Republic of Iraq

Ministry of Higher Education

and Scientific Research

Ashur University

Nitrous Oxide

A Project Submitted to

The College of Dentistry, Ashur University, Department of Pediatric and Preventive in Partial Fulfillment for the Bachelor of Dental Surgery

By

Yaqoub Saad Dhari

Zahra Raad

Supervised by:

Dr.Tabark Adil Rasool

B.D. S, M.Sc, Preventive Dentistry

March, 2025

Certification of the Supervisor

I certify that this project entitled "**Nitrous Oxide**" was prepared by the fifth-year student (**Yaqoub Saad Dhari),(Zahra Raad)** under my supervision at the College of Dentistry/Ashur University in partial fulfilment of the graduation requirements for the Bachelor Degree in Dentistry.

Supervisor's name:

A.L. Tabarak Adel Rasool

Date :

Dedication

It wasn't a short flight, nor should it have been. It didn't come close, nor was the road paved with facilities, but I did it. I dedicate my graduation to the one whose name I carry with all my heart. To the one who removed the thorns from my path, to pave the way for me to knowledge. To my dear father.

To the invisible hand that removed the difficulties from my path and who bore every moment of pain that I went through and supported me when I was weak and helpless, to my beloved mother.

to my support and the shoulder that I always lean on, my brothers who have always been the shadow of this success, and I would like to conclude by dedicating to those who have done me great favor, the friends of success, to those who stood by me whenever I was about to stumble, grateful to all of you, I would not have arrived without your favor, after God

Yaqoub Saad Dhari & Zahra Raad

Acknowledgment

I wish to thank my committee members who were more than generous with their expertise and precious time.We would like to extend our deepest respect and gratitude to the president of ashur university, **Professor Dr. Kadhum Aboud Issa Al-Majidi.** And Dean of College of Dentistry **Asst.Prof.Dr. saja kareem esmael** We would like to show our deep and sincere gratitude to our research supervisor, Asst.Lec. **Dr. Tabarak Adel Rasool** for her advice, encouragement, and guidance in planning and conductig this project.

List Of Content

List Of Figures

List Of Tables

Introduction

Gas anesthesia, such as nitrous oxide (commonly known as "laughing gas"), has been widely used in dentistry to help patients relax and manage pain during procedures. It is particularly effective for individuals with dental anxiety or for more invasive treatments. Nitrous oxide is administered through a mask, allowing the patient to remain conscious but deeply relaxed. (Academy of Medical Royal Colleges,2023)

An anesthetic which is ideally suited to clinical dentistry is nitrous oxide or N2O as nitrous oxide is commonly abbreviated. Nitrous oxide produces analgesic and anxiolytic effects when used correctly in a clinical setting. Nitrous oxide (N20 on many forms or chemical symbol N2O) gas has been available to the medical and dental community for over 150 years. The use of nitrous oxide as an anesthetic is common for anesthesiologists and dental practitioners as an adjunct to local anesthetic agents, and fulfills almost all of the criteria listed above. (Craig,2004)

According to international guidelines, titrated nitrous oxide in oxygen (N2O/O2) is considered a safe and effective dental sedation technique, and recommended as a first-line option especially for children. (Emmanouil et al,.2007)

Unlike pre-mixed medical gas mixtures of 50:50 N2O:O2, for example Entonoxr (widely used in maternity wards), dentists commonly use modern mixer machines to titrate and deliver a patient-specific therapeutic mixture of N2O/O2, according to individual patient responses. These machines are designed with features to facilitate easy and safe use of N2O/O2 by dentists who serve as both the sedationist and operator. With careful patient selection, N2O/O2 sedation can be successful in at least 90% of patients. Despite a long international history of safe use, safety concerns still persist in countries where N2O/O2 sedation is less commonly practised. (Brown et al,.2016)

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. When used for analgesia/anxiolysis (i.e., a single agent with nitrous oxide concentration less than 50 percent 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. 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. (Hosey,2002)

In children, analgesia/anxiolysis may expedite the delivery of procedures that are not particularly uncomfortable but require that the patient not move. 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. (Chellappah et al,.1990)

Aims Of Review

The present Review aims to provide an overview of:

1. the pharmacological properties of N_2O and
2. the indications, technique, staffing and equipment required for safe and effective N_2O/O_2 dental sedation. The pharmacological basis and scientific evidence for safety concerns are also discussed in this review, with a focus on outpatient dentistry.

Review Of Literature

1. History of Nitrous Oxide and Use in Dentistry

Nitrous oxide, one of the first modern anesthetics, was first manufactured in 1772 by English chemist, Joseph Priestly. About 1800, Sir Humphrey Davy experimented with the physiological properties of the gas and stated: “As nitrous oxide in its extensive operation appears capable of destroying physical pain, it may probably be used with advantage during surgical operation”. The surgical world ignored his suggestion, and interest in the surgical use of nitrous oxide would have to wait another half century. After Sir Davy observed the amusing effects on people who inhaled nitrous oxide, he coined the term “laughing gas” which is also commonly used today. (Foley,2005)

Nitrous oxide was used for the first time as a dental anesthetic drug in 1844. Dr. Horace Wells, with assistance by Gardner Quincy Colton and John Mankey Riggs, collaborated successfully to use nitrous oxide on a patient for an extraction. In the following weeks, Wells treated the first 12-15 patients with nitrous oxide, and according to his own record only failed in two cases. In spite of these convincing results reported by Wells to the medical society in Boston, this new method of pain management was not immediately adopted by other dentists. In early 1845, Wells’ first public demonstration of nitrous oxide anesthesia for the medical faculty in Boston, was only partly unsuccessful, leaving his colleagues doubtful regarding its efficacy and safety. Wells was booed off the stage and in the aftermath, he lost his reputation and eventually committed suicide. However, to this day, Dr. Wells is considered the “discoverer of anesthesia”. (Hosey et al,.2006)

In 1863 nitrous oxide anesthesia came into general use, when Gardner Quincy Colton successfully began to use nitrous oxide in all his “Colton Dental Association” clinics. Up to the 1860’s nitrous oxide was used alone as an inhalational anesthetic with 100% concentration of the gas administered to patients. Oxygen was added to the gas mix, and soon Colton and his associates successfully administered nitrous oxide to more than 25,000 patients, with over. (Blain et al,.1998)

75,000 extractions completed with the use of N2O as an anesthetic. Now with the efficacy and safety demonstrated by large numbers of successful procedures, the use of nitrous oxide rapidly became the preferred anesthetic method in dentistry. The gas is mild enough to keep a patient in a conscious and conversational state, and in most cases is strong enough to suppress the pain caused by dental procedures. Therefore, nitrous oxide remains today as the preferred anesthetic gas used in dentistry. (Wilson et al,.2003)

Every year approximately 45 million dental patients undergo anesthesia in North America, with nitrous oxide constituting a major component in about half of these procedures. A significant percentage of general dentists use nitrous oxide sedation in their practices to manage pain, anxiety, and excessive gag reflex. Nitrous is the most used gaseous anesthetic in the world, commonly administered for the purpose of decreasing the amount of more potent and usually more toxic agents during general anesthesia cases. (Allen et al,.2014)

2. Mechanism of action

N2O is a mildly sweet-smelling and colourless gas that is non-irritant to tissues, with a minimal alveolar concentration of 105. Emmanouil and Quock (2007) proposed respective mechanisms of actions for its analgesic, anxiolytic and anaesthetic effects, but emphasised that these mechanisms are yet to be fully understood. Its anxiolytic effect is believed to be from agonism at benzodiazepine binding sites on the GABAA receptor and a potentiation of a signalling pathway that involves nitric oxide synthase, soluble guanylyl cyclase and cGMP-dependent protein kinase. Its analgesic effect arises from the release of endogenous opioid peptides in the central nervous system and subsequent inhibition of pain pathways via opioid receptors.10 For its anaesthetic effect, N2O acts as an antagonist on the N-Methyl-D-aspartate receptor, a glutamate binding, non-selective ion channel that is involved in synaptic plasticity and memory formation. (Paterson et al,.2003)

During administration, N2O is rapidly taken up from the lung alveoli into the blood. As N2O has low blood solubility, it quickly diffuses out of blood down the concentration gradient into tissues including the central nervous system, resulting in a rapid onset (a few minutes). The reverse process also occurs rapidly, with N2O excreted from lungs quickly at the cessation of its inhalation. (Campbell et al,.2011)

3. Effectiveness

N2O/O2 sedation is recommended for dental sedation due to its wide safety margins and minimal effect on cardiovascular and respiratory function. (Wilson,2013)

It is also particularly helpful in preventing and managing dental anxiety in children. Almost one-fifth of children aged 10– 14 years have been found to have dental anxiety and fear; N2O/O2 sedation can therefore be a particularly useful behavioural management tool for paediatric dentists. In a 1- year prospective study, 93% of 312 paediatric patients (4.1– 16.0 years old) were successfully treated; almost threequarters had 30:70 N2O/O2 mixture for up to 40 min. Most were treated for dental extractions, with > 40% being permanent teeth extractions. However, failure of treatment under sedation seems to be associated with lower operator experience, highlighting the importance of staff training. (Donaldson et al,.2012)

General anaesthesia (GA) may sometimes be the only viable option for managing anxious paediatric dental patients. However, children undergoing GA may suffer from induction distress and associated post-operative morbidities, including feeling sick and poor sleep, with some symptoms lasting for a week.[16] In a matched pair study, 83.4% of 256 children aged 3–16 years originally referred for dental extraction under GA were successfully treated under inhalation sedation instead of GA. Furthermore, inhalation sedation was found to be cheaper than GA and had a higher parental satisfaction. (Council of European Dentists,2012)

Likewise, when compared with buccal (transmucosal) midazolam (0.5 mg/min to maximum 5 mg) or intravenous midazolam in 10–16-year olds (0.2 mg/kg) for orthodontic extractions, 30:70 N2O/O2 sedation was found to be as effective as midazolam, but required lesser time to reach the desired level of sedation and to recover. (Kupietzky et al,.2008)

Adult studies are rarer, but international guidelines have also recommended N2O/O2 sedation to be the first-line basic sedation technique for adults. In an equivalence study, N2O (at concentrations below 40%) and sevoflurane (at concentrations below 0.3%) in anxious adults between 18 and 62 years old undergoing dental restorations, were found to be similar in efficacy. (Malamed et al,.2003)

N2O/O2 sedation can be a more pleasant and cost effective alternative to GA, and as effective as other forms of sedation, when delivered by trained staff in the appropriate patient and in the appropriate setting.

4. Signs and Symptoms of Exposure

Acute exposure: The signs and symptoms of acute exposure to nitrous oxide include dizziness, difficult breathing, headache, nausea, fatigue, and irritability. Acute exposure to nitrous oxide concentrations of 400,000 to 800,000 ppm may cause loss of consciousness. (Cantlay et al,.2005)

Chronic exposure: The signs or symptoms of chronic overexposure to nitrous oxide may include tingling, numbness.

5. Indications

- American Society of Anaesthesiologists Physical Grade (ASA) I and II
- Mature enough to cooperate and understand
- Mild-to-moderate dental anxiety
- Unpleasant procedures including dental extractions and management of acute dental trauma (Becker & Rosenberg,2008)
- Management of certain medically compromised patients where dental stress could trigger exacerbation, e.g. asthma, epilepsy, etc.
- Needle phobia
- Gag reflex
- Other sedation methods contraindicated . Alternative to GA (Duncan et al,.1984)

6. Contraindications

- Children who are not able or too young to cooperate or understand
- Inability to breathe nasally with mouth open due to acute/chronic nasal obstruction, common cold or tonsillitis (Roberts et al,.1982)
- Chronic obstructive pulmonary diseases
- Nasal or facial deformity
- Nasal hood phobia
- First trimester of pregnancy
- Bleomycin (sulphate) chemotherapy
- Myasthenia gravis and multiple sclerosis
- Severe psychological disorders or drug-related dependencies
- Methylenetetrahydrofolate reductase deficiency
- Cobalamin deficiency (Chi et al,.2018)
- Otitis media and pneumothorax

7. N2O/O2 sedation technique in dentistry

In outpatient dentistry, N2O is delivered with O2 via a purpose-made mixer system that allows easy titration of gas concentrations. The titrated gases may be inhaled through the patient's nose using a specialised nasal hood (Fig. 1), allowing unobstructed oral access for dental treatment. Nasal hoods are available in different sizes to fit patients of different ages and sizes; some are pre-scented to help increase acceptability in children. (Balasubramaniam et al,.1982)

Figure. 1. Nasal hood permits oral access for dental procedures. The use of a dental rubber dam is recommended to reduce atmospheric pollution.

The "Singapore Guidelines On Safe Sedation Practice for Non-Anaesthesiologists in Medical Clinics" 21 state that "non-anaesthesiologists shall limit their sedation techniques to achieve a level of minimal or moderate sedation" only "Minimal to moderate sedation" is defined by the American Society of Anaesthesiologists (Table 1) and is consistent with providing anxiolysis and some analgesia, while allowing the patient to remain responsive and maintain airway reflexes. (Cohen et al,.1980)

Patients are initially administered 100% O2 (0% N2O), with N2O concentrations incrementally increased (with simultaneous reduction in O2 concentrations) until a desired level of sedation is achieved — often at 30–50% N_2O, after which the dental procedure is performed. At such N_2O concentrations, the analgesic effect is minimal and local infiltration of local anaesthesia is still required for painful procedures. At the end of procedure, 100% O_2 is administered for 3–5 min to flush N_2O out from the system and to prevent diffusion hypoxia. Careful titration tailors N_2O administration to individual responses, and allows the regulation of the depth of sedation, thereby reducing the risk of over-sedation. (Gilchrist et al,.2007)

N_2O/O_2 sedation is a complement to, but not a replacement of, basic non-pharmacological behaviour management techniques. These include tell-show-do, distraction, semi-hypnotic suggestions, and relaxation techniques to help anxious patients to relax, thereby keeping the required level of N_2O to a minimum while increasing the likelihood of treatment success. For instance, children may be asked to imagine themselves at a beach while breathing in N_2O with long, deep and controlled breaths. They are more susceptible to these semi-hypnotic suggestions under the effect of N_2O. (Molina et al,.2016)

Table 1. Continuum of sedation and definition of GA and levels of sedation, adapted from the American Society of Anaesthesiologists. (Molina et al,.2016)

	Minimal sedation (Anxiolysis)	Moderate sedation/analgesia ("Conscious sedation")	Deep sedation/analgesia	GA
Responsiveness	Normal response to verbal stimulation	Purposeful response to verbal or tactile stimulation	Purposeful response following repeated or painful stimulation	Unarousable even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous Ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular Function	Unaffected	Usually maintained	Usually maintained	May be impaired

The objectives of nitrous oxide/oxygen inhalation include:

- Reduce or eliminate anxiety.
- Reduce untoward movement and reaction to dental treatment.
- Enhance communication and patient cooperation.
- Raise the patient's pain reaction threshold.
- Increase tolerance for longer appointments.
- Aid in the treatment of the mentally/ physically disabled or medically compromised patient.
- Reduce gagging.
- Potentiate the effects of sedatives. (Wilson,2013)

8. Technique of N2 O/O2 administration

A fitted nasal hood should be selected. A flow rate of five to seven liters per minute (L/min) generally is acceptable for older children and adult patients, whereas three- to four-yearold patients typically require three to five L/min.(Anand et al,.2022)

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. (Anand et al,.2022)

N2 O/O2 can be administered via either standard titration (introduction of 100 percent oxygen for one to two minutes followed by titration of nitrous oxide in 10 percent intervals) or rapid induction (administration of fixed dose or percentage of N2 O/O2 without titration) technique. Administration of 30 to 40 percent nitrous oxide usually can achieve analgesia/anxiolysis. Nitrous oxide concentration may be decreased during minor procedures (e.g., restorations) and increased during more stimulating ones (e.g., extraction, injection of local anesthetic). One study found no benefit to continuous administration of nitrous oxide after profound anesthesia had been achieved. The effects of nitrous oxide largely are dependent on psychological reassurance. Therefore, continuing traditional behavior guidance techniques during treatment can help maximize effectiveness. (Ashley et al,.2021)

During N2 O/O2 analgesia/anxiolysis, the concentration of nitrous oxide should not routinely exceed 50 percent to decrease incidence of adverse events. If concentration of nitrous oxide exceeds 60 percent, patients may experience ataxia, giddiness, dysphoria, increased sleepiness, and/ or delirium and, subsequently, become uncomfortable and uncooperative. Whilst some studies on the safety and effectiveness of delivery of greater than 50 percent nitrous oxide did not show an increase in adverse reactions, such concentrations also did not result in better patient behaviors scores. (Craig et al,.2019)

9. Equipment

Mixtures of N2O and oxygen have been used in dentistry as general anesthetic agents, analgesics, and sedatives for more than 100 years. The usual analgesia equipment used by dentists includes a N2O and O2 delivery system, a gas mixing bag, and a nasal mask or nasal canula with a positive pressure relief valve. (Ashley et al,.2021)

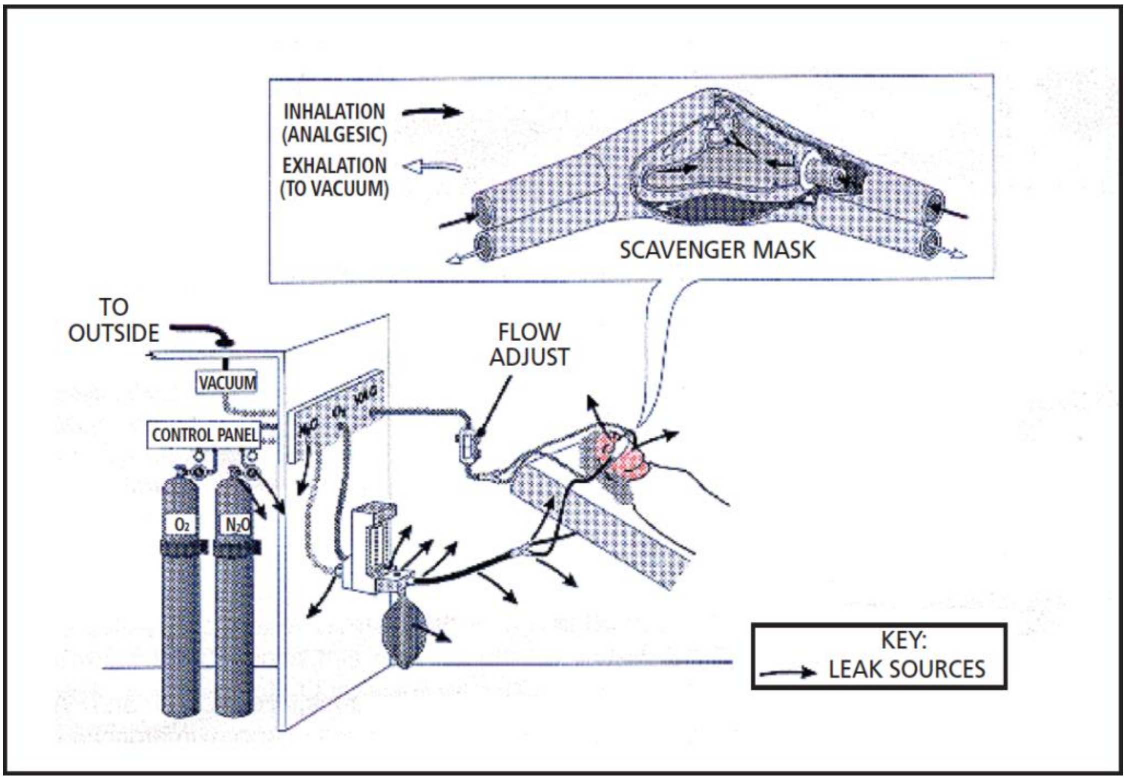

FIGURE 2. This illustration of a nitrous oxide anesthetic delivery and scavenging system indicates potential leak sources of waste gas that can enter the operatory. Operating a delivery system without a scavenging unit to decrease the amount of waste gas in the air fails to meet the minimum standard of care.[10]

10. Side Effects of Nitrous Oxide / Oxygen Inhalation

The side effects of N2O take three main forms: (Lim et al,.2022)

1. Metabolic inhibition
2. Pressure/volume problems
3. Problems related to the administration of oxygen.

10.1 Metabolism of Nitrous Oxide

Nitrous oxide irreversibly oxidizes the cobalt atom of vitamin B12, inhibiting the activity of the cobalamin-dependent enzyme methionine synthase. Synthesis of the enzyme is required to restore activity and takes several days. A 50% decrease in methionine synthase activity is seen after only 2 hours of exposure. Loss of this enzyme shuts off the synthesis of methionine, a principle substrate for assembly of myelin sheaths and DNA synthesis, and leads to an accumulation of its precursor homocysteine. In adults with untreated B12 deficiency exposed to nitrous or those who chronically abuse N2O leading to depletion of body stores of cobalamin, a myeloneuropathy is seen which is identical to subacute combined degeneration of the spinal column as seen in pernicious anemia. A high degree of suspicion is necessary for any patient who develops neurologic symptoms after nitrous anesthesia. For these reasons, patients with suspected B12 deficiency (history of B12 supplementation, post gastrectomy, ileal malabsorption) or anemia should not receive nitrous. (Yee et al,.2019)

10.2 Pressure/Volume Toxicity

The other major cause of adverse events from nitrous oxide is due to pressure/volume complications. Compared to nitrogen, nitrous oxide is 34 times more soluble in blood. It will thus diffuse from the blood into any closed air-filled cavity in the body faster than the nitrogen can diffuse out. In a cavity with thick or noncompliant walls, the pressure inside such a cavity will immediately begin to increase. On the other hand, if the nitrous diffuses into a compliant, thin-walled air-filled space such as a pulmonary cyst or a loop of incarcerated bowel, the elevation in pressure will lead to distention of the structure. The major example of nitrous diffusing into a poorly compliant cavity is the eyeball. (Alrayyes et al,.2018)

Ophthalmologists frequently inject inert gases, e.g., sulfur hexafluoride or perfluoropropane, into the eye to treat retinal detachments. These injections are administered during retinal surgery but may also be done in an office setting. These gas bubbles can remain in the eyeball for weeks before they are reabsorbed. If a patient with an intraocular gas bubble receives nitrous oxide anesthesia, the nitrous will diffuse into the gas bubble and lead to an immediate and dangerous elevation of intraocular pressure. (Buhre et al,.2019)

The elevated pressure leads to central retinal artery occlusion and irreversible vision loss. Cases of total vision loss have been reported in patients with diabetic retinopathy followed by nitrous anesthesia. Therefore, the first question to be asked of any patient before nitrous oxide anesthesia is given should ascertain whether the patient has had any ocular procedures, injections, or surgery in the previous 3 months prior to the contemplated use of nitrous oxide. (Yee et al,.2019)

Ideally, such a patient will still be wearing their green plastic wristband, issued by the ophthalmologist warning against the use of nitrous oxide.

10.3 Oxygen Toxicity

Nitrous oxide administration should be avoided in patients who have received therapy with Bleomycin, an anti-neoplastic antibiotic, which is known to cause pulmonary toxicity. Acute respiratory distress syndrome has occurred in patients who have received bleomycin and is felt to be due to fluid overload and high inspired oxygen. (Cantlay et al,.2005)

11. In-built safety features of dedicated dental mixer machines

Dental N2O/O2 mixer machines can be mobile standalone units with gas cylinders or wall-mounted with a central gas supply (Figs. 2(a) and 2(b)). They can also have analogue or digital interfaces (Figs. 2(c) and 2(d)). Modern units are designed with the following safety features incorporated (Fig. 3): (Clark et al,.2008)

- N2O and O2 cylinders/tanks are colour-coded (commonly blue for N2O, black with a white collar for O2 in Singapore/ UK).
- Tubing is often colour-coded and matches the colours used on the cylinders (commonly blue for N2O and white/black for O2, though this may not always be the case). (Clark et al,.2008)
- Unique pin-index system for each tubing/fixture pair ensures correct fitting of tubing to corresponding fixture.
- Mixer dial ensures that a minimum of 30% O2 is delivered (and a maximum of 70% N2O), to prevent the delivery of a hypoxic gas mixture.
- O2 flush button allows 100% O2 to be delivered quickly and immediately during an emergency. (Clark et al,.2008)
- Reservoir bag allows respiration rate monitoring.
- Oxygen fail-safe valve ensures that N2O supply is automatically turned off when the O2 supply runs out, ensuring that 100% N2O is never delivered.
- Air intake valve allows in-flow of atmospheric gases, should either N2O or O2 runs out. **(**Clark et al,.2008)

- Many nasal hoods have a built-in scavenger system connected to a dental suction/scavenger unit to actively remove excess gases. (It is usually recommended that the windows are also kept open to allow some passive scavenging.) (Clark et al,.2008)

Figure. 3. (a) Mobile dental inhalation sedation machine. (b) Wallmounted inhalation sedation machine.

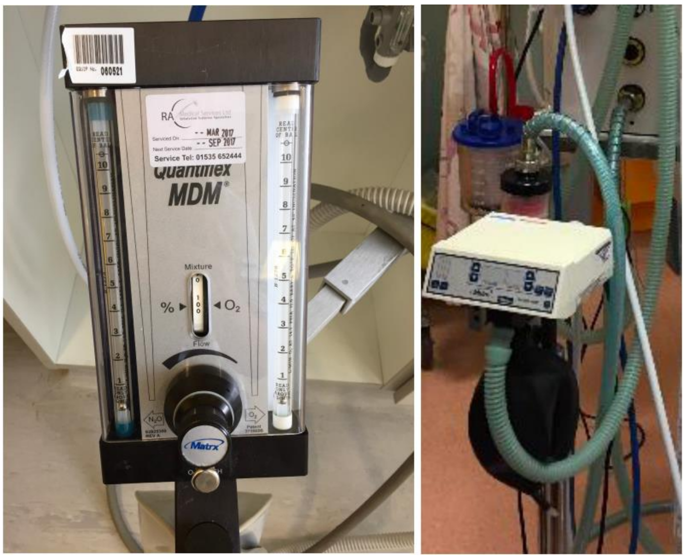

Figure. 4. Analogue mixer flowmeter. (d) Digital mixer flowmeter.

All equipment should be checked daily for defects prior to use and maintained regularly according to manufacturers' recommendations. Incorrect equipment usage and defects can lead to adverse outcomes even with in-built safety features. (Donaldson et al,.2012)

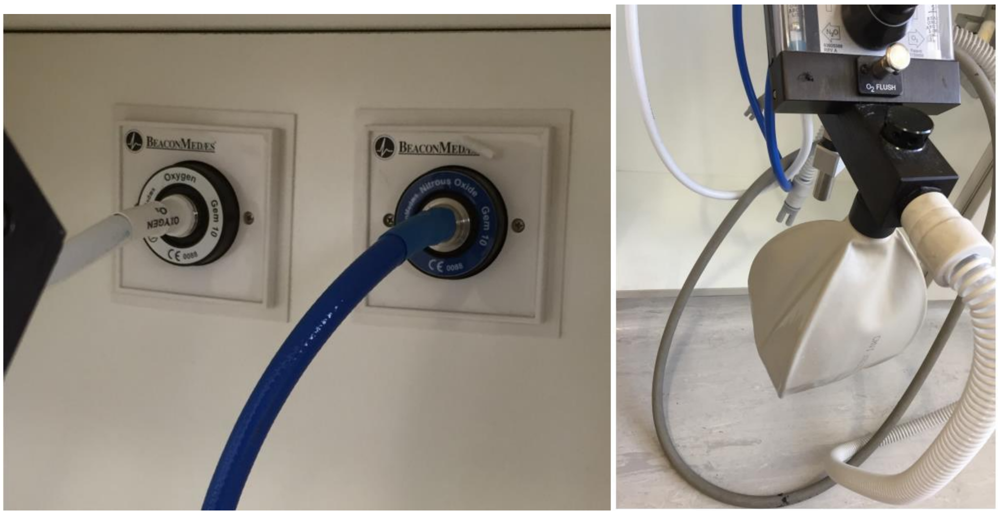

Figure. 5. Safety features of the Matrx MDMr N2O/O2 Mixer machine for dental sedation. (a) Colour coding of tubings and (b) oxygen flush button and reservoir bag**.**

12. Pre-sedation assessment, fasting, monitoring and discharge

Pre-sedation assessment of patients' medical history, anxiety level, dental needs and indications is important. International guidelines recommend that pre-sedation fasting is not required for N2O/O2 inhalation sedation; only a light meal two hours prior sedation is advised. The American Academy of Paediatric Dentistry, Australian Dental Association and the Intercollegiate Advisory Committee on Sedation in Dentistry (UK) 2015 report all recommend that clinical patient monitoring is required during N2O/O2 sedation. This includes observing the patient's level of consciousness, responsiveness to verbal commands and physical stimulation, mucosa/skin colour and breathing rhythm/rate. Anecdotally, some clinicians prefer to have additional pulse oximetry monitoring. It is important to refer to the local hospital/practices policies regarding fasting and monitoring requirements. (American Academy of Paediatric Dentistry,2022)

After administration of 100% O2 for a few minutes, the patient should continue to be monitored, and discharge should only be considered when pre-sedation level of consciousness is regained with stable vital signs. A responsible adult escort should be present for children. (Dorsch et al,.2010)

13. Documentation

Contemporary documentation and records should be kept at all stages. The European Academy of Paediatric Dentistry's (EAPD) "Guidelines on Sedation in Paediatric Dentistry 2005" provide a recommended list of items to be included in documentation. The present paper adapted these guidelines into a sedation checklist for systematic documentation, which could be easily adopted into routine clinical practice as follows: (Cantlay et al,.2005)

13.1 Pre-sedation assessment

- Medical history, medications and allergies;
- Dental needs and anxiety level
- Previous dental history and treatment;
- Previous history of sedation and GA with any adverse events;
- Indication for the use of N2O/O2 sedation and alternatives;
- Written information leaflet given to patient.

13.2 During and after sedation

- Dose (level and flow rate of N2O:O2Þ and if any other sedative drugs given (Yee et al,.2019)
- Time of start and end of sedation, duration of 100% administration at recovery and time of discharge
- Sedation level
- Patient's acceptance of sedation and treatment, for example Frankl Behaviour Scale

- Any adverse events/complications and management, for example nausea and vomiting
- Dose and type of LA administered;
- Dental treatment performed
- Post-sedation assessment and written post-operative instructions given to patient.

14. Potential concerns/adverse effects in patients

14.1 Nausea and Vomiting

The most common side effect is nausea and vomiting; this is infrequent (0.5% of patients) and occurs mostly when appropriate titration techniques are not practised. (Craig et al,.2019)

14.2 Diffusion Hypoxia and Pressure Volume Effect

N2O is less soluble than O2 in blood; thus, when it washes out of the patient, its rapid diffusion into alveoli reduces the alveolar oxygen concentration and may result in "diffusion hypoxia." This occurs when high N2O concentrations are used, that are not commonly administered during dental sedation, and is also rare due to the co-administration of oxygen. Furthermore, it can be prevented by administering 100% O2 for 3–5 min at recovery while N2O washes out of the circulation. (Becker et al,.2008)

N2O enters a gas-filled body space faster than nitrogen can escape from the space, for example an inflamed tympanic cavity. This results in an increase of the gas volume/ pressure in the space. This in turn can lead to adverse consequences, for example rupture of the tympanic membrane. It is therefore contraindicated in patients with otitis media and pneumothorax. (Malamed et al,.2003)

14.3 Hypoxia

Modern dental N_2O/O_2 delivery machines obligate a minimum of 30% O_2 to be delivered, a level that is higher than atmospheric O_2 levels. For another layer of precaution, they incorporate the pin-index system to ensure fixing of tubing to correct the N_2O/O_2 gas outlets (Fig. 2). However, misconnection of supposedly fail-safe machines can still occur. For example, pins of pin-index system can dislodge and result in hypoxia of patient, when N_2O is wrongly delivered to the O_2 gas outlet instead of the N_2O gas outlet. Therefore, frequent equipment checks are essential. (Wilson et al,.2013)

14.4 Loss of Protective Reflexes

Roberts and Wignall (1982) placed radio-opaque dye on the tongues of children undergoing dental restorations, with and without inhalation sedation. Post-operative medical radiographs revealed the absence of dye in the larynx and chest in the patients that had received inhalation sedation. This means that the dye was not aspirated during inhalation sedation and allayed concerns of N_2O-induced laryngeal reflex depression. Laryngospasm, desaturation, apnoea and seizures have been reported in isolated reports of the use of high levels of N_2O (in the range of 50%–70%) for medical procedures mostly in children aged 3 years. (Paterson et al,.2003)

Although a causative relationship cannot be established between these serious adverse events and the use of N_2O, such high dosages in young children are not recommended for use by dentists because patients can transit to deeper planes of sedation with a potential loss of protective reflexes and consciousness. (Allen et al,.2014)

14.5 Systemic Effects and Its Use in the Medically Compromised Patients

Unlike most drugs that are excreted by the liver/kidney, N2O is eliminated by lungs without metabolism. Hence, it can be used safely in patients with chronic liver or kidney disease. (Chellappah et al,.1990)

Typical dental sedation units deliver < 0:5 MAC and have minimal respiratory and cardiac effects. (Blain et al,.1998)

N2O/O2 inhalation sedation has been suggested as an alternative to GA to manage selected medically compromised patients. The high oxygen tension, anxiolytic and mild analgesic properties are invaluable in patients with cardiac conditions, sickle cell disease and severe asthma. Notwithstanding, it is advisable that only American Society of Anesthetists I and II patients should receive N2O/O2 sedation outside hospital settings. (Wilson et al,.2007)

14.6 Hallucination

Patients' sexual hallucinations have been reported in previous case reports. Dentists risk sexual abuse allegations and hence should be chaperoned by a dental assistant at all times. (Paterson et al,.2003)

15. Occupational safety

Chronic staff exposure to N2O has been associated with various adverse effects, including the risk of spontaneous abortion, bone marrow suppression, liver disease, kidney disease and neurological disease. However, the evidence for these effects is conflicting and weak, and mostly from retrospective studies that are prone to bias, or studies with small sample sizes.

Reproductive risk has been reported, but the evidence is equivocal. A survey by Cohen et al. (1980) reported that heavily exposed (> 8 hours/week) male dentists' spouses and female assistants were 1.5 and 2.3 times more likely to have spontaneous abortion respectively, than non-exposed controls. (Kharouba et al,.2022)

In contrast, spontaneous abortion and congenital malformations were not observed in a survey of nurses exposed to anaesthetic gases, including N2O and halothane gases.44 Moreover, these aforementioned surveys were retrospective and prone to recall/respondent bias. Hence, the Health Services Advisory Committee of the Health and Safety Commission concluded that insufficient human evidence exists to prove reproductive risks. Nevertheless, Paterson and Tahmassebi (2003) advised that staff who are expecting or attempting to conceive to avoid N2O exposure. (Kharouba et al,.2022)

Bone marrow suppression from chronic exposure has also been reported. Sweeney et al. (1985) performed bone marrow aspiration examinations and deoxyuridine suppression tests (to measure Vitamin-B12-dependent DNA synthesis) in a small sample of 21 dentists, and compared these baseline results with the results after N2O exposure sampled over a period of 3–11 weeks. Of 21 dentists investigated, only two reported bone marrow changes (megaloblastic and white blood cells changes); the majority had no abnormalities detected. Moreover, there were no definite neurological problems in all subjects. (Mosca et al,.2005)

A number of steps can be taken to mitigate against the occupational risks of prolonged exposure to N2O. The United Kingdom recommends occupational exposure levels of < 100 ppm over an 8-hour time-weighted average reference period. Regular ambient N2O checks are important to ensure that the scavenging system is effective and well-maintained. With effective scavenging, it is generally accepted that risks of occupational exposure are rendered insignificant. In Singapore, the long-term Permissible Exposure Level (maximum time-weighted average concentration of N2O to which an individual may be exposed over an 8-hour working day and a 40-hour work week) is 50 ppm. (Myles et al,.2007)

15.1 Pregnancy and Nitrous Usage

It is wise NOT to use nitrous sedation in pregnant patients, no matter what trimester they are in, though it is believed to be most harmful in the 1st trimester. (Ryding et al,.2007)

It is important to keep in mind that some cases of miscarriages in female practitioners can be attributed to having worked on patients undergoing nitrous sedation, though scavenger systems WERE in use. Nitrous escaping out of the patient's mouth, while in use, from talking or from moving around can be just as damaging as a failing scavenger system. Having an assistant use the high vacuum suction and a rubber dam in place can reduce nitrous escaping from a patient's mouth, but in some treatments, such as procedures by Hygienists, this is not practical. (Spielberger et al,.1998)

If Pregnant, It Is Best To Avoid Working On Patients, Directly, Who Will Be Using Nitrous In Procedures!

16. Abuse of Nitrous Oxide

- The substance disrupts learning ability. In a typical experiment volunteers who inhaled a low dose of the drug showed worsened reaction time, worsened ability to do arithmetic, and general sedation accompanied by nervous system depression (as opposed to stimulation). (Spielberger et al,.1998)
- Interference with driving ability has been noted one-half hour after a dose.
- Short-term exposure can cause dizziness, nausea, vomiting, and breathing difficulty.
- Some recreational users quickly inhale as much nitrous oxide as possible and hold their breath. This technique causes a sudden change of pressure

inside the lungs and can rupture small interior structures needed for breathing.

- Blood pressure can go up or down, depending on dosage. Users can lose consciousness, which may be hazardous in a recreational context due to falls or inability to shut off the gas source. (Verwest et al,.1998)
- The substance deactivates vitamin B12, an effect that can cause numbness and difficulty in moving arms and legs.
- Other results can be impotence and involuntary discharge of urine and feces.
- Nitrous oxide interferes with blood clotting, and long-term exposure has caused blood abnormalities.
- Persons with chronic industrial exposure have more kidney and liver disease than usual.
- Nitrous oxide can become very cold when released as a gas from a pressurized container, cold enough to cause frostbite upon meeting skin or throat. (Zafirova et al,.2013)
- Breathing nitrous oxide without an adequate supply of oxygen can be fatal; a little in a closed space or a lot from a face mask can suffocate a user.
- Although nitrous oxide is called nonflammable, when inhaled it can seep into the abdominal cavity and bowels, mixing with body gases to create a flammable combination. If ignited the result would be like setting off an explosive inside the body; the danger is real enough that surgical personnel administering nitrous oxide as an anesthetic have been warned about it**.** (Zafirova et al,.2013)

17. Conclusion

Nitrous oxide / oxygen anesthesia is used in a standard way in dentistry and medicine. And review of the standards on a regular basis is invaluable to maintain the highest standard of care. Professional use and administration of nitrous oxide is a tried and true method to manage patients' anxiety for dental procedures. The overall patient experience is enhanced by careful and professional use of this practice-building anesthetic gas. Dental team members must adhere to the best clinical protocols and know the standard of care to ensure absolute safety for the patient and to minimize exposure to themselves. Nitrous oxide is safe and effective for use by qualified dental professionals in a wide variety of situations requiring pain and anxiety management in the dental office setting.

References

1. Academy of Medical Royal Colleges. Safe sedation practice for healthcare procedures: standards and guidance. 2013.
2. Allen M, Thompson S. An equivalence study comparing nitrous oxide and oxygen with low-dose sevoflurane and oxygen as inhalation sedation agents in dentistry for adults. Br Dent J 2014;2179: E18.
3. Alrayyes S, Compton AA, Kawar N. Oral health considerations for pediatric patients with sickle cell disease. Dis Mon. 2018;64(6):302–305. doi: 10.1016/j.disamonth.2017.12.006.
4. Amess JAL, Rees GM, Burman JF, Nancekievill DG, Mollin DL. Megaloblastic haemopoiesis in patients receiving nitrous oxide. Lancet 1978;3128085:339–42.
5. American Academy of Paediatric Dentistry. Guideline on use of nitrous oxide for pediatric dental patients. 2013.
6. American Society of Anaesthesiologists. Continuum of depth of sedation: definition of general anaesthesia and levels of sedation/analgesia. 2009.
7. Anand, P.S. and Adams, L.R., 2022. Using inhalation sedation in practice. Dental Update, 49(2), pp.166-171.
8. Ashley, P., Anand, P. and Andersson, K., 2021. Best clinical practice guidance for conscious sedation of children undergoing dental treatment: an EAPD policy document. European Archives of Paediatric Dentistry, pp.1-14.
9. Australian Dental Association. Policy statement 6.17 — conscious sedation in dentistry [Including the ADA recommended guidelines for conscious sedation in dentistry and guidelines for the administration of nitrous oxide inhalation sedation in dentistry]. 2017.
10. Balasubramaniam B, Park GR. Sexual hallucinations during and after sedation and anaesthesia. Anaesthesia 2003;586:549–53.; 2019:157–8.
11. Banks RGS, Henderson RJ, Pratt JM. Reactions of gases in solution. Part III. Some reactions of nitrous oxide with transition-metal complexes. J Chem Soc A 1968;0:2886–9.
12. Becker DE, Rosenberg M. Nitrous oxide and the inhalation anesthetics. Anesth Prog 2008;554:124–31.
13. Blain KM, Hill FJ. The use of inhalation sedation and local anaesthesia as an alternative to general anaesthesia for dental extractions in children. Br Dent J 1998;18412:608–11.
14. British Society of Paediatric Dentistry. UK National Clinical Guidelines in Paediatric Dentistry. Managing anxious children: the use of conscious sedation in paediatric dentistry. 2002.
15. Brown SM, Sneyd JR. Nitrous oxide in modern anaesthetic practice. BJA Educ 2016;163:87–91.
16. Buhr VS. Letter to the JPO editors re: article by Andreacchio et al entitled "lateral column lengthening as treatment for planovalgus foot deformity in ambulatory children with spastic cerebral palsy"(J Pediatr Orthop 2000;20:501-505) J Pediatr Orthop. 2006;26:412.
17. Campbell C, Soldani F, Busuttil-Naudi A, Chadwick B. UK National Clinical Guidelines in Paediatric Dentistry: update of non-pharmacological behaviour management guideline. 2011.
18. Cantlay K, Williamson S, Hawkings J. Anesthesia for dentistry. Contin Educ Anaesth Crit Care Pain 2005;5:71-5.
19. Chellappah NK, Vignehsa H, Milgrom P, Lam LG. Prevalence of dental anxiety and fear in children in Singapore. Community Dent Oral Epidemiol 1990;185:269–71.
20. Chi SI. Complications caused by nitrous oxide in dental sedation. J Dent Anesth Pain Med 2018;182:71–8.
21. Clark MS, Brunick AL. Handbook of nitrous oxide and oxygen sedation. Elsevier Health Sciences; 2008.

22. Craig D, Skelly M. Practical Conscious Sedation: Quintessence. London: Quintessence Publishing, 2004.
23. Craig, David, and Carole Boyle. Practical conscious sedation. Vol. 15. Quintessenz Verlag, 2019.
24. Council of European Dentists (CED). The use of nitrous oxide inhalation sedation in dentistry. 2012.
25. Cunningham GH. Nitrous oxide in paediatric dentistry: safety aspects. Br Dent J 2010;125:126.
26. Dorsch JA, Dorsch SE. Understanding anesthesia equipment: construction, care. 2010.
27. Donaldson M, Donaldson D, Quarnstrom FC. Nitrous oxide–oxygen administration: when safety features no longer are safe. J Am Dent Assoc. 2012;1432:134–43.
28. Duncan GH, Moore P. Nitrous oxide and the dental patient: a review of adverse reactions. J Am Dent Assoc 1984;1082:213–9.
29. Emmanouil DE, Quock RM. Advances in understanding the actions of nitrous oxide. Anesth Prog 2007;541:9–18.
30. EU Directive. The use of nitrous oxide inhalation sedation in dentistry. Community of European Dentists European Directive. 2015.
31. 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;104:345–6.
32. Foley J. A prospective study of the use of nitrous oxide inhalation sedation for dental treatment in anxious children. Eur J Paediatr Dent 2005;6:121–128.
33. 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;125:359–72.
34. Hosey MT, Macpherson LM, Adair P, Tochel C, Burnside G, Pine C. Dental anxiety, distress at induction and postoperative morbidity in children undergoing tooth extraction using general anaesthesia. Br Dent J 2006;2001:39–43; discussion 27; quiz 50.
35. Intercollegiate Advisory Committee for Sedation in Dentistry (IACSD). Standards for conscious sedation in the provision of dental care. RCS Publications. 2020.
36. Lim, Jane WH, et al. Nitrous Oxide-Oxygen Inhalation Sedation in Paediatric Dental Patients: A Review. Malaysian Journal of Paediatrics and Child Health 2022;28:91–10.
37. Malamed SF, Clark MS. Nitrous oxide–oxygen: a new look at a very old technique. J Calif Dent Assoc 2003;315:397–403.
38. Mosca VS. Letter to the JPO editors. J Pediatr Orthop. 2006;26:412.
39. Myles PS, Leslie K, Chan MT, Forbes A, Paech MJ, Peyton P, Silbert BS, Pascoe E, ENIGMA Trial Group. Avoidance of nitrous oxide for patients undergoing major surgery: a randomized controlled trial. Anesthesiology 2007;28:001.
40. National Institute for Health and Clinical Excellence (NICE). Sedation for diagnostic and therapeutic procedures in children and young people. 2010.
41. Scottish Dental Clinical Effectiveness Programme (SDCEP). Conscious Sedation in Dentistry. 2017.
42. Singapore Academy of Medicine. Guidelines on safe sedation practice for non-anaesthesiologists in medical clinics. 2014.
43. Spielberger CD, Lushene RE, Gorsuch RL, Vagg PR, Jacobs GA. State-Trait Anxiety Inventory (Professional Manual). Redwood City, CA: Mind Garden Inc, 1998.
44. Wilson KE, Welbury RR, Girdler NM. Comparison of transmucosal midazolam with inhalation sedation for dental extractions in children. Acta Anaesthesiol Scand 2007;518:1062–7.

45. Wilson KE, Girdler NM, Welbury RR. Randomized, controlled, crossover clinical trial comparing intravenous midazolam sedation with nitrous oxide sedation in children undergoing dental extractions. Br J Anaesth 2003;916:850–6.
46. Yagiela JA. Health hazards and nitrous oxide: a time for reappraisal. Anesth Prog 1991;381:1–11.
47. Yee, Ruixiang, et al. Nitrous oxide inhalation sedation in dentistry: An overview of its applications and safety profile. Singapore Dental Journal 2019;39:01.
48. Zafirova Z, Sheehan C, Hosseinian L. Update on nitrous oxide and its use in anesthesia practice. Best Pract Res Clin Anaesthesiol. 2018.