dexmedetomidine

1. Introduction
Pediatric dentists have always faced the difficult task of managing dental fear and anxiety, which is an obstacle to successful treatment of children and even impedes the quality of care by the dentist [1].

Patients with particular medical conditions and extensive dental complications tend to show greater fear and lack of cooperation in their treatment, mainly due to physical problems, mental disabilities, or behavioral management problems [2]. Nowadays, there are different techniques used to manage them, among which sedation with different anesthetic agents has become popular [3].

Conscious sedation is a technique of administering sedatives or dissociative agents with or without analgesics that induce a state that allows the patient to tolerate unpleasant procedures while maintaining cardiorespiratory function. This achieves a depressed level of consciousness that allows the patient to maintain oxygenation and airway control independently [4]. It is considered the most used technique for children with dental anxiety [5], as consciousness is minimally depressed, but the ability to maintain an open airway, protective reflexes and a response to verbal and physical stimulation is maintained [6].

Sedation can be performed by different methods, either orally, through parenteral route with benzodiazepines, inhaled with nitrous oxide, or intravenously [7]. The most used anesthetic agents, administered individually or in combination, are diazepam, midazolam, propofol, ketamine, opiate agonists such as fentanyl or remifentanil, and dexmedetomidine; and on the other hand, the most used inhalation agents are nitrous oxide and sevoflurane [8].

In pediatric dental practice we encounter multiple complications that reduce the success rate of treatment. Therefore, conscious sedation is considered an effective technique, since it reduces patient anxiety, can be used in patients with disabilities, avoids abrupt movements, dental treatment is carried out in a short period of time, and is safe. The aim of this research is to analyze the literature on the types of sedation used and the different medications that can be used for conscious sedation in pediatric dentistry, such as midazolam, dexmedetomidine, propofol and nitrous oxide.

2. Materials and Methods

Articles on the subject published through the PubMed, SCOPUS and Google Scholar databases were analyzed, with emphasis on the last 5 years. The quality of the articles was evaluated using guidelines, i.e., identification, review, choice and inclusion. The quality of the reviews was assessed using the measurement tool for evaluating systematic reviews. The search was performed using Boolean logical operators AND, OR and NOT. The search was performed using Boolean logical operators AND, OR and NOT; with the keywords: "sedation", “conscious sedation”, "pediatric dentistry", "midazolam”, “dexmedetomidine”, “propofol” and “nitrous oxide”. The keywords were used individually, as well as each of them related to each other.

3. Results and Discussion

3.1 Types of sedation

Drugs must provide sedative, analgesic, and amnesic properties, as well as a rapid onset of action and a short duration to allow safe and rapid recovery [4].

There are different types of sedation, established by the guidelines of the American Academy of Pediatric Dentistry (AAPD), the American Academy of Pediatrics (AAP), and the American Dental Association (ADA) [9].

Minimal sedation, i.e., the lowest depth of sedation can be easily obtained using oral sedatives, requires no special equipment or tools, and does not affect ventilatory and cardiovascular function [10]. This type of sedation is also called anxiolysis and the patient is awake and relaxed and able to respond normally to verbal stimuli [11].

Moderate sedation is drug-induced, during which patients respond with determination to verbal commands, no interventions are required to maintain a patent airway, spontaneous ventilation is adequate and cardiovascular function is usually maintained [12].

Deep sedation is a drug-induced depression of consciousness during which, patients cannot be easily awakened, as there is a loss of protective reflexes; however, they respond purposefully after repeated verbal or painful stimulation. Cardiovascular function is maintained, but it is necessary to keep the airway patent [13,14].

General anesthesia (GA) involves a drug-induced loss of consciousness during which patients cannot be awakened, even by painful stimulation. The ability to maintain ventilatory function independently is often impaired as its cardiovascular function [15]. This type of analgesia is used because of the extensive and complex treatment requirements and insufficient cooperation often related to the patient's age [16].

In the oral route agents administered that are absorbed through the gastrointestinal (GI) tract or oral mucosa are referred to as enteral sedation, and are subject to enterohepatic circulation and first-pass effect before the drug is released into the systemic circulation. The parenteral route bypasses the GI tract and enters directly into the systemic circulation; within this, administration via the inhaled route has become increasingly popular in pediatric dentistry [9].

It is important to know the types of sedation (minimal, moderate, deep, and general anesthesia) used in pediatric dentistry so that professionals in this area can offer the best option according to the age of the patient and the level of anxiety they present, as well as knowing the type of sedation suitable for patients with special conditions, since sometimes airway and/or cardiovascular assistance is required.

3.2 Midazolam

It is one of the benzodiazepines used for perioperative conscious sedation [17]. Midazolam can be administered orally, intranasally and through parenteral route, but has an unpredictable response, it can be safely used as an oral premedication for intravenous (IV) sedation of pediatric dental patients [18,19]. Oral administration of midazolam in doses of 0.5 mg per 1 kg body weight of the child is safe [20], as it does not produce any respiratory depression in children, decreases the need for analgesics, increases the recovery rate in children undergoing general anesthesia for dental treatment [21] and makes patients more cooperative [22]. One of the advantages of midazolam is that it can be combined with other drugs such as ketamine, which provides moderate dental sedation when administered intranasally, and presents minor adverse events, with marked variability in the behavior of children during dental treatment [23]. The combination of midazolam and chloral hydrate also shows improved cooperation for dental treatment in children [24].

Midazolam is often used as a sedative preoperative medication in pediatric dentistry, with benefits of good behavior, patient cooperation and decreased anxiety.

3.3 Dexmedetomidine

Dexmedetomidine (DEX) is a highly selective α-2 agonist that produces sedative, anxiolytic and analgesic effects without causing respiratory depression and with a low incidence of postoperative agitation [25]; it is an effective and safe drug and that is why it is gaining importance in pediatric sedation. This drug can be administered orally, intravenously, intranasally and intramuscularly [26]. Oral DEX is often used as a premedication, provides satisfactory levels of sedation, ease of separation from parents and mask acceptance in children [27]. In addition, it decreases unexpected patient movements during dental surgery compared to sedation with Propofol and Midazolam [28]. It can be combined with other oral medications such as Ketamine and Fentanyl, serving as an alternative in pediatric sedation, as the combination of dexmedetomidine and oral fentanyl also promises to be a potential sedative agent for children with respect to their successful anxiolysis during treatment procedures [29]. It has been reported that this intravenous drug can be combined with a low dose of Midazolam, being useful for dental treatment of an uncooperative pediatric patient requiring minimal treatment [30]. Intranasal DEX also has satisfactory and effective premedication regimens for uncooperative children [31]. The intravenous moderate sedation regimen with DEX has been shown to produce a milder sedation event. This method of anesthesia may be effective in reducing the waiting time for GA treatment as well as the morbidity associated with GA [32].

This drug has been shown to be a good choice as a sedative in pediatric dentistry due to its anxiolytic and analgesic effects and low postoperative agitation. One of the advantages of this

sedative is the reduction of unexpected movements of the patient during treatment and its combination with other drugs.

3.4 Propofol

Propofol is an intravenous anesthetic used for sedation during monitored anesthetic care or as an induction agent for general anesthesia [33]. 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 [34]. It allows dental procedures in uncooperative pediatric patients to be performed safely and effectively in an outpatient setting by qualified personnel in the management of any complications [2]. This anesthetic can be combined with Midazolam, offering acceptable side effects as an advantage. Lin *et al*, reported that the factors associated with the combined use of Propofol and Midazolam are young age, male sex, recognition problems and type of dental procedure in the dental treatment of patients with special needs [35]. It can also be administered together with Ketamine (ketofol) achieving adequate sedation and good hemodynamic stability [36], a 1:2 ratio dose of ketofol is related to a decreased side effect profile and high parental satisfaction with rapid recovery, however, dentists' satisfaction is lower [37]. The use of Propofol with remifentanil is contraindicated due to changes in drug concentration over time, non-uniform mixing of these two, risk of bacterial contamination and potential for drug administration errors [38]. However, better parental satisfaction is observed after total intravenous anesthesia (TIVA) with Propofol. In addition, TIVA results in a more comfortable postoperative period due to reduced postoperative pain, extubation time and recovery time [39].

Propofol is a commonly used anesthetic for sedation in pediatric dentistry due to its rapid effect, short duration, and rapid elimination, helping dentists to effectively carry out dental treatments, as well as making the patient's parents feel satisfied.

3.5 Nitrous Oxide

Nitrous oxide is an anesthetic gas also known as an inhaled anesthetic. It is administered as a primary treatment for preoperative sedation and maintenance of anesthesia adjunct to intravenous anesthetic agents in the perioperative setting [40]. It is a safe, practical, and effective drug with minimal side effects for emergency dental treatment of uncooperative pediatric patients [41]. It is administered through specific vaporizers that transform liquids into gases, and these decrease, or at higher doses eradicate, the patient's consciousness [42]. It is a useful technique to add to the arsenal used in the treatment of teeth with symptomatic irreversible pulpitis [43]. Sedation with this drug has become the advanced technique of choice for parents [44], and no significant differences in the behavior of children under conscious sedation have been detected using different nitrous oxide gas delivery systems [45]. It can be administered in conjunction with oxygen in patients with behavioral disorders, mental retardation or excessive anxiety about dental care, and patient cooperation has been shown to improve [46].

One study found that this drug can be administered in conjunction with Midazolam and Promethazine, resulting in physiological parameters within normal limits; however, children given Midazolam were significantly more sedated and had superior behavior compared to children given Promethazine. Despite these results, there was no difference in the final phase of treatment between the two drugs [47].

Nitrous oxide is an anesthetic gas very frequently used in pediatric dentistry and preferred by parents. It is a safe sedative that provides good working time and has the advantage of being administered to patients with mental retardation, excessive anxiety, and behavioral disorders.

4. Conclusions

From a practical point of view, the best drug for conscious sedation in pediatric dentistry is nitrous oxide. Nitrous oxide is generally preferred by the parents of patients because it is safe, effective, and has minimal side effects, in addition, it provides a good working time, and can be used in patients with special needs, excessive anxiety or behavioral disorders, making it a good alternative for pediatric conscious sedation.

5. References

1. Preethy NA, Somasundaram S. Sedative and Behavioral Effects of Intranasal Midazolam in Comparison with Other Administrative Routes in Children Undergoing Dental Treatment - A Systematic Review. Contemp Clin Dent. 2021 Apr-Jun;12(2):105-120.
2. Ferrazzano GF, Cantile T, Quaraniello M, Iannuzzi M, Palumbo D, Servillo G, *et al*. Effectiveness and Safety of Intravenous Sedation with Propofol in Non-Operating Room Anesthesia (NORA) for Dental Treatment in Uncooperative Paediatric Patients. Children (Basel). 2021 Jul 28;8(8):648.
3. Attri JP, Sharan R, Makkar V, Gupta KK, Khetarpal R, Kataria AP. Conscious Sedation: Emerging Trends in Pediatric Dentistry. Anesth Essays Res. 2017 Apr-Jun;11(2):277-281.
4. Benzoni T, Cascella M. Procedural Sedation. 2022 Feb 5. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 31869149.
5. Shaat MA, Bakry NS, Elshafie AM, Talaat DM. Intranasal versus sublingual route of dexmedetomidine sedation in paediatric dentistry: A randomized controlled clinical trial. Int J Paediatr Dent. 2021 Jun 8.; 00: 1– 8.
6. Ashley P, Anand P, Andersson K. Best clinical practice guidance for conscious sedation of children undergoing dental treatment: an EAPD policy document. Eur Arch Paediatr Dent. 2021 Aug 28.
7. Fiorillo L. Conscious Sedation in Dentistry. Medicina (Kaunas). 2019 Dec 7;55(12):778.
8. Kramer KJ, Brady JW. Anesthetic Agents Commonly Used by Oral and Maxillofacial Surgeons. Oral Maxillofac Surg Clin North Am. 2018 May;30(2):155-164.
9. Cooke M, Tanbonliong T. Sedation and Anesthesia for the Adolescent Dental Patient. Dent Clin North Am. 2021 Oct;65(4):753-773
10. Song SR, You TM. Minimal sedation using oral sedatives for multi-visit dental treatment in an adult patient with dental phobia. J Dent Anesth Pain Med. 2021 Aug;21(4):369-376.
11. Stern J, Pozun A. Pediatric Procedural Sedation. 2021 Jun 3. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021.
12. Alrayyes SM, Capezio N, Kratunova E, LeHew CW, Alapati S. Factors associated with moderate sedation attendance at a university-based pediatric dental clinic. J Dent Educ. 2021 Jul 26. 1- 7.
13. Kim K, Kim S. Application of sevoflurane inhalation sedation in dental treatment: a mini review. J Dent Anesth Pain Med. 2021 Aug;21(4):321-327.
14. De Stefano R. Psychological Factors in Dental Patient

Care: Odontophobia. Medicina (Kaunas). 2019 Oct 8;55(10):678.
15. Green SM, Roback MG, Krauss BS, Miner JR, Schneider S, Kivela PD, *et al*. Unscheduled Procedural Sedation: A Multidisciplinary Consensus Practice Guideline. Ann Emerg Med. 2019 May;73(5):e51-e65.
16. Möhn M, Bulski JC, Krämer N, Rahman A, Schulz-Weidner N. Management of Amelogenesis Imperfecta in Childhood: Two Case Reports. Int J Environ Res Public Health. 2021 Jul 5;18(13):7204.
17. Estefó M, Ojeda D, Cisternas P, Arraño N, Zanetta H. Factores de riesgo de reacción paradójica asociados a sedación endovenosa con midazolam [Paradoxical reactions associated with midazolam conscious sedation]. Rev Med Chil. 2021 Feb;149(2):237-241.
18. Gupta A, Gunjan, Shekhar S, Gupta S, Gupta A. Comparison of Oral Triclofos and Oral Midazolam as Premedication in Children undergoing Elective Surgery. Anesth Essays Res. 2019 Apr-Jun;13(2):366-369.
19. Ansari G, Fathi M, Ghajari MF, Bargrizan M, Eghbali A. Oral Melatonin Versus Midazolam as Premedication for Intravenous Sedation in Pediatric Dental Patients. J Dent (Tehran). 2018 Sep;15(5):317-324.
20. Vasakova J, Duskova J, Lunackova J, Drapalova K, Zuzankova L, Starka L, *et al*. Midazolam and its effect on vital signs and behavior in children under conscious sedation in dentistry. Physiol Res. 2020 Sep 30;69(Suppl 2):S305-S314.
21. Faghihian R, Eshghi A, Faghihian H, Kaviani N. Comparison of Oral Melatonin and Midazolam as Premedication in Children Undergoing General Anesthesia for Dental Treatment. Anesth Pain Med. 2018 Apr 16;8(2):e64236.
22. Ashley PF, Chaudhary M, Lourenço-Matharu L. Sedation of children undergoing dental treatment. Cochrane Database Syst Rev. 2018 Dec 17;12(12):CD003877.
23. Sado-Filho J, Viana KA, Corrêa-Faria P, Costa LR, Costa PS. Randomized clinical trial on the efficacy of intranasal or oral ketamine-midazolam combinations compared to oral midazolam for outpatient pediatric sedation. PLoS One. 2019 Mar 11;14(3):e0213074.
24. Mehran M, Ansari G, Vahid Golpayegani M, Shayeghi S, Shafiei L. Comparison of sedative effects of oral midazolam/chloral hydrate and midazolam/promethazine in pediatric dentistry. J Dent Res Dent Clin Dent Prospects. 2018 Summer;12(3):221-226.
25. Wang L, Huang L, Zhang T, Peng W. Comparison of Intranasal Dexmedetomidine and Oral Midazolam for Premedication in Pediatric Dental Patients under General Anesthesia: A Randomised Clinical Trial. Biomed Res Int. 2020 Apr 24;2020:5142913.
26. Mohite V, Baliga S, Thosar N, Rathi N. Role of dexmedetomidine in pediatric dental sedation. J Dent Anesth Pain Med. 2019 Apr;19(2):83-90.
27. Keles S, Kocaturk O. Comparison of oral dexmedetomidine and midazolam for premedication and emergence delirium in children after dental procedures under general anesthesia: a retrospective study. Drug Des Devel Ther. 2018 Mar 28;12:647-653.
28. Togawa E, Hanamoto H, Maegawa H, Yokoe C, Niwa H. Dexmedetomidine and Midazolam Sedation Reduces Unexpected Patient Movement During Dental Surgery Compared With Propofol and Midazolam Sedation. J Oral Maxillofac Surg. 2019 Jan;77(1):29-41.
29. Jaikaria A, Thakur S, Singhal P, Chauhan D, Jayam C, Syal K. A Comparison of Oral Midazolam-ketamine, Dexmedetomidine-fentanyl, and Dexmedetomidine-ketamine Combinations as Sedative Agents in Pediatric Dentistry: A Triple-Blinded Randomized Controlled Trial. Contemp Clin Dent. 2018 Sep;9(Suppl 2):S197-S203.
30. Sago T, Shiiba S, Ando E, Kondo K, Tsunakake M, Akitomi S, *et al*. Sedation With a Combination of Dexmedetomidine and Midazolam for Pediatric Dental Surgery. Anesth Prog. 2018 Summer;65(2):124-126.
31. Mahdavi A, Fallahinejad Ghajari M, Ansari G, Shafiei L. Intranasal Premedication Effect of Dexmedetomidine Versus Midazolam on the Behavior of 2-6-Year-Old Uncooperative Children in Dental Clinic. J Dent (Tehran). 2018 Mar;15(2):79-85.
32. Mincer RC, Lee CJ, Chung EM, Huang B, Sung EC. Dexmedetomidine reduces the amount of benzodiazepines and opioids administered during moderate conscious sedation for dental treatment. Spec Care Dentist. 2020 Sep;40(5):437-442.
33. Folino TB, Muco E, Safadi AO, Parks LJ. Propofol. 2021 Jul 31. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 28613634.
34. Secor T, Safadi AO, Gunderson S. Propofol Toxicity. 2021 Sep 21. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 31082121.
35. Lin IH, Huang MS, Wang PY, Huang TS, Chong SY, Chen SL, *et al*. A comparative study of propofol alone and propofol combined with midazolam for dental treatments in special needs patients. Medicine (Baltimore). 2021 Jun 4;100(22):e26199.
36. Joshi AB, Shankaranarayan UR, Hegde A, Manju R. To Compare the Efficacy of Two Intravenous Combinations of Drugs Ketamine-Propofol vs Ketamine-Dexmedetomidine for Sedation in Children Undergoing Dental Treatment. Int J Clin Pediatr Dent. 2020 Sep-Oct;13(5):529-535.
37. Kip G, Atabek D, Bani M. Comparison of three different ketofol proportions in children undergoing dental treatment. Niger J Clin Pract. 2018 Nov;21(11):1501-1507.
38. Absalom AR, Rigby-Jones AE, Rushton AR, Robert Sneyd J. De-mystifying the "Mixifusor". Paediatr Anaesth. 2020 Dec;30(12):1292-1298.
39. Kocaturk O, Keles S. Recovery characteristics of total intravenous anesthesia with propofol versus sevoflurane anesthesia: a prospective randomized clinical trial. J Pain Res. 2018 Jul 6;11:1289-1295.
40. Clar DT, Patel S, Richards JR. Anesthetic Gases. 2021 Dec 9. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 30725698.
41. Ferrazzano GF, Quaraniello M, Sangianantoni G, Ingenito A, Cantile T. Clinical effectiveness of inhalation conscious sedation with nitrous oxide and oxygen for dental treatment in uncooperative paediatric patients during COVID-19 outbreak. Eur J Paediatr Dent. 2020 Dec;21(4):277-282.
42. Hoggard A, Shienbaum R, Mokhtar M, Singh P. Gaseous Anesthetics. 2021 Oct 16. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 30969702.
43. Gupta PD, Mahajan P, Monga P, Thaman D, Khinda VIS, Gupta A. Evaluation of the efficacy of nitrous oxide inhalation sedation on anxiety and pain levels of patients

undergoing endodontic treatment in a vital tooth: A prospective randomized controlled trial. J Conserv Dent. 2019 Jul-Aug;22(4):356-361.
44. Al Zoubi L, Schmoeckel J, Mustafa Ali M, Splieth CH. Parental acceptance of advanced behaviour management techniques in paediatric dentistry in families with different cultural background. Eur Arch Paediatr Dent. 2021 Aug;22(4):707-713.
45. Vanhee T, Lachiri F, Van Den Steen E, Bottenberg P, Vanden Abbeele A. Child behaviour during dental care under nitrous oxide sedation: a cohort study using two different gas distribution systems. Eur Arch Paediatr Dent. 2021 Jun;22(3):409-415.
46. Prud'homme T, Allio A, Dajean-Trutaud S, Bulteau S, Rousselet M, Lopez-Cazaux S, *et al*. Assessment of an Equimolar Mixture of Oxygen and Nitrous Oxide: Effects in Pediatric Dentistry. Int. J Clin Pediatr Dent. 2019 Sep-Oct;12(5):429-436.
47. Mozafar S, Bargrizan M, Golpayegani MV, Shayeghi S, Ahmadi R. Comparison of nitrous oxide/midazolam and nitrous oxide/promethazine for pediatric dental sedation: A randomized, cross-over, clinical trial. Dent Res J (Isfahan). 2018 Nov-Dec;15(6):411-419.