

VASCULAR

INSIGHT INTO THE DIAGNOSIS AND TREATMENT OF VASCULAR DISEASE

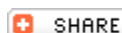
DISEASE MANAGEMENT

Nitrous Oxide Sedation-Analgesia in a Phlebology Practice

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“Since the operation the patient...expresses a strong affection for the gas-bag, and an earnest desire to retain it in his possession as the grand balm for the pains and trouble of this life.”¹ — 1847 advertisement

Phlebology has become primarily an office-based specialty thanks in no small part to the success of minimally invasive procedures, such as endovenous catheter ablation and microincisional ambulatory phlebectomy done under tumescent local anesthesia, which have largely replaced traditional vein stripping done under general anesthesia. Tumescent anesthesia is not painless, however. Volumes of dilute local anesthetic of a few dozen cc's up to a liter in some cases are typically used for these procedures. A recent study found that patients treated with tumescent local anesthetic for varicose vein surgery found the procedure to be “more painful than they expected.”² Many phlebology patients are “needle phobic” and express concern to the physician that they do not want to feel any pain whatsoever during the procedure. In fact, the fear of painful surgery and needles is sufficient to keep many patients from ever seeking care for a condition that is easily treatable.

Many practicing phlebologists who perform surgery employ oral sedative/anxiolytics, intravenous (IV) conscious sedation, or a combination of the two. A few surgeons in Europe³ have used general anesthesia for these procedures, but studies show that local anesthetic is safe and effective.⁴ Oral anxiolytics such as diazepam and alprazolam are quite safe and effective for mild anxiolysis when used in one-time preoperative doses in appropriate patients, but they provide no analgesia. Conscious sedation is also relatively safe in experienced hands, provided that appropriate intraoperative monitoring of vital signs, pulse oximetry and patient level of consciousness are done and appropriate reversal agents and resuscitation equipment are available for the rare case of excessive sedation.

An ideal sedative/analgesic agent for varicose vein surgery would have fairly rapid onset of action, good therapeutic effectiveness, a wide safety margin, no drug interactions, quick recovery time, no “hangover” or excessive sedative effects, and would not require the presence of an anesthesiologist. One analgesic/sedative agent that has been available to the medical community for over 150 years and is used daily by anesthesiologists, dentists and some emergency departments is nitrous oxide (Figure 1). As will be outlined below, this agent, when used for varicose vein surgery, fulfills almost all of the criteria listed above, but unfortunately has been largely ignored, unused and untaught by anyone outside of general anesthesia or dentistry. Clinical trials of nitrous oxide use as an adjunct to

local anesthesia in dermatologic surgery were published in 1980,⁵ but widespread adoption of nitrous oxide usage is still lacking, perhaps because most non-anesthesiologist physicians have never seen nitrous oxide used and have never been taught how to use it.

History of Nitrous Oxide Use

Nitrous oxide, the first anesthetic ever discovered,⁶ was first manufactured in 1772 by Joseph Priestly, an English chemist. Around 1800, Sir Humphrey Davy experimented with 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 operations...”⁷ The surgical world tragically ignored his suggestion, and interest in the surgical use of nitrous oxide would have to wait another half century.

In Hartford, Connecticut, in 1884, a “professor” named Gardner Quincy Colton was making a living traveling from town to town giving demonstrations of the intoxicating effects of nitrous. Present at one such demonstration was a local Hartford dentist named Horace Wells. Wells convinced Colton to come to his dental office and Colton administered nitrous to Wells while his partner Dr. Riggs pulled one of Wells’s teeth. The procedure was a resounding success...Wells felt no pain at all. He immediately began using nitrous regularly on patients in his dental practice. The American Dental Association finally recognized Wells as the discoverer of anesthesia in 1864 and the American Medical Association recognized the same in 1870.⁸

Nitrous oxide was used alone as an inhalational anesthetic until the 1860s when oxygen began to be administered simultaneously. Prior to that time, anoxic anesthesia was possible and not uncommon when patients were given only 100% nitrous (Figure 2). Currently, available nitrous oxide/oxygen delivery systems are manufactured with oxygen fail-safe devices that stop the flow of nitrous when the flow of oxygen is stopped, thus preventing this catastrophe.

Every year, approximately 45 million patients undergo anesthesia in North America, with nitrous oxide constituting a major component in about half of these procedures.⁹ A significant percentage of general dentists use nitrous oxide sedation in their practices. Nitrous is the most used gaseous anesthetic in the world, commonly administered for the purpose of enabling a lesser amount of a more potent and usually more toxic general anesthetic agent to be employed.⁹ It is available in fixed concentrations of 50% nitrous/50% oxygen in some countries for use by paramedical personnel as prehospital treatment of the pain of acute myocardial infarction.¹⁰

Properties

Nitrous oxide is the weakest of the inhalant anesthetics. It is commonly used as a “carrier” gas to facilitate the absorption and allow lower concentrations of more potent and toxic general anesthetic gases. It is an N-methyl-D-aspartate receptor antagonist with an experimental ability to block post-operative hyperalgesia.¹¹ The chemical formula is N₂O. It is colorless, nonflammable, with a slightly sweet odor.

Nitrous oxide has low solubility in blood, diffuses rapidly across the alveolar-arterial membrane and is excreted unchanged through the lungs. As a result, nitrous takes effect rapidly and is quickly reversible on discontinuation.¹² Nitrous oxide can induce loss of consciousness at high concentrations, typically 70% or higher. Nitrous oxide produces either no change, or a slight increase in blood pressure, while all other volatile anesthetics reduce blood pressure. There is no effect on heart rate, but high doses may cause myocardial depression.¹³

In 2002, the American Society of Anesthesiologists adopted guidelines for sedation for non-anesthesiologists. The guidelines stress the concept of “rescue,” *i.e.*, physicians administering mild or moderate sedation should have the skills and equipment necessary to rescue a patient should

they reach the next deeper level of sedation. Noteworthy is that these guidelines do not apply to patients who receive “minimal sedation” defined as less than 50% nitrous oxide/oxygen alone, or a single oral sedative or analgesic alone in appropriate doses.^{14,15} As will be seen below, however, many phlebology patients will require doses of nitrous of 50% or higher.

Contraindications

There are important contraindications to nitrous oxide/oxygen sedation (Table 1). Nitrous is the only inhaled anesthetic proven to be teratogenic in animals,⁶ so it is best avoided during the first trimester of pregnancy. It can lead to an increase in pulmonary vascular resistance, so it should not be used in patients with pulmonary hypertension or major intracardiac right-to-left shunts.¹³ High doses of nitrous have a myocardial depressant effect, but patients with severely compromised cardiac function are not candidates for varicose vein surgery anyway.

Some patients are claustrophobic and will not tolerate wearing the nasal mask. Despite reassurance, the occasional patient refuses to consider nitrous oxide use because they fear “losing control” of themselves. These patients require an alternate form of sedation. Patients with persistent nasal congestion or obstruction will be unable to breathe comfortably through their nose.

Side Effects

The side effects of N₂O take two main forms: metabolic inhibition and pressure/volume problems. Other potential problems relate to the administration of oxygen.

Metabolism of Nitrous Oxide

Nitrous oxide irreversibly oxidizes the cobalt atom of vitamin B12, inhibiting the activity of the cobalamine-dependent enzyme methionine synthase. De novo synthesis of the enzyme is required to restore activity and this takes several days.¹⁶ A 50% decrease in methionine synthase activity is seen after only 2 hours of exposure.¹⁷ 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 cobalamine, 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.

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.¹⁸ 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.

Ophthalmologists frequently inject inert gases, e.g., sulfur hexafluoride or perflouropropane, into the eye to tamponade retinal detachments (pneumatic retinopexy). These injections are done during

retinal surgery but may also be done in an office setting, so the patient may not remember this being done or may deny having any ocular “surgery”. 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. 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 who have had pneumatic retinopexy followed by nitrous anesthesia.¹⁹ 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. Ideally, such a patient will still be wearing their green plastic wristband warning against the use of nitrous oxide (Figure 3).

In the absence of studies proving otherwise, it would seem relatively safe to use foam sclerotherapy after nitrous oxide has been terminated and the patient given 100% oxygen for at least 5 minutes, ensuring that the nitrous oxide concentration in the blood is minimal. However, it would be safer still to perform foam sclerotherapy on an alternate day when nitrous oxide has not been administered. Likewise, foam sclerotherapy should not be given before nitrous oxide sedation, as bubbles could persist for many minutes after injection.

Nitrous oxide should be avoided in patients with active middle ear or sinus problems due to the potential for uncomfortable pressure changes.

Oxygen Toxicity

Bleomycin, an antineoplastic antibiotic, 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 concentrations given during the surgical procedure.²⁰ The resulting interstitial pneumonitis may be fatal.²¹ For this reason, nitrous oxide administration should be avoided in patients who have received therapy with bleomycin.

Post-inhalation Hypoxia

In 1955, Dr. Raymond Fink published a paper documenting oxygen desaturation of up to 10% occurring after patients given N₂O/O₂ anesthesia were placed on room air, with the effect lasting up to 10 minutes. This phenomenon was felt to be secondary to the rapid diffusion of N₂O into the alveolar air spaces and the subsequent drop in the partial pressure of oxygen. For this reason, it has been the standard of care to administer 100% oxygen for at least 5 minutes to all patients at the conclusion of inhalation anesthesia with N₂O/O₂. This has been shown to completely prevent this so-called “diffusion anoxia”, even though alveolar collapse or atelectasis is now recognized as the major contributor to the hypoxemia observed after anesthesia.²²

Occupational Exposure

In 1995 the American Dental Association published a formal position statement that the maximum N₂O exposure limit was not yet known.⁸ It is considered standard of care to connect the exhaust tubing of the nitrous machine to wall suction of at least 45 liters per minute capacity to ensure adequate venting of waste nitrous to the outside air. Ensuring proper fit of the patient’s nasal hood and limiting the patient from talking will also decrease levels of ambient nitrous in the operatory. Early studies linked occupational exposure of nitrous to reproductive problems, but these were neither definitive nor reproducible.

Patient Selection

We employ a printed checklist of contraindications for nitrous oxide and review the entire list during the patient's preoperative workup, checking "yes" or "no", as appropriate. This checklist goes into the patient's record (Figure 4). Most contraindications are recognized and such patients excluded during the initial consultation or during subsequent discussions with the patient regarding the planned procedures, but the checklist serves as a final reminder.

Because of the success of nitrous oxide use in our cosmetic patients, we have begun using nitrous in our vein surgery patients. We feel it is best used for "short cases" such as an endovenous laser ablation therapy alone, or with a minimal amount of concomitant phlebectomy or for small phlebectomies. For our more extensive cases, we will usually use IV conscious sedation. We may or may not give the patient a single dose of oral alprazolam 0.5–1.0 mg 15–30 minutes prior to the procedure. For claustrophobic patients or patients who are rather histrionic or extremely anxious, we opt for IV conscious sedation, which they seem to tolerate better. Effective nitrous sedation requires a lot of patient "coaching". Patients are told that the gas is more effective when they try to "block out" what's going on around them and focus entirely upon their breathing. The patient has to be instructed to relax and breathe normally through the nose. Patients are asked not to speak at all during nitrous administration unless they need to say "ouch", or otherwise inform the surgical team of a problem. In order to minimize unnecessary talking, patients are asked to give the "thumbs up" sign in response to questions during the case if all is well and they are not feeling any discomfort. The typical inhalation sedation patient requires 30–40% of nitrous oxide to achieve ideal sedation according to Clark,⁸ but in our experience, there will be numerous patients who will require levels of 50–60% for adequate analgesia. Even at 60%, there are some patients who complain of persistent discomfort during tumescent anesthesia. The discomfort with nitrous oxide is certainly a lot less than patients would feel with no analgesia, and they are happy not to have to go home and "sleep off" a stronger sedative. Conversely, there are patients who are quite happy with nitrous oxide, experience complete analgesia during the procedure, sometimes with amnesia regarding what occurred, and express the desire to extend the time of their inhalation therapy!

Nitrous Oxide Protocol

The patients are told that they will not "go to sleep" with nitrous oxide, but will feel "relaxed". We instruct the patients that they will only need the nitrous oxide during the tumescent anesthesia and that once this is completed, the nitrous oxide will be turned off, but they should feel no pain. It is important to reassure them that touch and pressure sensation will still be intact. Accordingly, we discontinue the nitrous oxide and give 100% oxygen as soon as the tumescent anesthesia is completed. After 5 minutes of 100% oxygen, the nasal hood is removed from the patient. Thus, the patient is more or less completely awake and lucid during the bulk of the procedure itself, only having been under the influence of the gas during the painful injections of tumescent anesthetic. In patients who require endovenous catheter ablation and concomitant phlebectomy, we usually perform the catheter ablation first, then finish the tumescent anesthesia for the phlebectomy, however, it would be just as easy to perform all the required tumescent anesthesia at the same time. The sheath and laser fiber should be inserted into the saphenous vein before any tumescent anesthesia is begun, or the epinephrine in the anesthetic and the trauma of multiple needle punctures will cause the saphenous vein to spasm, making percutaneous access more difficult.

We start the nitrous after the patient has been prepped and draped and immediately before we scrub in for the case. This has shortened nitrous oxide administration time from 30–40 minutes to 10–20, and sometimes even less. The circulating nurse makes adjustments to the nitrous oxide administration at the direction of the physician. We place a pulse oximeter on the patient, start the recorder and then turn on the nitrous oxide machine. Our digital flow machine automatically adjusts flow rates according to the desired percentage of oxygen and nitrous. The flow rate is set to 100% oxygen, and then we place the nasal hood on the patient and adjust the tubing either behind their head if they are prone, or if supine, draped around and behind the head of the surgical table, making

sure that there are no kinks in the hoses and the mask fits snugly but not uncomfortably tight. The patient may be allowed to hold the mask over their own nose, but in practice, this rarely works as well. The patient is instructed to breathe through the nose and asked to take one or two deep breaths to make sure the reservoir bag deflates properly with each inhalation. Once the nasal hood is in place and the patient is breathing comfortably, we start the flow of nitrous oxide at 20% and start a small electronic timer placed on the top of the nitrous oxide machine. It is stopped when the nitrous oxide is stopped at the end of the tumescent anesthesia. Once the nitrous oxide is started, the patient is assessed every minute or two. The desired effects may include any or all of the following: a feeling of relaxation, heaviness or lightness of the limbs, tingling in the fingertips, circumoral numbness and total body warmth. If after a minute or two the appropriate effects are not felt, the nitrous concentration is increased by 10% and the patient observed for another minute or two. This titration procedure is essential in the success of nitrous oxide administration. Nausea and vomiting are the most well-known side effects of nitrous oxide. Properly done, titration allows administration to each patient of the minimally effective concentration of nitrous oxide and greatly decreases the incidence of nausea and vomiting. If at any time a patient under nitrous oxide sedation develops irritability, hallucinations, nausea or vomiting, confusion, combativeness, uncooperativeness or just complains of not feeling well, they are probably overmedicated and the concentration of nitrous oxide should be reduced immediately.

Equipment

A digital nitrous oxide flow meter is highly recommended for in-office administration (Figure 5). The digital panel displays the total gas flow rate in liters per minute, the percentage of oxygen being delivered, and has two LEDs that flash when the corresponding gas is flowing (Figure 6). All currently available nitrous oxide machines are manufactured with oxygen fail-safe devices that stop the flow of nitrous oxide if the flow of oxygen is interrupted, thus preventing anoxic anesthesia. It is important to test a new digital system when it first arrives to make sure the fail-safe alarms are functioning. Our flow meter's alarms were not working after delivery and set-up (the technician did not perform a proper diagnostic test before leaving our office). This required another service call and turned out to be nothing more than a loose connection inside the digital head. A 4-tank yoke system is recommended versus the 2-tank system, as oxygen tanks will run out fairly frequently during daily use, about two times faster than nitrous oxide tanks. The yoke should be on wheels so it can easily be rolled from room to room as needed. With our 4-tank system, we turn on only the front 2 tanks during a case, and if either the oxygen or the nitrous oxide runs out and the machine's alarm sounds, it takes only seconds to turn on the spare tank, silencing the alarm and allowing the case to continue. After the case is over, the empty front tank is removed, the "spare" is moved to the front of the yoke and a fresh tank is replaced in the rear of the yoke as the new "spare". An ample supply of fresh tanks should be kept on hand in the office if the machine is used daily, and more oxygen tanks will be needed than nitrous oxide tanks. Note that oxygen and nitrous will need to be obtained from an industrial gas supplier, not the supplier of the nitrous machine. A digital flow system with a 4-tank yoke will run somewhere around \$4,000. It is wise to obtain equipment prices from several different suppliers.

One problem we have seen with this machine that we were not warned about is gasket wear. Each tank connection has a small round brass gasket with a rubber seal on each side. The rubber seals on these gaskets wear out with frequent use (Figure 7). This will become fairly evident when a new tank is connected and a gas leak is heard when the tank valve is turned on. When the machine is first purchased, insist on getting a supply of spare gaskets (10 to 15). When the gaskets fail and no spares are available, the machine cannot be used. Do not ever use any sort of grease or oil on these rubber gaskets.

Before starting the case, plug in the nitrous oxide machine and turn on the front nitrous oxide and oxygen tanks. The nitrous pressure gauge should read approximately 750 psi. The nitrous oxide

pressure will not fall until the tank is almost empty. This is because nitrous oxide inside the tank is in mostly liquid form, and the partial pressure of the gas does not drop until the liquid has completely evaporated. The oxygen pressure gauge will read between 0 and 2,000 psi: the lower the reading, the emptier the tank. Oxygen in the tank is pressurized gas with no liquid component.⁸

During nitrous oxide administration, the flow rate is adjusted based on the patient's overall ventilation. The initial flow rate is set at 5–6 liters per minute. If the reservoir bag becomes deflated, the patient is either anxious and breathing too rapidly (encourage them to relax and slow down), or the flow rate is too low and should be increased by a liter per minute as needed. Conversely, if the bag becomes hyperinflated, the most common reason is a kink in the flow tubing. Ask the patient if they feel like they are getting enough air. If the answer is “no”, look for a kinked hose. If yes, then the mask may not be snug enough and the patient may be inhaling room air around the mask. If the bag deflates normally when the patient is asked to inhale a deep breath, then the flow rate may just be too high. The flow rate may have to be adjusted several times during a more lengthy procedure, as the patient's respiratory rate may vary.

Be sure to instruct clinical staff to turn off the nitrous oxide and oxygen tanks at the end of each day. The connecting hoses should be checked periodically for leaks by painting them with a brush dipped in soapy water. Bubble formation at any connection site indicates a gas leak which must be fixed before the machine can be used. The face of the digital display can be wiped clean with disinfectant wipes like those used for an ultrasound machine probe. Purchase a supply of disposable rubber nasal masks which are now available in various sizes and scents (plain, orange, vanilla, bubblegum and strawberry!). Medium- or large-sized masks from Matrix Environmental Technologies, Inc. (*Orchard Park, New York*) will fit most adults.

Conclusion

The search for the perfect sedative/analgesic may never end. We have at our disposal an agent that comes fairly close. Nitrous oxide/oxygen administration provides a technique that is rapid in onset, effective, devoid of drug interactions, extremely safe when known contraindications are observed and whose effects are rapidly reversed with no hangover. We believe that this method will be preferred by a majority of patients if given the option. With an aging population seeking more and more phlebological treatments, safer alternatives to general anesthesia and intravenous conscious sedation are desperately needed.

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