Use of Nitrous Oxide for Pediatric Dental Patients

Latest Revision
2023

How to Cite: American Academy of Pediatric Dentistry. Use of nitrous oxide for pediatric dental patients. *The Reference Manual of Pediatric Dentistry*. American Academy of Pediatric Dentistry; 2026:439-446.

Abstract

The goal of this best practice is to provide dental professionals with recommendations on the safe and effective use of nitrous oxide/oxygen (N_2O/O_2) analgesia/anxiolysis for treating children. Recommendations for use of N_2O/O_2 address goals, general considerations, indications, and contraindications of this inhalation method of analgesia/anxiolysis management. Factors to consider before using N_2O/O_2 for pediatric patient treatment include: the patient's physical and emotional development, medical and dental histories, and dental treatment needed; alternative behavior guidance options; credentials and training of the dentist and other dental personnel; equipment and facilities; administration techniques and monitoring of use; potential adverse effects and outcomes; and occupational safety. Documentation of its use is discussed. Judicious use of N_2O/O_2 can provide a safe and effective method of controlling anxiety associated with dental treatment in children, adolescents, and persons with special health care needs.

This document was developed through a collaborative effort of the American Academy of Pediatric Dentistry Councils on Clinical Affairs and Scientific Affairs to offer updated information and recommendations for dental professionals regarding development of safe practices in using N_2O/O_2 analgesia/anxiolysis for pediatric dental patients.

KEYWORDS: ADOLESCENT; ANALGESIA; ANXIETY; ANTI-ANXIETY; CHILD; HEALTH CARE DELIVERY; NITROUS OXIDE; OXYGEN

Purpose

The American Academy of Pediatric Dentistry (**AAPD**) recognizes nitrous oxide/oxygen (**N_2O/O_2**) inhalation as a safe and effective technique to reduce anxiety, produce analgesia, and enhance effective communication between a patient and health care provider. By producing this best practice, the AAPD intends to assist the dental profession in developing safe and effective practices in the use of N_2O/O_2 analgesia/anxiolysis for pediatric patients.

Methods

These recommendations were developed by the Council on Clinical Affairs, adopted in 2005[1], and last revised in 2018.[2] The revision is based on a review of the current dental and medical literature related to nitrous oxide use for analgesia/anxiolysis. A search was conducted using the database of PubMed/MEDLINE with the parameters: *nitrous oxide* [**MeSH**] OR *nitrous oxide reductase* [Supplementary Concept] AND *dental* [MeSH], publication date from January 1, 2012; humans; child: birth-18 years. Two hundred eighty-eight articles met these criteria. Papers for review were chosen from this list and from references within the selected articles. When data did not appear sufficient or were inconclusive, recommendations were based upon expert and/or consensus opinion by experienced researchers and clinicians.

Background

Nitrous oxide/oxygen inhalation, also referred to as N_2O/O_2 analgesia/anxiolysis, is a safe and effective technique used to manage dental pain and anxiety. It is preferred by parents over advanced behavior guidance techniques such as restraint and general anesthesia.[3,4] When used for analgesia/anxiolysis (ie, a single agent with nitrous oxide concentration less than 50% with or without local anesthesia), N_2O/O_2 inhalation allows for diminution or elimination of pain and anxiety in a conscious patient, while entailing minimum risk.[5,6] The patient's response to verbal commands and protective reflexes remain unchanged, and preprocedural mobility returns after discontinuing the use of N_2O/O_2.[7,8] In children, analgesia/anxiolysis may expedite the delivery of procedures that are not particularly uncomfortable but require that the patient not move.[8] It also may allow the patient to tolerate unpleasant procedures by reducing or relieving anxiety, discomfort, or pain. Furthermore, it increases reaction time and reduces pressure-induced pain but does not affect pulpal sensitivity, as shown in a double-blind, crossover study.[9]

Mechanisms of action

Nitrous oxide, a colorless and virtually odorless inorganic gas with a faint, sweet smell[10,11(p362)], is an effective analgesic/anxiolytic agent causing central nervous system (**CNS**) depression and euphoria with little effect on the respiratory system.[12(p78)] Nitrous oxide has multiple mechanisms of action.[13,14] The analgesic effect appears to be initiated by neuronal release

ABBREVIATIONS

AAPD: American Academy of Pediatric Dentistry. **ASA:** American Society of Anesthesiologists. **CNS:** Central nervous system. **$GABA^A$:** Gamma-aminobutyric acid type A. **L/min:** Liters per minute. **MeSH:** Medical subject heading. **MTHFR:** Methylenetetrahydrofolate reductase. **N_2O/O_2:** Nitrous oxide/oxygen.

of endogenous opioids (eg, enkephalins) with subsequent activation of opioid receptors, descending gamma-aminobutyric acid type A (**GABA^A**) receptors, and noradrenergic pathways that modulate nociceptive processing at the spinal level.[13,14] The anxiolytic effect involves activation of the GABA^A receptor either directly or indirectly through the benzodiazepine binding site.[13,14] Antagonism of the N-methyl-D-aspartate (NMDA) receptors also aids in the anesthetic, analgesic, and amnestic properties of nitrous oxide.[12(pp91,93)] However, nitrous oxide is the weakest of all inhalation agents with its low tissue solubility and minimum alveolar concentration (MAC) value of 105.[7,11(p362),15] Nitrous oxide has a rapid onset and recovery (2 to 3 minutes).[7,15,16] It is transported as free gas, does not combine with hemoglobin, and does not undergo biotransformation.[17] Elimination occurs quickly via the lungs, and nitrous oxide has little effect on kidney and liver function.[14] It causes minimal impairment of any reflexes, thus protecting the cough reflex.[16,18] Nitrous oxide causes minor depression in cardiac output while peripheral resistance is slightly increased, thereby maintaining the blood pressure.[9] This is of particular advantage in treating patients with cardiovascular system disorders.

Goals

When used in the dental setting, N_2O/O_2 inhalation serves any of the following goals.

- To reduce or eliminate fear and anxiety
- To enhance communication between the patient and dental team
- To instill a positive attitude towards dental care[19(p25)]
- To raise the pain reaction threshold
- To reduce untoward movement
- To help control a hyperactive gag reflex that can interfere with dental care[7,19(p26)]
- To decrease patient fatigue and increase operator efficiency for longer appointments[11(p367),19(pp25,26)]
- To provide an amnesic effect[15,20] thus creating a more positive outlook towards dental care

Use with other agents (eg, benzodiazepines, opioids) can potentiate their sedative effects but risks CNS depression.[7]

Candidates for N_2O/O_2 analgesia/anxiolysis

Considerations in the decision to use N_2O/O_2 analgesia/anxiolysis include alternative behavioral guidance modalities, the patient's dental needs, the effect on the quality of dental care, and the patient's emotional development, medical comorbidities, and physical considerations.[21] Careful review of the patient's medical history is critical prior to the use of nitrous oxide. Patients who are in American Society of Anesthesiologists (**ASA**) Physical Status Classification I and II are considered appropriate candidates for N_2O/O_2 analgesia/anxiolysis.[8] Children in ASA Class III as well as those with special health care needs, anatomic airway abnormalities, or moderate to severe tonsillar hypertrophy require additional and individual consideration.[8]

The anxiolytic/analgesic success of N_2O/O_2 inhalation depends on the patient's acceptance of the nasal hood, nasal breathing, and psychological reassurance. Patients who are primarily mouth breathers may find the use of nasal hood challenging. If a patient is crying uncontrollably or unable to accept breathing through the nasal hood, inspired concentration of nitrous oxide would be diminished thereby decreasing effects.[17,19(pp32,33)] Sinus infection, congestion, upper respiratory infection, and active tuberculosis may decrease the efficacy of N_2O/O_2 inhalation.[19(pp33,34)] Because N_2O/O_2 does not irritate the trachea and bronchial tree, its use is not contraindicated for patients with asthma.[22(p121)] In fact, N_2O/O_2 inhalation can reduce stress thereby decreasing risk of an asthma attack.[23]

Nitrous oxide also can inflate air-filled body spaces. This can cause distention of the abdomen or bowel, which can contribute to postoperative pain and nitrous oxide-related postoperative nausea and vomiting.[19(p30),24] Patients with bowel obstruction[15,19(p30)] or raised intraocular pressure (glaucoma)[24] as well as those who have recently undergone certain surgical procedures (eg, retinal surgery[24], craniotomy[24], correction of intestinal obstruction[15]) are not candidates for N_2O/O_2 analgesia/anxiolysis.

Studies[25-29] have evaluated metabolic consequences of nitrous oxide administration during general anesthesia, albeit at higher concentrations and for significantly longer duration than most dental procedures. The exposure to nitrous oxide has been linked to irreversible inactivation of cobalamin (vitamin B_{12}) which can impact myelin and DNA synthesis.[17,27] Cobalamin is a water-soluble vitamin found in animal foods, and therefore, vegans/vegetarians may be at risk for vitamin B_{12} deficiency.[30] Due to concerns for myeloneuropathy, patients with untreated vitamin B_{12} deficiency are not candidates for nitrous oxide inhalation.[13,17]

Nitrous oxide exposure also can result in an acute increase in plasma homocysteine by irreversible inactivation of vitamin B_{12} with certain variants (eg, C677T, A1298C) in the methylenetetrahydrofolate reductase (**MTHFR**) gene.[27,29] One article[29] reported the death of a child with previously undiagnosed MTHFR deficiency following 2 surgeries 4 days apart utilizing 0.75% halothane and 60% nitrous oxide. While some authors discourage the routine use of N_2O/O_2 with or without the use of anesthesia in these at-risk patients[15,29], not all reports are in agreement[25-27]. Metabolic consequences of nitrous oxide in patients with certain variants of MTHFR deficiency appear dependent on the exposure, with short exposure unlikely to be of significance.[25,28] Significant to the patient's exposure is the system used for delivery of inhalation agents. Nitrous oxide administered during general anesthesia exists largely in a closed system where gases cannot be exchanged with the surrounding environment and concentrations are measured; in comparison, nitrous oxide can be freely exchanged in an open system during N_2O/O_2 inhalation, impacting the inspired concentration. Some studies have proposed using prophylactic vitamin B_{12} therapy to reduce the metabolic consequences of nitrous oxide under general anesthesia, but the findings were equivocal.[25,27,31] Pediatric patients with severe MTHFR deficiency

may benefit from consultation with a geneticist or anesthesiologist prior to the use of N_2O/O_2 in the dental setting. Additional research is needed for better understanding of the metabolic consequences of nitrous oxide exposure, especially at the concentration and duration used in dentistry.

General considerations

Nitrous oxide generally is acceptable to children and can be titrated easily. Most children are enthusiastic about the administration of N_2O/O_2; children may report feeling a tingling, warm sensation or lightheadedness[32] or a feeling of floating[11(p367)]. Indicators of effective N_2O/O_2 inhalation include relaxation of limbs and jaw muscles, ptosis of the eyelids, blank stare, open palms, and lowered heart rate.[22(p120)] However, for some patients, the feeling of losing control may be troubling, and children with claustrophobia may find the nasal hood confining and unpleasant.[33]

N_2O/O_2 analgesia/anxiolysis has an excellent safety record.[11(p363),22(p121),24] Acute and chronic adverse effects of nitrous oxide on the patient are rare.[11(p363)] The most common adverse effects, occurring in 0.5-1.2% of patients, are nausea and vomiting.[20,35,36] A higher incidence is noted with longer administration of N_2O/O_2, fluctuations in nitrous oxide levels, lack of titration, increased concentrations of nitrous oxide, and a heavy meal prior to administration of nitrous oxide.[37,38(pp228,229)] Fasting is not required for patients scheduled for N_2O/O_2 analgesia/anxiolysis[15,20] although a light meal is sometimes suggested[38(p228)]. Other side effects are oversedation[7], sweating[7], dysphoria[7], restlessness[7], panics[7], and headache[7,39(p189)], in addition to dizziness[39(p189)], hallucination[39(p189)], diffusion hypoxia[39(p189)], and expansion of gas-filled spaces[39(p189)]. Diffusion hypoxia can occur because of rapid release of nitrous oxide from the blood stream into the alveoli, thereby diluting the concentration of oxygen.[39(p189)] This may lead to headache, disorientation, nausea, and lethargy and can be avoided by administering 100% oxygen for at least 5 minutes once the nitrous oxide flow is terminated.[5,39(pp190,191)] Studies have reported negative outcomes associated with use of nitrous oxide greater than 50%, in longer (greater than 45 minutes) administration time, and as an anesthetic during major surgery.[39(p189),40,41] With use of 70% nitrous oxide, laryngospasm and, although rare, silent regurgitation and aspiration are of concern.[42] Pharyngeal-laryngeal reflexes can be maintained by not allowing the patient to go into an unconscious state.[43]

Because N_2O/O_2 is rapidly cleared from the body, it does not provide postoperative analgesia. Additional disadvantages to the use of N_2O/O_2 inhalation include weak potency, interference of the nasal hood with treatment to the anterior maxillary region, equipment cost and maintenance, potential occupational health hazards, and environmental impacts.[5,7,11(p367),19(pp37-39)]

Bioenvironmental concerns

When administered in accordance with recommended therapeutic practices, toxic or harmful effects would not be expected for a healthy patient.[17,44] Occupational exposure to ambient nitrous oxide has been studied for decades, yet its effects on dental personnel remain uncertain. Early reports, many of which came from retrospective[10,45] or animal[10,46] studies and/or preceded scavenging devices[47] and ventilation systems, implicated chronic occupational exposure of unscavenged nitrous oxide in reproductive effects[48,49], liver and kidney damage[48], and neurologic considerations[46]. In dental offices using scavenging systems, studies found risks of reduced fertility and spontaneous abortion were not significantly elevated.[50,51] A recent systematic review on workplace exposure to volatile anesthetics including nitrous oxide reported evidence is both scarce and inconsistent regarding adverse effects.[52] The mechanism for toxicity is thought to be the inhibition of vitamin B_{12} and, subsequently, myelin and DNA synthesis; the thresholds for exposure duration, concentration, and frequency to produce such harms have not been determined.[17,44,53]

Nitrous oxide has been associated with environmental concerns because of its contribution to the greenhouse effect.[15,54] Nitrous oxide is emitted naturally by bacteria in soils and oceans; humans produce it through the burning of fossil fuels and forests and the agricultural practices of soil cultivation and nitrogen fertilization. The medical use of nitrous oxide is estimated to represent less than 1% of global nitrous oxide pollution, most of which comes from use of nitrogenous fertilizers in agriculture along with aviation, industry, and automotive use.[15]

Recommendations

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

- a fearful or anxious patient.
- certain patients with muscular tone disorders prone to unintentional movement.[7]
- a patient whose strong or hypersensitive gag reflex interferes with dental care.[55]
- a patient for whom profound local anesthesia or analgesia cannot be obtained.[56]
- a cooperative child undergoing a lengthy dental procedure who would benefit from alleviating treatment fatigue.

Contraindications for use of nitrous oxide/oxygen inhalation may include

- chronic obstructive pulmonary diseases.[7,19(pp29,30),57]
- current upper respiratory tract infections[7,22(p121)] (eg, cold, cough, tonsillitis), sinusitis,[7,17] or other conditions (eg, seasonal allergies) that inhibit nasal breathing.
- recent middle ear disturbance or infection (eg, acute otitis media).[7,19(p30),22(p121)]
- recent (within 14 days) ear, nose, and/or throat operations.[7,17]
- raised intraocular pressure (eg, glaucoma), up to 3 months post retinal surgery.[7,15]

- severe emotional disturbances or drug-related dependencies.[7,19(pp31-32)]
- first trimester of pregnancy.[17]
- treatment with bleomycin sulfate.[7,19(p31),58]
- untreated cobalamin (vitamin B_{12}) deficiency.[7,13,19(p31)]

Whenever possible, relevant medical specialists should be consulted before administering analgesic/anxiolytic agents to patients with significant underlying medical conditions (eg, severe obstructive pulmonary disease, emphysema, cystic fibrosis, congestive heart failure, sickle cell disease[59-61], acute otitis media, recent tympanic membrane graft[62], acute severe head injury[63]). Intracranial pressure may be increased following severe trauma to the head and neck; use of N_2O/O_2 analgesia/anxiolysis should be avoided until the patient is cleared from intracranial injuries or head concussion.[39(p194),63] Consultation with the prenatal medical provider should precede use of N_2O/O_2 analgesia/anxiolysis during pregnancy.[64] As noted previously, patients with severe MTHFR deficiency also may benefit from a consultation prior to nitrous oxide use in the dental setting.

Technique of N_2O/O_2 administration

A fitted nasal hood should be selected. A flow rate of 5 to 7 L/min generally is acceptable for older children and adult patients, whereas 3- to 4-year-old patients typically require 3 to 5 L/min.[22(p121)] 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 under-inflated.

N_2O/O_2 can be administered via either standard titration (introduction of 100% oxygen for 1 to 2 minutes followed by titration of nitrous oxide in 10% intervals) or rapid induction (administration of fixed dose or percentage of N_2O/O_2 without titration) technique.[7,22(pp120,121),65] Administration of 30 to 40% nitrous oxide usually can achieve analgesia/anxiolysis.[6,66] Nitrous oxide concentration may be decreased during minor procedures (eg, restorations) and increased during more stimulating ones (eg, extraction, injection of local anesthetic). One study found no benefit to continuous administration of nitrous oxide after profound anesthesia had been achieved.[67] The effects of nitrous oxide largely are dependent on psychological reassurance.[68] Therefore, continuing traditional behavior guidance techniques during treatment can help maximize effectiveness.

During N_2O/O_2 analgesia/anxiolysis, the concentration of nitrous oxide should not routinely exceed 50% to decrease incidence of adverse events.[11(p362)] If concentration of nitrous oxide exceeds 60%, patients may experience ataxia, giddiness, dysphoria, increased sleepiness,[11(p362)] and/or delirium and, subsequently, become uncomfortable and uncooperative.[22(p121)] Whilst some studies on the safety and effectiveness of delivery of greater than 50% nitrous oxide did not show an increase in adverse reactions,[24] such concentrations also did not result in better patient behaviors scores than lower concentrations during restorative treatment[69]. Gas concentrations dispensed by the flow meter vary significantly from the end-expired alveolar gas concentrations; the latter is responsible for the clinical effects.[37,70] To achieve the desired effects, clinicians should keep the patient's talking and mouth-breathing to a minimum, and the scavenging vacuum should not be so strong as to prevent adequate ventilation of the lungs with nitrous oxide.[38(p231)]

Once the nitrous oxide flow is terminated, 100% oxygen should be administered for at least 5 minutes until the patient has returned to pretreatment status.[47] Oxygen administration can be extended for patients who experience postoperative nausea and vomiting with longer N_2O/O_2 exposure.[39(pp189-191)] 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. Continuous clinical observation of the patient must be performed during any dental procedure involving N_2O/O_2 inhalation; observation of the patient's responsiveness, color, and respiratory rate and rhythm is recommended. If any other pharmacologic agent (eg, chloral hydrate, benzodiazepine, opioid) is used in addition to N_2O/O_2 and a local anesthetic, or if nitrous oxide concentrations greater than 50% are maintained, the likelihood for a deeper sedative effect increases.[8] Monitoring should be tailored to the actual, not the intended, response to the administered agents.[8]

Documentation

Informed consent from the parent should be documented in the patient's record prior to administration of N_2O/O_2.[71] The practitioner should provide instructions to the parent regarding pretreatment dietary precautions, if indicated. In addition, the patient's record should document indication for use of N_2O/O_2 inhalation, nitrous oxide dosage (ie, percent and/or flow rate of gases), duration of the procedure, and posttreatment oxygenation procedure.[11(p368)]

Facilities/personnel/equipment

All newly installed facilities for delivering N_2O/O_2 must be checked for proper gas delivery and fail-safe function prior to use. Inhalation equipment must have the capacity for delivering 100%, and never less than 30%, oxygen concentration at a flow rate appropriate to the child's size. Additionally, inhalation equipment must have a fail-safe system that turns off the nitrous oxide supply when oxygen delivery falls below an established minimum (eg, 2.5 to 3.0 L/min).[5] Other equipment safety features include an emergency air inlet, permitting ambient air to enter the system and patients to continue breathing through the nasal hood if gas flow stops, and quick connection for positive pressure and oxygen flush. N_2O/O_2 equipment must be checked and calibrated for proper gas delivery and fail-safe function according to the practitioner's state laws and regulations.[72] The system components, including

the reservoir bag, should be inspected routinely for cracks, wear, and tears. If detected, replacement should be made immediately. Pressure connections should be tested for leaks when the delivery system is turned on and each time a tank is changed. State and federal guidelines address 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.[72] The equipment must have an effective scavenging system to minimize room air contamination and occupational risk.

The potential for fire with the use of oxygen delivery systems is a safety concern. Fire can be created in the presence of an oxidizer (eg, oxygen, nitrous oxide), an ignition source (eg, handpieces, high-speed burs, lasers), and a fuel.[73] Risks associated with a patient fire can be reduced by monitoring the flow of gases, using high volume suction for at least 1 minute prior to the use of a potential ignition source, maintaining a moist working field, and avoiding cutting dry.[74,75]

The practitioner who utilizes N_2O/O_2 analgesia/anxiolysis for a pediatric dental patient shall possess appropriate training and skills and have available the proper facilities, personnel, and equipment to manage any reasonably foreseeable emergency. The practitioner is responsible for managing the potential complications associated with the intended response and a deeper level of sedation. When nitrous oxide concentration is maintained at 50% or less, ventilatory and cardiovascular functions generally are unaffected; for some patients, however, the effects may be more profound, resulting in moderate sedation.[8] In addition, maintaining nitrous concentration at levels exceeding 50% increase the likelihood of moderate sedation. Therefore, practitioners should have the skills and emergency equipment to manage this.[8,47] 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 cart (kit), and simulated exercises to assure proper emergency management response.

An emergency cart must be readily accessible. Emergency equipment must be able to accommodate children of all ages and sizes. It should include equipment to resuscitate a nonbreathing, unconscious patient and provide continuous support until trained emergency personnel arrive. A positive pressure oxygen delivery system capable of administering greater than 90% 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 positive pressure oxygen, a 15 L/min flow is recommended. Documentation that all emergency equipment and drugs are checked and maintained on a scheduled basis is recommended.[8] Where state law mandates equipment and facilities, such statutes should supersede these recommendations.

Occupational safety

In an effort to reduce occupational health hazards associated with nitrous oxide, use of effective scavenging systems and periodic evaluation and maintenance of the delivery and scavenging systems is recommended.[5,76-79] Room air exchange, use of larger operatories, routine review of equipment for leakage, nasal hood selection, use of rubber dam and high-speed suction, as well as limiting exposure time to N_2O/O_2 inhalation can help improve scavenging and decrease indirect N_2O/O_2 exposure in the clinical setting.[80] The dentist's exposure often is noted to be greater than that of the dental assistant.[81-83] Clinicians should try to minimize the patient's talking and mouth breathing during nitrous oxide administration to prevent expired gas from contaminating the operatory.[39(p175)] Additional discussion of minimizing occupational exposure can be found in the AAPD's *Policy on Minimizing Occupational Health Hazards Associated with Nitrous Oxide*.[76]

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