Neuraxial anesthesia, including epidural and combined spinal-epidural anesthetics, are the “gold standard” interventions for pain relief during labor because they provide a superb combination of reliable pain relief and safety for the mother and child.1 Many US birthing centers also offer additional options for managing labor pain, including continuous labor support,2 hydrotherapy,3 and parenteral opioids.4 In 2012, the US Food and Drug Administration (FDA) approved equipment to deliver a mixture of 50% nitrous oxide and 50% oxygen, which has offered a new option for laboring mothers.

Nitrous oxide is widely used for labor pain in the United Kingdom, Finland, Sweden, Canada, Australia, and New Zealand.5 In the United States, nitrous oxide has been a long-standing and common adjunct to general anesthetics, although it recently has fallen out of favor in place of better, more rapidly acting inhalation and intravenous general anesthetics. With these agents not suitable for labor analgesic use, however, nitrous oxide is undergoing a resurgence in popularity for obstetric analgesia in the United States, and we believe that it will evolve to have a prominent place among our interventions for labor pain.6 In this editorial, we detail the mechanism of action and the equipment’s use, as well as benefits for patients and cautions for clinicians.

How does nitrous oxide work?

**Pharmacology.** Nitrous oxide (N₂O) was first synthesized by Joseph Priestley in 1772 and was used as an anesthetic for dental surgery in the mid-1800s. In the late 19th Century, nitrous oxide was tested as an agent for labor analgesia.7 It was introduced into clinical practice in the United Kingdom in the 1930s.8

It is thought that the gas may produce analgesia by activating the endogenous opioid and noradrenergic systems, which in turn, modulate spinal cord transmission of pain signals.5

**Administration to the laboring mother.** For labor analgesia, nitrous oxide is typically administered as a mix of 50% N₂O and 50% O₂ using a portable unit with a gas mixer that is fed by small tanks of N₂O and O₂ or with a valve fed by a single tank containing a mixture of both N₂O and O₂. The portable units approved by the FDA contain an oxygen fail-safe system that ensures delivery of an
appropriate oxygen concentration. The portable unit also contains a gas scavenging system that is attached to wall suction. The breathing circuit has a mask or a mouthpiece (according to patient preference) and demand valve. The patient places the mask over her nose and mouth, or uses just her mouth for the mouthpiece. With inhalation, the demand valve opens, releasing the gas mixture. On exhalation, the valve shunts the exhaled gases to the scavenging system.

Proper and safe use requires adherence to the principles of a true “patient-controlled” protocol. Only the patient is permitted to place the mask or mouthpiece over her nose and/or mouth. If the patient becomes drowsy, such that she cannot hold the mask to her face, then the internal demand valve will not deliver nitrous oxide and she will return to breathing room air. No one should hold the mask over the patient’s nose or mouth, and the mask should not be fixed in place with elastic bands because these actions may result in the inhalation of too much nitrous oxide.

Nitrous oxide has a rapid onset of action after inhalation and its action quickly dissipates after discontinuing inhalation. There is likely a dose-response relationship, with greater use of the nitrous oxide producing more drowsiness. With the intermittent inhalation method, the laboring patient using nitrous oxide is advised to initiate inhalation of nitrous oxide about 30 seconds before the onset of a contraction and discontinue inhalation at the peak of the contraction.

There is no time limit to the use of nitrous oxide. It can be used for hours during labor or only briefly for a particularly painful part of labor, such as during rapid cervical dilation or during the later portions of the second stage.

Patients report that nitrous oxide does not completely relieve pain but creates a diminished perception of the pain.9 As many as one-third of women are nonresponders and report no significant pain improvement with nitrous oxide use.10

The main side effects of inhalation of the gas are nausea, vomiting, dizziness, and drowsiness. Nausea has been reported in 5% to 40% of women, and vomiting has been reported in up to 15% of women using nitrous oxide.11

Cautions

Contraindications to nitrous oxide include a baseline arterial oxygenation saturation less than 95% on room air, acute asthma, emphysema, or pneumothorax, or any other air-filled compartment within the body, such as bowel obstruction or pneumocephalus. (Nitrous oxide can displace nitrogen from closed body spaces, which may lead to an increase in the volume of the closed space.12)

Nitrous oxide inactivates vitamin B₁₂ by oxidation; therefore, vitamin B₁₂ deficiency or related disorders may be considered a relative contraindication. However, compared with more extensive continuous use, such as during prolonged general anesthesia, intermittent use for a limited time during labor is associated with minimal to no hematologic effects.

If a laboring woman is using NO₂, parenteral opioids should be administered only with great caution by an experienced clinician.

What do the data indicate?
The Agency for Healthcare Research and Quality (AHRQ) recently invited the Vanderbilt Evidence-based Practice Center to review the world literature on nitrous oxide for labor pain and to provide a summary of the research. Fifty-eight publications were identified, with 46 rated as poor quality.11,13 Given this overall poor quality of available research, many of the recommendations concerning the use of nitrous oxide for labor pain are based on clinical experience and expert opinion.
Considering a nitrous oxide program for your birthing unit? Helpful hints to get started.

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1. Do your research to determine which type of equipment is right for the size and volume of your organization.
   You need to consider ease of access and use for staff to bring this option to the bedside in a prompt and safe manner. Initial research includes visiting or speaking with practitioners on units currently using nitrous oxide. Use of nitrous oxide is growing, and networking is helpful in terms of planning your program. Making sure you have the correct gas line connectors for oxygen as well as for suction when using a scavenger system is a preliminary necessity.

2. Determine storage ability.
   Your environmental safety officer is a good resource to determine location and regulations regarding safe storage as well as tank capacity. He or she also can help you determine where else in your organization nitrous oxide is used so you may be able to develop your unit-specific protocol from hospital-wide policy that is already in place.

3. Collaborate on a protocol.
   After determining which type of equipment is best for you, propose the idea to committees that can contribute to the development of pain and sedation management protocols. The anesthesia department, pain committee, and postoperative pain management teams are knowledgeable resources and can help you write a safe protocol. Keep as the main focus the safe application and use of nitrous oxide for various patient populations. Potential medication interactions and contraindications for use should be discussed and included in a protocol.

   One more department you want to include in your planning is infection control. For our unit, reviewing various types of equipment to determine the best infection control revealed some interesting design benefits to reduce infection risk. Because the nitrous oxide equipment would be mobile, the types of filter options, disposal options, and cleaning ability are important components for final equipment choice.

4. Include all parties in training and final roll out.
   Once you develop your policy with input from all stakeholders, make sure you share it early and often before you go live. Include midwives, physicians, nurses, technicians, and administrative staff in training, which will help to dispel myths and increase awareness of availability within your unit. Provide background information to all trainees to ensure safe use and appropriate patient selection.

   The most important determinant of success is the formation of an interprofessional team that works well together to develop a safe clinician- and patient-friendly program for the use of nitrous oxide.

The experts concluded that, for the relief of labor pain, neuraxial anesthesia was more effective than nitrous oxide inhalation. In one randomized trial included in their systematic review, nulliparous laboring women were randomly assigned to neuraxial anesthesia or nitrous oxide plus meperidine. About 94% of nulliparous laboring women reported satisfaction with neuraxial anesthesia, compared with 54% treated with nitrous oxide and meperidine.

Nitrous oxide is believed to be generally safe for mother and fetus. Its use does not impact the newborn Apgar score or alter uterine contractility.

Nitrous oxide, a bridge to an epidural or a natural childbirth

Many women start labor unsure about whether they want to use an epidural. For these women, nitrous oxide may be an option for reducing labor pain, thereby giving the woman more time to make a decision about whether to have an epidural anesthetic. In our practice, a significant percentage of women who use nitrous oxide early in labor subsequently request a neuraxial anesthetic. However, many women planning natural childbirth use nitrous oxide to reduce labor pain and successfully achieve their goal.

Postpartum pain reliever

Some women deliver without the use of any pain medicine. Sometimes birth is complicated by perineal lacerations requiring significant surgical repair. If a woman does not have adequate analgesia after injection of a local anesthetic, nitrous oxide may help reduce her pain during the perineal repair and facilitate quick completion of the procedure by allowing her to remain still. NO2 also has been used to facilitate analgesia during manual removal of the placenta.

We predict an expanding role

There are many pharmacologic and nonpharmacologic options for managing labor pain, including a supportive birth environment, touch and massage, maternal positioning, relaxation and breathing techniques, continuous labor support,
hydrotherapy, opioids, and neuraxial anesthesia. Midwives, labor nurses, and physicians have championed increasing the availability of nitrous oxide to laboring women in US birthing centers.\textsuperscript{17–20} With the FDA approval of inexpensive portable nitrous oxide units, it is likely that we will witness a resurgence of its use and gain important clinical experience in the role of nitrous oxide for managing labor pain.

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