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Best Practices on Use of Nitrous Oxide for Pediatric Dental Patients

Review Council

Council on Clinical Affairs

Latest Revision

~~2013~~ 2018

Purpose

The American Academy of Pediatric Dentistry (**AAPD**) recognizes nitrous oxide/oxygen inhalation as a safe and effective technique to reduce anxiety, produce analgesia, and enhance effective communication between a patient and health care provider. The need to diagnose and treat, as well as the safety of the patient and practitioner, should be considered before using nitrous oxide. By producing this guideline, the AAPD intends to assist the dental profession in developing appropriate practices in the use of nitrous oxide/oxygen analgesia/anxiolysis for pediatric patients.

Methods

This guideline was originally developed by the Council on Clinical Affairs ~~Committee~~ and adopted in 2005. This document is a revision of the previous version, last revised in 2013~~09~~. The revision is based on a review of the current dental and medical literature related to nitrous oxide use. An electronic search was conducted using PubMed® with the terms: nitrous oxide, analgesia, anxiolysis, behavior management, diffusion hypoxia, scavenging, occupational exposure, and dental treatment; fields: all; limits: within the last 10 years, humans, English, and clinical trials. Forty articles met these criteria, and papers were added to the references from the previous document. Additionally, the American Dental Association Guideline for the use of sedation and general anesthesia by dentists and the American Dental Association Oral Health Topics – Nitrous oxide dental best practices for nitrous oxide-oxygen use were reviewed. When data did not appear sufficient or were inconclusive, recommendations were based upon expert and/or consensus opinion by experienced researchers and clinicians.

Background

Dentists have expertise in providing anxiety and pain control for their patients. While anxiety and pain can be modified by psychological techniques, in many instances pharmacological approaches are required[1]. Analgesia/anxiolysis is defined as diminution or elimination of pain and anxiety in a conscious

patient[2]. The patient responds normally to verbal commands. All vital signs are stable, there is no significant risk of losing protective reflexes, and the patient is able to return to pre-procedure mobility. In children, analgesia/anxiolysis may expedite the delivery of procedures that are not particularly uncomfortable, but require that the patient not move[2]. It also may allow the patient to tolerate unpleasant procedures by reducing or relieving anxiety, discomfort, or pain. The use of nitrous oxide increases reaction time, reduces pressure-induced pain, but does not affect pulpal sensitivity, as shown in a double-blind, crossover study[3]. The outcome of pharmacological approaches is variable and depends upon each patient's response to various drugs. The clinical effect of nitrous oxide/oxygen inhalation, however, is more predictable among the majority of the population.

Nitrous oxide is a colorless and virtually odorless gas with a faint, sweet smell. It is an effective analgesic/anxiolytic agent causing central nervous system (**CNS**) depression and euphoria with little effect on the respiratory system[4,5]. Nitrous oxide has multiple mechanisms of action. The analgesic effect of nitrous oxide appears to be initiated by neuronal release of endogeneous opioid peptides with subsequent activation of opioid receptors and descending Gamma-aminobutyric acid type A (**GABAA**) receptors and noradrenergic pathways that modulate nociceptive processing at the spinal level. The anxiolytic effect involves activation of the GABAA receptor either directly or indirectly through the benzodiazepine binding site[6,7]. Nitrous oxide has rapid uptake, being absorbed quickly from the alveoli and held in a simple solution in the serum. It is relatively insoluble, passing down a gradient into other tissues and cells in the body, such as the CNS. It is excreted quickly from the lungs. ~~As nitrous oxide is 34 times more soluble than nitrogen in blood, diffusion hypoxia may occur~~. ~~Studies (Patel et al 1994, Patel, Norden and Hannallah 1988, Kinouci et al 1992) have shown that children desaturate more rapidly than adolescents, and administering 100 percent oxygen to the patient once the nitrous oxide in a closed system has been terminated is important (Patel et al 1994).~~ Nitrous oxide causes minor depression in cardiac output while peripheral resistance is slightly increased, thereby maintaining the blood pressure[4]. This is of particular advantage in treating patients with cerebrovascular system disorders.

Nitrous oxide is absorbed rapidly, allowing for both rapid onset and recovery (two to three minutes). It causes minimal impairment of any reflexes, thus protecting the cough reflex[4]. It exhibits a superior safety profile with no recorded fatalities or cases of serious morbidity when used within recommended concentrations[8-11] ~~(Nathan 1989). Studies have reported negative outcomes associated with use of nitrous oxide greater than 50 percent and as an anesthetic during major surgery (Schmitt and Baum 2008, Zeir and Doescher 2010). Although rare, silent regurgitation and subsequent aspiration need to be considered~~

~~with nitrous oxide/oxygen sedation. The concern lies in whether pharyngeal-laryngeal reflexes remain intact. This problem can be avoided by not allowing the patient to go into an unconscious state (Hogue, Ternisky and Iranour 1971). Side effects such as nausea and vomiting are more likely to be observed when titration is not employed (Malamed and Clark 2003). As nitrous oxide is 34 times more soluble than nitrogen in blood, diffusion hypoxia may occur. This can be avoided by administering 100 percent oxygen for five minutes once the nitrous oxide flow is terminated.~~

The decision to use nitrous oxide/oxygen analgesia/anxiolysis must take into consideration alternative behavioral guidance modalities, the patient's dental needs, the effect on the quality of dental care, the patient's emotional development, and the patient's physical considerations. Nitrous oxide generally is acceptable to children and can be titrated easily. Most children are enthusiastic about the administration of nitrous oxide/oxygen; many children report feeling a tingling or warm sensation. Objectively, children may appear with their hands open, legs limp, and with a trancelike expression[12]. ~~dreaming or being on a "space-ride" (Hogue, Ternisky and Iranour 1971).~~ For some patients, however, the feeling of "losing control" may be troubling and children with claustrophobia~~e patients~~ may find the nasal hood confining and unpleasant[13].

Nitrous oxide has been associated with bioenvironmental concerns because of its contribution to the greenhouse effect[14]. Nitrous oxide is emitted naturally by bacteria in soils and oceans; it is produced by humans through the burning of fossil fuels and forests and the agricultural practices of soil cultivation and nitrogen fertilization. Altogether, nitrous oxide contributes about five percent to the greenhouse effect[15,16]. Only a small fraction of this five percent (0.35 to two percent), however, is actually the result of combined medical and dental applications of nitrous oxide gas[16].

The objectives of nitrous oxide/oxygen inhalation include:

1. Reduce or eliminate anxiety.
2. Reduce untoward movement and reaction to dental treatment.
3. Enhance communication and patient cooperation.
4. Raise the pain reaction threshold.
5. Increase tolerance for longer appointments.
6. Aid in treatment of the mentally/physically disabled or medically compromised patient.
7. Reduce gagging.
8. Potentiate the effect of sedatives.

Disadvantages of nitrous oxide/oxygen inhalation may include[4]:

1. Lack of potency.
2. Dependant largely on psychological reassurance.
3. Interference of the nasal hood with injection to anterior maxillary region.
4. Patient must be able to breathe through the nose.
5. Nitrous oxide pollution and potential occupational exposure health hazards.

Recommendations

Indications for use of nitrous oxide/oxygen analgesia/anxiolysis include:

1. A fearful, anxious, or obstreperous patient.
2. Certain patients with special health care needs.
3. A patient whose gag reflex interferes with dental care.
4. A patient for whom profound local anesthesia cannot be obtained.
5. A cooperative child undergoing a lengthy dental procedure.

Review of the patient's medical history should be performed prior to the decision to use nitrous oxide/oxygen analgesia/anxiolysis. This assessment should include:

1. Allergies and previous allergic or adverse drug reactions.
2. Current medications including dose, time, route, and site of administration.
3. Diseases, disorders, or physical abnormalities and pregnancy status.
4. Previous hospitalization to include the date and purpose.
5. Recent illnesses (e.g., cold or congestion) that may compromise the airway.

Contraindications for use of nitrous oxide/oxygen inhalation may include:

1. Some chronic obstructive pulmonary diseases[17].
2. Current upper respiratory tract infection[18].
3. Recent middle ear disturbance/ surgery[18].
4. ~~2.~~ Severe emotional disturbances or drug-related dependencies[18].
5. ~~3.~~ First trimester of pregnancy[19].
6. ~~4.~~ Treatment with bleomycin sulfate[20].
7. ~~5.~~ Methylenetetrahydrofolate reductase deficiency[21].
8. ~~6.~~ Cobalamin (Vit B12) deficiency[7].

Whenever possible, appropriate medical specialists should be consulted before administering analgesic/anxiolytic agents to patients with significant underlying medical conditions (e.g., severe obstructive pulmonary disease, congestive heart failure, sickle cell disease[22], acute otitis media, recent tympanic membrane graft[23], acute severe head injury[24]. In addition, consultation with the prenatal medical provider should precede use of nitrous oxide/oxygen analgesia/ anxiolysis during pregnancy[25].

Technique of nitrous oxide/oxygen administration

Nitrous oxide/oxygen must be administered only by appropriately licensed individuals, or under the direct supervision thereof, according to state law. The practitioner responsible for the treatment of the patient and/or the administration of analgesic/anxiolytic agents must be trained in the use of such agents and techniques and appropriate emergency response.

Selection of an appropriately sized nasal hood should be made. A flow rate of five to six L/min generally is acceptable to most patients. The flow rate can be adjusted after observation of the reservoir bag. The bag should pulsate gently with each breath and should not be either over- or underinflated. Introduction of 100 percent oxygen for one to two minutes followed by titration of nitrous oxide in 10 percent intervals is recommended. During nitrous oxide/oxygen analgesia/anxiolysis, the concentration of nitrous oxide should not routinely exceed 50 percent. Studies have demonstrated that gas concentrations dispensed by the flow meter vary significantly from the end-expired alveolar gas concentrations; it is the latter that is responsible for the clinical effects[26,27]. To achieve sedation, the scavenging vacuum should not be so strong as to prevent ad-equate ventilation of the lungs with nitrous oxide[28]. A review of records of patients undergoing nitrous oxide-oxygen inhalation sedation demonstrated that the typical patient requires from 30 to 40 percent nitrous oxide to achieve ideal sedation ~~(Malamed and Clark 2003)~~. Clinicians should keep patients' talking and mouth breathing to a minimum to prevent expired nitrous oxide from contaminating the operatory[29]. Nitrous oxide concentration may be decreased during easier procedures (e.g., restorations) and increased during more stimulating ones (e.g., extraction, injection of local anesthetic). One study found that there was no benefit to continuous administration of nitrous oxide after profound anesthesia had been achieved[30]. ~~Side effects such as nausea and vomiting are more likely to be observed when titration is not employed (Malamed and Clark 2003).~~ During treatment, it is important to continue the visual monitoring of the patient's respiratory rate and level of consciousness. The effects of nitrous oxide largely are dependent on psychological reassurance. Therefore, it is important to continue traditional behavior guidance techniques during treatment. Once the nitrous oxide flow is

terminated, 100 percent oxygen should be administered until the patient has returned to pre-treatment status[31]. ~~should be delivered for five minutes~~. The patient must return to pretreatment responsiveness before discharge.

Monitoring

The response of patients to commands during procedures performed with analgesia/anxiolysis serves as a guide to their level of consciousness. Clinical observation of the patient must be performed during any dental procedure. During nitrous oxide/oxygen analgesia/anxiolysis, continual clinical observation of the patient's responsiveness, color, and respiratory rate and rhythm must be performed. Spoken responses provide an indication that the patient is breathing[2]. If any other pharmacologic agent is used in addition to nitrous oxide/oxygen and a local anesthetic, monitoring guidelines for the appropriate level of sedation must be followed[32].

Adverse effects of nitrous oxide/oxygen inhalation

Nitrous oxide/oxygen analgesia/anxiolysis has an excellent safety record. When administered by trained personnel on carefully selected patients with appropriate equipment and technique, nitrous oxide is a safe and effective agent for providing pharmacological guidance of behavior in children. Acute and chronic adverse effects of nitrous oxide on the patient are rare[33]. Nausea and vomiting are the most common adverse effects, occurring in 0.5 – 1.2 percent of patients[34,35]. A higher incidence is noted with longer administration of nitrous oxide/oxygen, fluctuations in nitrous oxide levels, ~~and~~ lack of titration, increased concentrations of nitrous oxide, and a heavy meal prior to administration of nitrous oxide[4,28,29] . Fasting is not required for patients undergoing nitrous oxide analgesia/anxiolysis. The practitioner, however, may recommend that only a light meal be consumed in the two hours prior to the administration of nitrous oxide[36]. Studies have reported negative outcomes associated with use of nitrous oxide greater than 50 percent and as an anesthetic during major surgery[37,38]. Although rare, silent regurgitation and subsequent aspiration need to be considered with nitrous oxide/oxygen sedation. The concern lies in whether pharyngeal-laryngeal reflexes remain intact. This problem can be avoided by not allowing the patient to go into an unconscious state[39].

As nitrous oxide is 34 times more soluble than nitrogen in blood, diffusion hypoxia may occur. Diffusion hypoxia can occur as a result of rapid release of nitrous oxide from the blood stream into the alveoli, thereby diluting the concentration of oxygen. This may lead to headache, ~~and~~ disorientation, and nausea and can be avoided by administering 100 percent oxygen once the nitrous oxide flow is terminated[4]..

~~Diffusion hypoxia can occur as a result of rapid release of nitrous oxide from the blood stream into the alveoli, thereby diluting the concentration of oxygen. This may lead to headache, and disorientation, and nausea and can be avoided by administering 100 percent oxygen after nitrous oxide has been discontinued (Paterson and Tahmassebi 2003).~~ While the standard recommendation is to administer 100% oxygen at the end of the procedure, several studies have questioned the necessity for this step in nitrous oxide protocols in healthy patients[18,40-42].

Documentation

Informed consent must be obtained from the parent and documented in the patient's record prior to administration of nitrous oxide/oxygen. The practitioner should provide instructions to the parent regarding pretreatment dietary precautions, if indicated. In addition, the patient's record should include indication for use of nitrous oxide/oxygen inhalation, nitrous oxide dosage (i.e., percent nitrous oxide/oxygen and/or flow rate), duration of the procedure, and post treatment oxygenation procedure.

Facilities/personnel/equipment

All newly installed facilities for delivering nitrous oxide/oxygen must be checked for proper gas delivery and fail-safe function prior to use. Inhalation equipment must have the capacity for delivering 100 percent, and never less than 30 percent, oxygen concentration at a flow rate appropriate to the child's size. Additionally, inhalation equipment must have a fail-safe system that is checked and calibrated regularly according to the practitioner's state laws and regulations[38]. The system components, including the reservoir bag, should be inspected routinely for cracks, wear, and tears. If detected, repairs should be made immediately. Pressure connections should be tested for leaks when delivery system is turned on and each time a tank is changed. ~~Compressed gas tanks must be kept in a locked room.~~ Consult state and federal guidelines regarding storage of compressed gas tanks. Additional locks at the tanks, or mixer/ delivery level are available from many manufacturers to deter individuals from accessing nitrous oxide inappropriately[43]. If nitrous oxide/oxygen delivery equipment capable of delivering more than 70 percent nitrous oxide and less than 30 percent oxygen is used, an inline oxygen analyzer must be used. The equipment must have an appropriate scavenging system to minimize room air contamination and occupational risk. The scavenging system should vent outside[44]. Additionally, it has been shown that the double-mask system is more effective than the single-mask system in the removal of waste nitrous oxide[46,47].

The practitioner who utilizes nitrous oxide/oxygen analgesia/anxiolysis for a pediatric dental patient shall possess appropri-ate training and skills and have available the proper facilities, personnel, and equipment to manage any reasonably foresee-able emergency. The practitioner is responsible for managing the potential complications associated with the intended level of sedation and the next deeper level. Therefore, because moderate sedation may occur, practitioners should have the appropriate training and emergency equipment to manage this[31]. Training and certification in basic life support are required for all clinical personnel. These individuals should participate in periodic review of the office's emergency protocol, the emergency drug cart, and simulated exercises to assure proper emergency management response.

An emergency cart (kit) must be readily accessible. Emergency equipment must be able to accommodate children of all ages and sizes. It should include equipment to resuscitate a non-breathing, unconscious patient and provide continuous support until trained emergency personnel arrive. A positive-pressure oxygen delivery system capable of administering greater than 90 percent oxygen at a 10 L/min flow for at least 60 minutes (650 L, "E" cylinder) must be available. When a self-inflating bag valve mask device is used for delivering posi-tive pressure oxygen, a 15 L/min flow is recommended. There should be documentation that all emergency equipment and drugs are checked and maintained on a regularly scheduled basis[32]. Where state law mandates equipment and facilities, such statutes should supersede this guideline[32].

Occupational safety

In the medical literature, long-term exposure to nitrous oxide used as a general anesthetic has been linked to bone marrow suppression and reproductive system disturbances[7,47-49]. However, it has been shown that appropriate scavenging is effective in reducing these reproductive system effects[19,50]. In an effort to reduce occupational health hazards associated with nitrous oxide, the AAPD recommends exposure to ambient nitrous oxide be minimized through the use of effective scavenging systems and periodic evaluation and maintenance of the delivery and scavenging systems[51-53].

References

1. American Dental Association. Guideline for the use of sedation and general anesthesia by dentists. 2007~~0~~16. Available at "~~http://www.ada.org/sections/about/pdfs/anesthesia_guidelines.pdf".~~ http://www.ada.org/en/~/media/ADA/Education%20and%20Careers/Files/ADA_Sedation_Use_Guidelines". Accessed March 13, 2013 August 20, 2017.

2. American Society of Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists: An updated report by the American Society of Anesthesiologists task force on sedation and analgesia by non-anesthesiologists. Anesthesiology 2002;96:1004-17.
3. Groenbaek A, Svensson P, Vaeth M, Hansen I, Poulsen S. A placebo-controlled, double-blind, crossover trial on analgesic effect of nitrous oxide-oxygen inhalation. Int J Paediatr Dent 2014;24:69-75.
4. Paterson SA, Tahmassebi JF. Pediatric dentistry in the new millennium: Use of inhalation sedation in pediatric dentistry. Dent Update 2003;30(7):350-6, 358.
5. Dock M, Creedon RL. Pharmacologic management of patient behavior. In: Dean JA, Avery DR, McDonald RE, eds. McDonald and Avery's Dentistry for the Child and Adolescent. 9th ed. Maryland Heights, Mo: Mosby; 2011:261-4.
6. Emmanouil DE, Quock RM. Advances in understanding the actions of nitrous oxide. Anesth Prog 2007;54(1):9-18.
7. Sanders RDB, Weimann J, Maze M. Biologic effects of nitrous oxide: A mechanistic and toxicologic review. Anesthesiology 2008;109(4):707-22.
8. Foley J. A prospective study of the use of nitrous oxide inhalation sedation for dental treatment in anxious children. Eur J Paediatr Dent 2005;6(3):21-7.
9. Holyroyd I. Conscious sedation in pediatric dentistry: short review of the current UK guidelines and the technique of inhalational sedation with nitrous oxide. Paediatr Anaesth 2008;18(1):13-7.
10. Lyratzopoulos G, Blain KM. Inhalation sedation with nitrous oxide as an alternative to dental general anesthesia for children. J Public Health Med 2003;25(4):303-12.
11. Wilson S, Gosnell E. Survey of American Academy of Pediatric Dentistry on nitrous oxide and sedation: 20 years later. Pediatr Dent 2016:38(5): 385-392.
12. Houpt M, Limb R, Livingston R. Clinical effects of nitrous oxide conscious sedation in children. Pediatr Dent 2004; 26 (1): 29-36.
13. Wilson S. Management of child patient behavior: quality of care, fear and anxiety, and the child patient. J Endod 2013; 39(3s): S73-S77.
14. Yasny J, White J. Environmental implications of anesthetic gases. Anesth Prog 2012;59:154-158.
15. Levering NJ, Welie JVM. Current status of nitrous oxide as a behavior management practice routine in pediatric dentistry. J Dent Child 2011;78(1):24-30.
16. McGain F. Why anesthetists no longer use nitrous oxide. Anaesth Intensive Care 2007;35(5):808-9.
17. Duncan GH, Moore P. Nitrous oxide and the dental patient: A review of adverse reactions. J Am Dent Assoc 1984;108(2):213-9.

18. Clark MS, Brunick AL. Handbook of nitrous oxide and oxygen sedation.4th ed. St. Louis, Mo: Mosby Elsevier; 2015:84-86;90-98.
19. Rowland AS, Baird DD, Shore DL, Weinberg CR, Savitz DA, Wilcox AJ. Nitrous oxide and spontaneous abortion in female dental assistants. Am J Epidemiol 1995;141(6):531-7.
20. Fleming P, Walker PO, Priest JR. Bleomycin therapy: A contraindication to the use of nitrous oxide-oxygen psychosedation in the dental office. Pediatr Dent 1988;10(4):345-6.
21. Selzer R, Rosenblatt D, Laxova R, Hogan K. Adverse effect of nitrous oxide in a child with 5,10-methylene-tetrahydrofolate reductase deficiency. N Engl J Med 2003;349(1):45-50.
22. Ogundipe O, Pearson MW, Slater NG, Adepegba T, Westerdale N. Sickle cell disease and nitrous oxide-induced neuropathy. Clin Lab Haematol 1999;21(6):409-12.
23. Fish BM, Banerjee AR, Jennings CR, et al. Effect of anaesthetic agents on tympanometry and middle-ear effusions. J Laryngol Otol 2000;114(5):336-8.
24. Moss E, McDowall DG. ICP increase with 50% nitrous oxide in oxygen in severe head injuries during controlled ventilation. Br J Anaest 1979;51(8):757-61.
25. American Academy of Pediatric Dentistry. Best practices on oral healthcare for the pregnant adolescent. Pediatr Dent 2017; 39(6):221-228.
26. Klein U, Robinson TJ, Allshouse A. End-expired nitrous oxide concentrations compared to flowmeter settings during operative dental treatment in children. Pediatr Dent 2011;33(1):56-62.
27. Klein U, Bucklin BA, Poulton TJ, Bozinov D. Nitrous oxide concentrations in the posterior nasopharynx during administration by nasal mask. Pediatr Dent 2004;26(5):410-6.
28. Malamed SF. Sedation: A Guide to Patient Management. 5th ed. St. Louis, MO: Mosby Elsevier; 2010:248-59.
29. Malamed SF, Clark MS. Nitrous oxide-oxygen: A new look at a very old technique. J Calif Dent Assoc 2003;31(5):397-403.
30. Guelmann M, Brackett R, Beavers N, Primosch RE, Effect of continuous versus interrupted administration of nitrous oxide-oxygen inhalation on behavior of anxious pediatric dental patients: a pilot study. J Clin Pediatr Dent 2012 Fall;37(1):77-82.
31. Clark MS. Contemporary issues surrounding nitrous oxide. In: Malamed SF, ed. Sedation: A Guide to Patient Management. 5th ed. St. Louis, Mo: Mosby Elsevier; 2018:256.
32. American Academy of Pediatrics, American Academy of Pediatric Dentistry. Guidelines for monitoring and management of pediatric patients before, during and after sedation for diagnostic and therapeutic procedures: An uUpdate 2016. Pediatr Dent 2016; 38(6):216-245.06;28(suppl):115-32.

33. Donaldson D, Meechan JG. The hazards of chronic exposure to nitrous oxide: An update. Br Dent J 1995;178(3):95-100.
34. 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(5):414-9.
35. Galeotti A, Garret ernardin A, D'Anto V, Ferrazzano GF, Gentile T, Viarani V, Cassabgi G, Cantile T. Inhalation Conscious Sedation with Nitrous Oxide and Oxygen as Alternative to General anesthesia in Precooperative, Fearful, and Disabled Pediatric DentalPatients: A Large Survey on 688 Working Sessions. Biomed Res Int. 2016;7289310. Epub Sep 26.
36. Hosey MT. UK National Clinical Guidelines in Paediatric Dentistry. Managing anxious children: The use of conscious sedation in paediatric dentistry. Int J Paediatr Dent 2002;12(5):359-72.
37. Schmitt EL, Baum VC. Nitrous oxide in pediatric anesthesia: Friend or foe? Curr Opin Anaesthesiol 2008;21(2):356-9.
38. Zeir JL, Doescher JS. Seizures temporarily associated with nitrous oxide administration for pediatric procedural sedation. J Child Neurol 2010;25(12):1517-20.
39. Hogue D, Ternisky M, Iranour B. The response to nitrous oxide analgesia in children. ASDC J Dent Child 1971;38(2):129-33.
40. Dunn-Russell T, Adair S, Sams DR, RussellCM, Barenie JT.Oxygen saturation and diffusion hypoxia in children following nitrous oxide sedation. Ped Dent 1993;16(2):88-92.
41. Quarnstrom FC, Milgrom P, BishopMJ, DeRouen TA. Clinical Study of Diffusion Hypoxia After Nitrous Oxide Analgesia. Anesth Prog 1991;38:21-23.
42. Khinda V, Bhuria P, Khinda P, Kallar S, Brar G. Comparative evaluation of diffusion hypoxia and psychomotor skills with or without postsedation oxygenation following administration of nitrous oxide in children undergoing dental procedures: a clinical study. J Indian Soc Pedod Prev Dent 2016; 34(3): 217-222.
43. Donaldson M, Donaldson D, Quarnstrom F. Nitrous oxide-oxygen administration: when safety features are no longer safe. JADA 2012;143(2):134-143.
44. American Dental Association. Oral Health Topics – Nitrous Oxide Dental Best Practices for Nitrous Oxide-Oxygen Use 2017 Available at "http://www.ada.org/en/member-center/oral-health-topics/nitrous-oxide".Accessed August 2017.
45. Chrysikopoulou A, Matheson p, Miles M, Shey Z, Houpt M, Effectiveness of Two Nitrous Oxide Scavenging Nasal Hoods During Routine Pediatric Dental Treatment. Ped Dent 2006, 28(3): 242-247.

46. Freilich MM, Alexander L, Sandor GKB, Judd P,. Effectiveness of 2 Scavenger Mask Systems for Reducing Exposure to Nitrous Oxide in a Hospital=Based Pediatric Dental Clinic: A Pilot Study. JCDA 2007;73(7);615-615d

47. Corcetti M, Serwint JR. Inhalants. Pediatr Rev 2008;29(1):33-4.

48. Lehmberg J, Waldner M, Baethmann, Eberhard UHL. Inflammatory response to nitrous oxide in the central nervous system. Brain Res 2008;1246:88-95.

49. Luhmann JD, Kennedy RM. Nitrous oxide in the pediatric emergency department. Clin Pediatr Emerg Med 2000;1(4):285-9.

50. Rowland AS, Baird DD, Shore DL, Weinberg CR, Shore DL, Shy CM, Wilcox AJ. Reduced Fertility among Women Employed as Dental Assistants Exposed to High Levels of Nitrous Oxide. N EnglJ Med 1992;327:993-997.

51. American Academy of Pediatric Dentistry. Policy on minimizing occupational health hazards associated with nitrous oxide. Pediatr Dent 2013;~~35(special issue):80-1~~ 38(6):92-93.

52. Rademaker AM, McGlothlin JD, Moenning JE, Bagnoli M, Carlson G, Griffin C. Evaluation of two nitrous oxide scavenging systems using infrared thermography to visualize and control emissions. J Am Dent Assoc 2009;140(2):190-9.

53. National Institute for Occupational Safety and Health (NIOSH). Control of nitrous oxide in dental operatories 1996. Available at, https://www.cdc.gov/niosh/docs/hazardcontrol/hc3.html. Accessed August 21, 2017.

~~Kinouci K, Tanigami H, Tashiro C, Nishimura M, Fukumitsu K, Takauchi Y. Duration of apnea in anesthetized infants and children required for desaturation of hemoglobin to 95%. Anesthesiology 1992;77(6):1105-7.~~

~~Nathan JE. Management of the difficult child: A survey of pediatric dentists' use of restraints, sedation, and general anesthesia. J Dent Child 1989;54(4):291-301.~~

~~Patel R, Lenczyk M, Hannallah RS, McGill WA. Age and onset of desaturation in apnoeic children. Can J Anaesth 1994;41(9):771-4.~~

~~Patel R, Norden J, Hannallah RS. Oxygen administration prevents hypoxemia during post-anesthesia transport in children. Anesthesiology 1988;69(4):616-8.~~

~~Stach DJ. Nitrous oxide sedation: Understanding the benefit and risks. Am J Dent 1995;8(1):47-50.~~