Review Article

Nitrous Oxide-Oxygen Inhalation Sedation: A Light on its Safety and Efficacy in Pediatric Dentistry

P V Samir[1], **Sandeep Suresh Fere**[2]

[1]Assistant Professor, Department of Pedodontics & Preventive Dentistry, Kalinga Institute of Dental Sciences, Bhubaneswar, Odisha, India, [2]Assistant Professor, Department of Prosthodontics, Maharashtra Institute of Dental Sciences & Research, Latur, Maharashtra, India

ABSTRACT

Pharmacological behavior management in pediatric dentistry includes measures involving anxiolysis to minimal sedation to even induction of general anesthesia. It can be used safely with great effect in patients who are unable to receive treatment for various reasons such as young age, compromised state of mind, or health (physically, mentally challenged, or those with medical illness). Anesthesia continuum is subject into minimal sedation, moderate sedation, deep sedation, and general anesthesia. In dentistry, use of minimal and moderate sedation is usually more beneficial because of its minimal pre-operative preparation and acceptable comfort level of patients post-operatively as they require no or minimal hospitalization. Procedural sedation can be administered through various routes such as oral, inhalational, rectal, intravenous, intramuscular, transmucosal, intranasal, and sublingual. Drugs the most common administered are the groups of barbiturates, benzodiazepines, and antihistamines. According to the recent survey on pharmacological management techniques, general anesthesia is considered to be the best followed by nitrous oxide (N_2O) inhalation sedation and oral sedation. N_2O-oxygen (O_2) inhalation sedation can be induced in two different techniques: Slow induction and rapid induction. Credentials of N_2O include its simple titration method, superior analgesic, anxiolytic, amnestic properties rapid onset of action, and equally rapid post-operative recovery. It is also preferred over other drugs in inhalation sedation because of its low tissue solubility, minimum alveolar concentration value of more than 1 atmosphere that accounts for its rapid onset and fast post-operative recovery within minutes and its non-irritant property to the respiratory tract. Incidence of adverse events associated with it include: Nausea, vomiting, dizziness, and headache, which is around 4-10% much less when compared to other drugs. N_2O-O_2 inhalation sedation aims at anxiolysis by raising the pain threshold of children during dental treatment with almost negligible adverse events and establishing a healthy communication with them for a cooperative future dental treatment.

Keywords: Adverse events, Diffusion hypoxia, Minimum alveolar concentration, Minimal sedation, Nitrous oxide, Oxygen saturation, Rapid induction, Slow induction, 50% Nitrous oxide-50% Oxygen premix

Corresponding Author: Dr. P V Samir, Department of Pedodontics & Preventive Dentistry, Kalinga Institute of Dental Sciences, Bhubaneswar, Odisha, India. E-mail: samirdiehard@gmail.com

INTRODUCTION

Most children during dental treatment are relaxed and relatively co-operative, but some display unwanted tantrums that may raise the difficulties of the practitioner in providing a safe acceptable treatment.[1] Ideally, various non-pharmacological behavior management techniques can be used to deliver a successful treatment to the child and guiding them to develop a positive behavior for the further appointments. Unfortunately, not all the children in pediatric practice can be managed by these techniques alone, pharmacological techniques of behavior management such as sedation and anesthesia are considered as a valuable tool by practitioners in such children.[2]

Sedation can be used safely and effectively in patients unable to receive proper dental treatment for reasons such as age, mental, physical, or medical conditions.[3] Treating the patients under some form of sedation to increase the comfort levels of patient is widely accepted by practitioners.[4] An ideal sedative agent for children should be easy to administer, have a rapid onset and offset, produce no residual symptoms, have minimal side effects, and should be cost-effective.[5]

The primary aims of sedation are:

- To reduce or eliminate anxiety
- To reduce any untoward movement and reaction of a child to the dental treatment
- To enhance communication and patient cooperation
- To comfort the child for longer appointments
- To render treatment to mentally, physically, or medically compromised patient
- To raise the patient's pain threshold.

American Dental Association classified levels of sedation into three categories: Conscious sedation, deep sedation, and general anesthesia.[6] American Academy of Pediatric Dentistry has described five levels of sedation according to the state of central nervous system (CNS) depression: Minimal sedation, moderate sedation, deep sedation, and general anesthesia.[7]

Levels of CNS depression state
Minimal sedation (level 1)
Moderate sedation (level 2, 3)
Deep sedation (level 3, 4)
General anesthesia (level 4, 5)

Minimal Sedation

It is a drug-induced state during which patients are awake and calm, and responds normally to verbal commands. Although cognitive function and coordination may be impaired, ventilatory, and cardiovascular functions are unaffected.[8]

Moderate Sedation

It is s drug induced state of CNS depression enabling the treatment to be carried out by maintaining verbal contact with the patient throughout the period of sedation.

Deep Sedation

It is a drug-induced depression of consciousness during which patients are asleep and cannot be easily roused but do respond purposefully to repeated or painful stimulation. The ability to maintain ventilatory function independently may be impaired. The patients may require assistance to maintain a patent airway. Spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.[9]

NITROUS OXIDE (N_2O) – OXYGEN (O_2) INHALATION SEDATION

Since, its introduction in 1844 by Horace wells N_2O has been widely used for sedation to manage pain and anxiety in the patients. It is a colorless and virtually odorless gas with a faintly sweet smell, slightly heavier than air with a specific gravity of 1.53 and blood: Gas coefficient of 0.47. The low solubility of N_2O in blood reasons for its very rapid onset and recovery time.[10]

On inhalation of N_2O to the lungs, it has a rapid uptake as it is quickly absorbed from the alveoli and is held in a simple solution in the serum. N_2O will become saturated in blood within 3-5 min following administration and the alveolar concentration rapidly approaches the inspired concentration. The relative insolubility and high partial pressure gradient of the N_2O in alveoli results in its passage to the low pressure gradient areas of the body such as CNS. The concentration required to produce sedation varies among the individuals.[11]

N_2O inhalation sedation has unique advantages such as rapid onset of action, maintaining the effect of sedation as long as administered, producing analgesia with minimal impairment of any reflexes, and fast post-operative recovery within 5 min.[12]

Indications and Contraindications

Inhalation sedation is indicated in apprehensive patients related with previous negative experiences of treatment, fear of the needle. It should not be used as a local analgesia for treatments such as surgical extractions in patients with bleeding disorders and pronounced gag reflex.[13] Its use is contraindicated in patients with chronic obstructive pulmonary diseases, cobalamin deficiency, severe emotional disturbances, drug-related dependencies, methylenetetrahydrofolate reductase deficiency, at first trimester of pregnancy, nasal blockade, and mouth breathing and those who cannot tolerate the use of mask.[14]

Mechanism of Action

N_2O produces "relative analgesia" - A term defined by Langa as a chemically induced altered psychological state which eliminates the fear and pain of dental experience. The term "relative analgesia" refers to the use of low concentrations of N_2O with high concentrations of O_2 to produce sedation and degree of analgesia. It helps in replacing patients fear and anxiety with a feeling of well-being and confidence (a state of euphoria). The patient remains conscious and cooperative with protective reflexes fully maintained, also experiences a pleasant, floating and detached sensation.[15]

Inhalation and exhalation maintain a barometric equilibrium between air present in the lungs and outside atmospheric pressure during respiration. The amount of gas inspired into the lungs per respiration is known as tidal volume. The amount of gas inspired into the lungs each minute is known as minute volume. Multiplying the tidal volume with a number of respirations per minute gives the minute volume of an individual.

The respiratory system divides itself into:

- A conducting zone: Consists of trachea, bronchus, and segmental bronchioles responsible for the transport of gases. This zone does not regulate the pressure gradient of the gases during respiration and makes up the anatomic dead space
- A respiratory zone: Continues down from segmental bronchioles as terminal bronchioles, alveolar ducts and alveolar sacs consisting of alveoli. The pressure gradient of gases during respiration is regulated by the alveoli present in this zone. There are about 300 million alveoli in human lung each of 1/3 mm in diameter constituting 85 m^2 of the surface area of the lung. Respiratory zone compared to the conducting zone is very small but constitutes the most of the lung volume known as alveolar ventilation.[11]

Checking the minute volume with O_2 before inducing N_2O helps in determining the flow rate of N_2O-O_2 administration. Induction of N_2O results in high partial pressure in the atmosphere and low partial pressure in the alveoli. The pressure gradient results in the rapid infusion of N_2O to the alveoli. From alveoli, the N_2O enters low pressure capillaries and then the brain where it causes anxiolytic and analgesic effect by acting on the gamma-aminobutyric acid receptors.[16]

Safety of N_2O

N_2O does not bind with hemoglobin resulting in its insolubility and very little absorption in the blood. It diffuses into the brain through the barriers of capillaries. Once terminated N_2O partial pressure gradient increases in capillaries resulting in rapid diffusion of N_2O from the capillaries to the alveoli and then exhaled out.[16]

N_2O is safe enough to be administered because of its relative insolubility with blood and rapid diffusion from lungs. N_2O exits faster than the traces of nitrogen that replace it. Any traces of nitrogen or N_2O in the anatomic dead space can be removed by administering 100% O_2 known as O_2 washout.

Resuscitation of a child from moderate sedation to the minimal sedation can also be done with ease during N_2O inhalation sedation. An over sedated child can be brought back to the minimal sedation by simple decrements of N_2O concentrations by 5-10%. The occurrence of adverse events like nausea and vomiting due to oversedation by N_2O are very rare, but knowledge for its management is mandatory for a sedationist. The child undergoing sedation should be advised to wear loosely fitting clothes before to increase the comfort levels of a child during the procedure.[17]

The earliest signs of vomiting such as hypersalivation, sweating and nausea should be seen in a patient before terminating the N_2O and inducing 100% O_2. The nasal hood, other apparatus on the patient's face and in oral cavity should be removed and the child's head and body should be turned away to the side opposite to the operator to allow pooling of the vomitus in the cheeks rather than flowing back to pharynx. An emesis basin and high pressure suction tip can be used to remove the vomitus completely if the patient is not able to vomit.

Following the complete retrieval of vomitus 100% O_2 should be administered for around 3-5 min and the procedure should be continued based on the patient's willingness to undergo further sedation.[18]

N_2O produces non-specific CNS depression. Although it is classified with inhalational general anesthetics, it also produces some analgesia. N_2O is the weakest of all inhalation agents, with a minimum alveolar concentration (MAC) of 105. The MAC of an inhalation agent is a measure of its potency. It is the concentration required to produce immobility in 50% of patients. At concentrations between 30% and 50%, N_2O will produce a relaxed, somnolent patient who may appear dissociated and easily susceptible to suggestions. Amnesia may occur in some patients, but there is a little alteration of learning or memory. At concentrations >60%, patients may experience dis-coordination, ataxia, giddiness, and increased sleepiness. It is not recommended that concentrations >50% be used in dental practice.[19] N_2O reduces hypoxic-driven ventilation and by itself will slightly increase the respiratory minute volume. As the patient becomes more relaxed from the effects of N_2O, the respiratory rate may decrease slightly. It is non-irritating to the respiratory tract and can be given to patients with asthma without fear of bronchospasm. Problems can arise, however, from the added respiratory effects when given in combination with narcotics or other CNS depressants. Cardiac output is decreased, and peripheral vascular resistance is increased when N_2O is used. This is usually of insignificant degree and would be a consideration only in patients with severe cardiac disease.[19]

Administration Techniques of N_2O-O_2 Inhalation Sedation

N_2O-O_2 inhalation sedation can be induced in two different techniques:

Slow induction technique

Initially, 100% O_2 is administered to about 5 L/min in children to determine the minute volume and flow rate of gases, followed by increments in the N_2O concentration of 5-10% for every 3 min. In general, between 20% and 40% of N_2O adequate sedation and analgesia is obtained called as minimal sedation. Local anesthesia is administered by further raising the N_2O concentrations by 10% to achieve the analgesic effect, and the required dental procedure is carried out by bringing back the N_2O concentration to the level of minimal sedation.

Rapid induction technique

Initially, higher concentrations of N_2O ≥50% are administered in young children who are extremely apprehensive and continuously crying. After the child regains his composure and attains the settling phase concentration of N_2O is reduced to 30% for administering local anesthesia known as injection phase and same concentration is maintained throughout the treatment. Precautions should be taken to avoid the roller coaster ride due to the sharp increase or decrease in the N_2O concentrations.[20]

N_2O can also be administered in a premix with O_2 at a concentration of 50% each in a single E-sized cylinder. The flow rate of the premix is initially set at 1 L/min, and the sedation levels are assessed, in case of inadequate sedation flow rate is increased at an increment of 1 L/min at every 1 min interval. In case of over sedation the flow rate is decreased by 1 L/min.[21]

Rapid induction by the premix of 50% N_2O-50% O_2 premix is well documented in literature with minimal complications and greater efficacy of producing anxiolysis and analgesia during the procedure.[22-30]

Rapid induction in the concentrations >50% N_2O is even found to be safe and efficient in producing greater anxiolysis and superior analgesia than the cutaneous application of EMLA cream.[25,31] The incidence of adverse events by rapid induction of 70% N_2O are very infrequent about.[32-34] The incidence rate of the adverse events increases when N_2O in high concentrations is used in combination with other drugs like propofol for deep sedation.[35]

Planes of Analgesia

N_2O-O_2 gas mixture for sedating child patients induces three levels or planes of analgesia and sedation.[36]

Plane 1 or moderate sedation and analgesia are usually obtained with concentrations of 5-25% N_2O (95-75% O_2). The patient may feel tingling in fingers, toes, cheeks, tongue, back of the head, or chest. There is a marked sense of relaxation; pain threshold is raised, and there is a diminution of fear and anxiety. The patient will be obviously relaxed and will respond clearly and sensibly to questions and commands. Other senses such as hearing, vision, touch, and proprioception are impaired in addition to the sensation of pain being reduced. The pupils are normal in appearance and contract with light. The perioral musculature often tensed involuntarily by the patient during treatment is more easily retracted when the dental surgeon attempts to obtain good access for operative work.

The absence of any sideeffects makes this an extremely useful plane when working on moderately anxious patients.[36]

Plane 2 or dissociation sedation and analgesia are usually obtained with concentrations of 20-55% N_2O (80-45% O_2). The patient may feel suffused by a warm wave, may experience a slight humming or buzzing in the ears and a drowsiness or light-headedness sometimes described by the patient as a “floaty” or “woozy” feeling. The overall demeanor of the patient will be relaxed and acquiescent. In a study by Berger *et al*. (1972), some children reported a “floating, warm, and tingling sensation” with N_2O. Apart from the overall appearance of relaxation, one of the few tangible physical signs is a reduction in the eye blink rate. At a deeper level of this plane of sedation, the psychological effects become more pronounced. Occasionally, a patient will repeat words or phrases several times in succession. The words repeated may or may not make sense. There is a noticeable tendency to dream, the dreams usually being of a pleasant nature. The sedative effect is considerably pronounced with both psycho-sedation and somatic sedation being present. The psycho-sedation takes the form of a relaxed demeanor and a willingness on the part of the previously unwilling patient to allow treatment regarded previously as frightening or especially traumatic. It has been reported that there are observable objective clinical signs of N_2O conscious sedation in children.[37] In addition; children reported differences in their subjective symptoms with N_2O conscious sedation. Furthermore, they found N_2O has a small but significant effect on the psychomotor ability of children at 50% concentration.

Plane 3 or total analgesia is usually obtained with concentrations of 50-70% N_2O and 50-30% O_2. The analgesia is almost complete and there is an increased tendency to dream. It is important to recognize that in a small number of patients 50% N_2O may bring loss of consciousness. So, dentists must exercise considerable caution while using N_2O more than 40%. If patient does become too deeply sedated and enters this third plane of total analgesia, he/she begins to lose the ability to independently maintain an open mouth and is unable to co-operate or respond to the dentist’s requests. If open mouth cannot be maintained by patient, the operator can be sure that the patient is too deep in the plane of total analgesia and within a few minutes is likely to enter the plane of light anesthesia. It is for this reason that a mouth prop must never be used, for if a prop is used the open mouth sign would not function.

If sedation is too deep, and the patient shows signs of failing to co-operate, then the dentist should reduce the N_2O concentration by 10% or 15% for 2 min. If it is considered necessary to lighten the sedation even more rapidly, the nasal hood should be removed, and the patient allowed breathing ambient air. The patient will return to a lighter plane within 15-20 s. Plane of total analgesia is regarded as a buffer zone between the clinically useful planes of moderate and dissociation sedation and analgesia and the potentially hazardous plane of light anesthesia.[38]

Analgesic effect of 30% N_2O is as effective as 10-15 mg of morphine.[39] American Society of Anesthesiologist's and American Academy of Pediatrics (AAP) accepts N_2O concentrations <50% as a drug for minimal sedation.[40] AAP cautions the increase in chances of moderate or deep sedation by N_2O concentrations >50%.[41]

Diffusion Hypoxia and Other Adverse Events

The incidence of diffusion hypoxia and other adverse events such as nausea, vomiting, dizziness, and sense of detachment, may increase due to rapid induction technique by administering of high concentrations of N_2O. The headache, nausea, and lethargy may occur due to decreased O_2 saturation (SpO_2) levels in blood caused by rapid exit of N_2O on its termination.[11]

SpO_2 is the ratio of O_2 loosely bound with hemoglobin to reduced hemoglobin not bound with O_2. SpO_2 in healthy person with no pulmonary or cardiovascular disease is 98-100%. (SpO_2) <90% is a matter of grave concern and clearly an early warning of impending rapid loss of O_2 to the brain. Therefore, continuous monitoring of SpO_2 of arterial blood by pulse oximeter is essential.[42]

Diffusion hypoxia may occur as the sedation is reversed at the termination of the procedure. The N_2O escapes into the alveoli with such rapidity that the O_2 present becomes diluted such that the O_2-carbon dioxide exchange is disrupted and a period of hypoxia is created. However, this phenomenon is reported not to occur in healthy pediatric patients. Nonetheless, to minimize this effect, the patient should be oxygenated for 5 min after a sedation procedure.[12]

The incidence of diffusion hypoxia during N_2O inhalation sedation, even at higher concentrations of ≥50% N_2O is very rarely documented in the available literature.

Quarnstrom *et al*. with his clinical experience in over 10,000 administrations of N_2O sedation without post-operative O_2 could not detect any clinical problems like hypoxia.[22]

Papageorge *et al*. monitored 80 patients and found that O_2 decreased with a mean of 2.1% in the study, all the decreased O_2 levels were stabilized independently within 12 s to 15 min.[43]

Dunn-Russell *et al*. assessed 24 children who were allowed to breathe room air after N_2O inhalation sedation. None of the children exhibited any abnormal levels of SpO_2 or any other side effects.[44]

Brodsky *et al*. observed 3 out of 60 patients with decreased levels of SpO_2 under N_2O inhalation sedation.[45]

Hovagim *et al*. even with the post-operative O_2 administration after N_2O inhalation sedation there may be a mild decrease in levels of SpO_2.[46]

Brodsky *et al*., Frumin and Edelist even very high levels of N_2O cannot cause clinically significant hypoxia in the healthy patients who maintain normal ventilation.[45,47]

Fink observed diffusion hypoxia in 8 healthy gynecologic patients undergoing endotracheal anesthesia using 75% N_2O in O_2 at 4 L/min supplemented with intravenous thiopental. Furthermore, reports of an average 8% drop in SpO_2 when the patients were switched to room air.[48]

Vetter TR:. 70% N_2O administered by face mask appears to provide greater anxiolysis and superior analgesia for pediatric venous cannulation than a cutaneous application of EMLA cream.[31]

N_2O-O_2 inhalation sedation has an excellent safety record. It is a safe and effective agent for providing pharmacological behavior guidance in children when administered by trained personnel with appropriate equipment and technique.

Fasting is not required for patients undergoing N_2O-O_2 inhalation sedation. However, a light meal 2 h prior to the administration of N_2O is can be recommended.[49]

Acute and chronic adverse events of N_2O are rare.[50] Nausea and vomiting are the most common adverse events, occurring in 0.5% of patients.[23] A higher incidence is noted with longer administration of N_2O-O_2, fluctuations in N_2O levels, and increased concentrations of N_2O.[12]

Efficacy of use of rapid induction by premix of 50% N_2O-50% O_2 for various medical and dental procedures is well documented in literature with very little incidence rate of diffusion hypoxia and any other adverse events.

Hennequin *et al*. strong supporting evidence for the safety and effectiveness of 50% N_2O-O_2 inhalation sedations use in general dental practice for healthy patients.[23]

Quarnstrom *et al*. evaluated 104 patients and found no drop in SpO_2, and even questioned the necessity of post-operative O_2 for 5 min.[22]

Keidan *et al*. continuous flow 50:50 $N_2O:O_2$ is effective for procedural pain in the pediatric emergency department. It is preferred in children particularly >3 years old with short recovery times and very rare minor adverse effects.[24]

Hee *et al*. EMLA and 50% N_2O are equally effective for pain reduction while a combination technique provides superior analgesia and satisfaction. N_2O has an advantage over EMLA in reduction of pain related behavior in older children.[25]

Fauroux *et al*. demonstrated the improved efficacy of sedation, pain control, and safety of premixed 50% N_2O-50% O_2 for fiberoptic bronchoscopy in children.[26]

Gall *et al*. premix 50% N_2O in O_2 induces conscious sedation, and can be considered as a first-line option for sedation of children with no other complications or adverse events.[27]

Saunders *et al*. 47 patients treated with 50% N_2O reported no headache, drowsiness in 3%, and hypotension in 7% of the cases.[28]

Castéra *et al*. demonstrated a higher incidence of headache in patients treated with 50% N_2O.[29]

Notini-Gudmarsson *et al*. no reports of headache in 38 patients treated with 50% N_2O.[30]

Rapid induction of N_2O with concentrations of N_2O ≥70% N_2O though can have a slightly higher incidence rate of adverse events as per the documented literature.

Pandit *et al*. severity and incidence of vomiting in children does not differ between patients treated with N_2O at 70% and those who did not receive the anesthetic.[32]

Crawford *et al*. associated increased incidence of post-operative vomiting when N_2O is combined with propofol.[35]

Babl *et al*. frequency of adverse events in patients administered with 70% N_2O and 50% N_2O had no difference, incidence of adverse events by 70% N_2O was found to be 8%.[33]

Frampton *et al*.[51] and Zier *et al*.[34] reported 27% and 4% incidence of adverse events on administration with 70% N_2O, respectively.

CONCLUSION

Efficacy of N_2O-O_2 inhalation sedation in raising the pain threshold, anxiolysis, negligible adverse events, and fast post-operative recovery in pediatric dental patients makes it the most preferred mode of pharmacological behavior management.

REFERENCES

1. Wright GZ. Children's behaviour in dental office. In: Wright GZ, Starkey PE, Gardner DE, editors. Behaviour Management in Dentistry for Children. Philadelphia: WB Saunders Co.; 1975. p. 55-72.
2. Webb MD, Moore PA. Sedation for pediatric dental patients. Dent Clin North Am 2002;46:803-14.
3. AAPD. Guideline on Behavior Guidance for the Pediatric Dental Patient - AAPD Reference Manual. Vol. 34. AAPD; 2012-13. p. 170-81.
4. Fuhrer CT 3rd, Weddell JA, Sanders BJ, Jones JE, Dean JA, Tomlin A. Effect on behavior of dental treatment rendered under conscious sedation and general anesthesia in pediatric patients. Pediatr Dent 2009;31:492-7.
5. Pedersen RS, Bayat A, Steen NP, Jacobsson ML. Nitrous oxide provides safe and effective analgesia for minor paediatric procedures – a systematic review. Dan Med J 2013;60:A4627.
6. Guidelines for teaching the comprehensive control of pain and anxiety in dentistry. Council on Dental Education, American Dental Association. J Dent Educ 1989;53:305-10.
7. American Academy of Pediatric Dentistry Clinical Affairs Committee – Behavior Management Subcomittee; American Academy of Pediatric Dentistry Council on Clinical Affairs – Committee on Behavior Guidance. Guideline on behavior guidance for the pediatric dental patient. Pediatr Dent 2005-2006;27:92-100.
8. Zier JL, Tarrago R, Liu M. Level of sedation with nitrous oxide for pediatric medical procedures. Anesth Analg 2010;110:1399-405.
9. ADA. Guidelines for the Use of Sedation and General Anesthesia by Dentists. ADA Reference Manual. Chicago, IL: ADA; 2007. p. 1-13.
10. Clark M, Brunick A, editors. Physical properties and pharmacokinetics of N_2O. In: Handbook of Nitrous Oxide and Oxygen Sedation. 2nd ed. St. Louis, MO: CV Mosby Co.; 2003. p. 33-8.
11. Clark M, Brunick A, editors. Anatomy and physiologyss of respiration and airway management. In: Handbook of Nitrous Oxide and Oxygen Sedation. 2nd ed. St. Louis, MO: CV Mosby Co.; 2003. p. 77-88.
12. Paterson SA, Tahmassebi JF. Paediatric dentistry in the new millennium: Use of inhalation sedation in paediatric dentistry. Dent Update 2003;30:350-6, 358.
13. Kaufman E, Weinstein P, Sommers EE, Soltero DJ. An experimental study of the control of the gag reflex with nitrous oxide. Anesth Prog 1988;35:155-7.
14. Ponte J, Craig DC. Sedation. Dent Update 1988;Suppl III:31-6.
15. Langa H. Relative Analgesia in Dental Practice: Inhalation Analgesia and Sedation with Nitrous Oxide Oxygen. Philadelphia: WB Saunders Co.; 1976. p. 164.
16. Emmanouil DE, Quock RM. Advances in understanding the actions of nitrous oxide. Anesth Prog 2007;54:9-18.
17. Clark M, Brunick A, editors. Techniques of N_2O/O_2 administration. In: Handbook of Nitrous Oxide and Oxygen Sedation. 2nd ed. St. Louis, MO: CV Mosby Co.; 2003. p. 118-43.
18. Clark M, Brunick A, editors. Recovery from N_2O/O_2 sedation. In:

Handbook of Nitrous Oxide and Oxygen Sedation. 2nd ed. St. Louis, MO: CV Mosby Co.; 2003. p. 144-8.
19. Dock M, Creedon RL. Pharmacological management of patient behaviour. In: McDonald RE, Avery DR, editors. Dentistry for the Child and Adolescent. 4th ed. St. Louis: CV Mosby Co.; 1983. p. 298.
20. Clark M, Brunick A, editors. Clinical application of N2O/O2 sedation in pediatrics. In: Handbook of Nitrous Oxide and Oxygen Sedation. 2nd ed. St. Louis, MO: CV Mosby Co.; 2003. p. 166.
21. Quarnstrom FC, Mar RS. A premix of 50% nitrous oxide - 50% oxygen for sedation during dental procedures. Anesth Prog 1983;30:197-8.
22. Quarnstrom FC, Milgrom P, Bishop MJ, DeRouen TA. Clinical study of diffusion hypoxia after nitrous oxide analgesia. Anesth Prog 1991;38:21-3.
23. Hennequin M, Collado V, Faulks D, Koscielny S, Onody P, Nicolas E. A clinical trial of efficacy and safety of inhalation sedation with a 50% nitrous oxide/oxygen premix (Kalinox™) in general practice. Clin Oral Investig 2012;16:633-42.
24. Keidan I, Zaslansky R, Yusim Y, Ben-Ackon M, Rubinstien M, Perel A, *et al*. Continuous flow 50:50 nitrous oxide: Oxygen is effective for relief of procedural pain in the pediatric emergency department. Acute Pain 2003;5:25-30.
25. Hee HI, Goy RW, Ng AS. Effective reduction of anxiety and pain during venous cannulation in children: A comparison of analgesic efficacy conferred by nitrous oxide, EMLA and combination. Paediatr Anaesth 2003;13:210-6.
26. Fauroux B, Onody P, Gall O, Tourniaire B, Koscielny S, Clément A. The efficacy of premixed nitrous oxide and oxygen for fiberoptic bronchoscopy in pediatric patients: A randomized, double-blind, controlled study. Chest 2004;125:315-21.
27. Gall O, Annequin D, Benoit G, Glabeke E, Vrancea F, Murat I. Adverse events of premixed nitrous oxide and oxygen for procedural sedation in children. Lancet 2001;358:1514-5.
28. Saunders BP, Elsby B, Boswell AM, Atkin W, Williams CB. Intravenous antispasmodic and patient-controlled analgesia are of benefit for screening flexible sigmoidoscopy. Gastrointest Endosc 1995;42:123-7.
29. Castéra L, Nègre I, Samii K, Buffet C. Patient-administered nitrous oxide/oxygen inhalation provides safe and effective analgesia for percutaneous liver biopsy: A randomized placebo-controlled trial. Am J Gastroenterol 2001;96:1553-7.
30. Notini-Gudmarsson AK, Dolk A, Jakobsson J, Johansson C. Nitrous oxide: A valuable alternative for pain relief and sedation during routine colonoscopy. Endoscopy 1996;28:283-7.
31. Vetter TR. A comparison of EMLA cream versus nitrous oxide for pediatric venous cannulation. J Clin Anesth 1995;7:486-90.
32. Pandit UA, Malviya S, Lewis IH. Vomiting after outpatient tonsillectomy and adenoidectomy in children: The role of nitrous oxide. Anesth Analg 1995;80:230-3.
33. Babl FE, Oakley E, Seaman C, Barnett P, Sharwood LN. High-concentration nitrous oxide for procedural sedation in children: Adverse events and depth of sedation. Pediatrics 2008;121:e528-32.
34. Zier JL, Drake GJ, McCormick PC, Clinch KM, Cornfield DN. Case-series of nurse-administered nitrous oxide for urinary catheterization in children. Anesth Analg 2007;104:876-9.
35. Crawford MW, Lerman J, Sloan MH, Sikich N, Halpern L, Bissonnette B. Recovery characteristics of propofol anaesthesia, with and without nitrous oxide: A comparison with halothane/nitrous oxide anaesthesia in children. Paediatr Anaesth 1998;8:49-54.
36. Wilson S, Vann WF, Dilley DC. Pain reaction control (sedation). In: Pinkham JR, editor. Pediatric Dentistry Infancy through Adolescence. 4th ed. St. Louis: Elsevier Saunders Co.; 2005. p. 116-39.
37. Houpt MI, Limb R, Livingston RL. Clinical effects of nitrous oxide conscious sedation in children. Pediatr Dent 2004;26:29-36.
38. Roberts GJ, Hosey MT. Pharmacological management of pain and anxiety. In: Welbury RR, Duggal MS, Hosey MT, editors. Pediatric Dentistry. 3rd ed. Oxford: St. Clarendon; 2005. p. 63-88.
39. Chapman WP, Arrowood JG, Beecher HK. The analgetic effects of low concentrations of nitrous oxide compared in man with morphine sulphate. J Clin Invest 1943;22:871-5.
40. American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. Anesthesiology 2002;96:1004-17.
41. American Academy of Pediatrics; American Academy of Pediatric Dentistry, Coté CJ, Wilson S; Work Group on Sedation. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: An update. Pediatrics 2006;118:2587-602.
42. Dock M. Pharmacological management of patient behavior. In: Mc Donald RE, Avery DR, editors. Dentistry for the Child and Adolescent. 9th ed. St. Louis; CV Mosby Co.; 2011. p. 274.
43. Papageorge MB, Noonan LW, Rosenberg M. Diffusion hypoxia: Another view. Anesth Pain Control Dent 1993;2:143-9.
44. Dunn-Russell T, Adair SM, Sams DR, Russell CM, Barenie JT. Oxygen saturation and diffusion hypoxia in children following nitrous oxide sedation. Pediatr Dent 1993;15:88-92.
45. Brodsky JB, McKlveen RE, Zelcer J, Margary JJ. Diffusion hypoxia: A reappraisal using pulse oximetry. J Clin Monit 1988;4:244-6.
46. Hovagim AR, Vitkun SA, Manecke GR, Reiner R. Arterial oxygen desaturation in adult dental patients receiving conscious sedation. J Oral Maxillofac Surg 1989;47:936-9.
47. Frumin MJ, Edelist G. Diffusion anoxia: A critical reappraisal. Anesthesiology 1969;31:243-9.
48. Fink BR. Diffusion anoxia. Anesthesiology 1955;16:511-9.
49. Kupietzky A, Tal E, Shapira J, Ram D. Fasting state and episodes of vomiting in children receiving nitrous oxide for dental treatment. Pediatr Dent 2008;30:414-9.
50. Donaldson D, Meechan JG. The hazards of chronic exposure to nitrous oxide: An update. Br Dent J 1995;178:95-100.
51. Frampton A, Browne GJ, Lam LT, Cooper MG, Lane LG. Nurse administered relative analgesia using high concentration nitrous oxide to facilitate minor procedures in children in an emergency department. Emerg Med J 2003;20:410-3.

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