Nitrous Oxide for Labor Analgesia: Expanding Analgesic Options for Women in the United States

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Nitrous oxide (N₂O) is a commonly used labor analgesic in many Western countries, but is used infrequently in the United States. The University of California at San Francisco has been offering N₂O for labor analgesia for more than 30 years. Vanderbilt University Medical Center recently began offering N₂O as an option for pain relief in laboring women. Many women report that N₂O provides effective pain relief during labor and argue that it should be made more widely available in the United States. This article discusses the use of N₂O for pain management during labor, including its history, properties, clinical indications, and use and environmental safety issues. Practical issues regarding implementation of N₂O service in a medical center setting are also discussed.

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KEY WORDS
Nitrous oxide • Labor analgesia

Women in the United States have fewer options for pain relief in labor than women in many other parts of the developed world.1 Although epidural analgesia is the most common and complete method of pain relief available, a majority of women surveyed in the 2006 Listening to Women Survey expressed interest in less invasive methods (Table 1).2 Recent reports support wider access to safe, less invasive options for comfort and labor pain as part of a program to achieve improved

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Clinical Use
N₂O can be used for analgesia during the first, second, and third stages of labor, as well as during postdelivery procedures such as laceration repair, manual removal of the placenta, and uterine curettage. It may also facilitate the initiation of epidural analgesia. N₂O is self-administered and has a rapid onset of 30 to 50 seconds, which correlates with volume and rate of inhalation. N₂O administration is intermittent and delivered via face mask. The patient’s inhalation triggers the opening of a negative pressure demand valve and is timed by the patient to coincide with uterine contractions. A need for further research on N₂O for labor has been proposed.

Background
N₂O is a nonflammable, tasteless, odorless gas. It was first synthesized by the English scientist and theologian Joseph Priestly in 1772, and was first used as a labor analgesic by Stanislav Klikovich in Poland in 1881. Klikovich published the results of his study wherein he utilized 80% N₂O with 20% oxygen in 25 laboring women, and demonstrated pain relief with no adverse fetal outcomes. Self-administration of N₂O for laboring women became widely available with the development of the Minnitt apparatus in 1933. In 1961, the British Oxygen Company introduced a single-tank delivery system marketed under the trade name Entonox® (The Linde Group, Munich, Germany) that continues to be used today in the United Kingdom. Entonox has never been approved by the US Food and Drug Administration (FDA) for use in the United States; the only delivery apparatus used for this purpose in the United States is Nitronox® (Porter Instrument Division, Parker Hannifin, Hatfield, PA). This delivery system combines 50% N₂O and 50% oxygen in a set concentration that cannot be altered, which differs from the apparatus used primarily in dental offices. The equipment used in dental practices allows for variable concentrations of N₂O delivery, and is not intended to be used for patient-controlled N₂O delivery. Although other approaches (such as continuous administration of concentrations < 50% N₂O in oxygen and intermittent administration of higher concentrations) have been employed and may offer modest improvements in pain relief, the intermittent use of 50% N₂O in oxygen probably optimizes patient safety and has thus been most widely adopted.
contractions. Anecdotal reports have noted patient report of greatest relief when the woman begins inhalation approximately 30 seconds prior to the start of her contraction. This pattern of inhalation allows for peak serum levels of N2O to coincide with the peak of the uterine contraction. Offset is rapid, with elimination of the N2O by exhalation occurring within a few minutes of discontinuation. It is important that the N2O be administered by the patient herself using a hand-held face mask; no straps or other devices should be used to secure the mask to the patient's face that could lead to excessive drowsiness. Learning the correct technique by practicing with the first few contractions is important in order to maximize results. Patient satisfaction and success with therapy can be enhanced by thorough teaching with a focus on the timing of breathing. Pain relief is generally less effective than with neuraxial analgesia utilizing local anesthetics. One earlier review examining N2O efficacy as a labor analgesic reported little change in maternal verbal and visual analog scale scores of pain during use in labor, but noted that many women still expressed satisfaction with the relief that it provided. When compared with patient-controlled administration of short-acting narcotics such as fentanyl and remifentanil, pain relief is reportedly similar.

The mechanism of action of N2O is complex and not clearly established. Endogenous opioid release occurs with associated analgesia, and N-methyl-D-aspartate receptor inhibition reduces hyperalgesia. Anxiolysis mediated by central gamma-aminobutyric acid receptors may enhance the euphoric properties. Of note, intermittent use of 50% oxygen and 50% N2O does not significantly alter the maternal hypocapnia that accompanies labor. The most commonly reported side effects are nausea and vertigo, although N2O use does not significantly increase the rates of maternal nausea or vomiting during labor. Fatigue may occur when used for prolonged periods. Also, although it is self administered, some women still find the sensation of breathing into a mask during contractions to be unpleasant. Newborn adverse side effects have not been described. Ingestion of modest amounts of clear fluids during uncomplicated labor appears safe. Although research specifically examining oral intake and safety of N2O use has not been undertaken, N2O analgesia should not be an impetus for altering an institution’s existing guidelines for oral intake during labor. Laboring women who have experienced nausea prior to initiating N2O therapy may benefit from prophylactic antiemetics prior to initiation of N2O therapy.

Safety Considerations
The use of N2O as a labor analgesic in the United Kingdom has produced a long track record of safe outcomes for both mother and child. Recent animal studies have suggested that some anesthetic agents may induce apoptotic changes within developing rodent and primate fetal brains if exposed either in utero or shortly after birth. Although short duration and modest concentrations of such analgesics would be expected to have negligible effects, high concentrations for prolonged periods may be deleterious. N2O is one of numerous agents that have been associated with these apoptotic changes in animal studies. Although an FDA advisory issued in 2007 recommended no change in anesthetic practice for children or fetuses, the precise effects on brain development in human fetuses exposed to N2O or other anesthetic agents in utero remain largely unknown.

Environmental pollution occurs frequently during inhaled anesthetic administration, and health care workers exposed to...
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Inhalational agents where scavenger systems are not simultaneously used are often exposed to levels of N₂O in excess of occupational exposure limits. For this reason, FDA requirements necessitate the use of a blender device with a scavenger, which provides superior environmental hygiene when compared with European delivery systems. One effective way to monitor staff exposure is through the use of commercially available dosimetry badges. This method of surveillance has been used by UCSF and VUMC as part of their safety monitoring system for N₂O. Badge dosimetry data from UCSF indicate ambient levels well below the current National Institute for Occupational Safety and Health threshold limit of 25 ppm for 8-hour time-weighted average values (J.T. Bishop, personal communication, 2010). Although the long-term effects on the health of workers exposed to N₂O are unclear, there does not appear to be an increased risk of adverse reproductive outcomes as a result of occupational exposure. Periodic environmental air sampling should be performed in accordance with current Occupational Safety and Health Administration standards.

Monitoring Considerations

The recommendation rationale for monitoring standards regarding the use of N₂O for labor rests upon the designation of the therapy as analgesia/minimal sedation. This definition is assigned by the American Society of Anesthesiologists (ASA) to N₂O, when used at concentrations of < 50% and as a sole agent, is defined by ASA criteria as analgesia minimal sedation. The patient is responsive and airway, ventilation, and cardiovascular function remain unaffected. Assuming these specific conditions, the use of pulse oximetry is not required. With intermittent use, room air entrainment will result in varying N₂O concentrations of < 50%. If N₂O is used by the patient continuously or is used intermittently in conjunction with intravenous or intramuscular narcotics, pulse oximetry should be employed.

Initiating an N₂O Service

Increased access to N₂O services in hospitals and birth centers has long been advocated by the midwifery profession. A position statement on Nitrous Oxide for Labor Analgesia issued by the American College of Nurse-Midwives in 2009 advocates for the availability of N₂O to all laboring women, and recommends that all certified nurse-midwives and certified midwives be trained to administer and oversee safe use of N₂O analgesia during labor. The American Congress of Obstetricians and Gynecologists does not currently have a position statement regarding N₂O use for labor analgesia.

UCSF has had an N₂O service for over 30 years, in which therapy is now administered by midwives, having been under the direction of the Department of Anesthesiology at its inception. Development of the N₂O program at VUMC was a joint effort between the Nurse-Midwifery Service of the School of Nursing and the Obstetric Anesthesia Division of the Department of Anesthesiology with support from the Department of Obstetrics and Gynecology. N₂O therapy is provided at VUMC by anesthesia providers under the Division of Obstetric Anesthesia. It is our belief that recent successful implementation was due to the committed support of key figures from both departments working together toward a common goal of making N₂O available to laboring women.

At VUMC, a working interest group was established with representatives from neonatology, obstetrics, maternal-fetal medicine, newborn nursery, nursing management, midwifery, obstetric anesthesia, risk management, and labor and delivery staff. Exchange of ideas was conducted in a group format. Each representative member of the group had unique concerns and the process of addressing these individual concerns within the working group was critical to the eventual success of the program.

Once all members’ concerns were addressed and available evidence reviewed, the initiative was able to move forward with the development of guidelines and policies (Table 2). Initial policy development was done by core team members using published guidelines from UCSF as a model template. The proposed policy was evaluated and approved by numerous bodies, including the Sedation and Analgesia Committee, in accordance with Centers for Medicare and Medicaid Services mandate. Educational materials and competency standards for staff were also developed and implemented prior to initiation of the service.

Visible sponsorship of the proposed change was also crucial to the successful implementation of change. In the VUMC experience, this equated to recruiting advocates for implementation from

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Nitrous Oxide for Labor Analgesia continued

TABLE 2

Key Points to Establishing a Nitrous Analgesia Service

- Establish lead partnership between obstetrical (OB/GYN, CNM) and anesthesia personnel
- Review available research and papers regarding use of nitrous oxide for labor analgesia
- Obtain sponsorship/buy-in from principal organization members
- Form working group of representatives from all involved (anesthesia, obstetrics, newborn nursery, neonatal intensive care, staff nursing, nursing management, maternal fetal medicine, risk management, building engineering)
- Address group concerns
- Construct unit policy/procedure
- Design method of staff education and proof of competency
- Obtain equipment

Most commercially available N₂O analgesia systems, such as those used in the dental industry, employ continuous-flow low-volume systems and are unsuitable for intermittent use with laboring women.

References

individuals whose influence was highly valued within the organization. Feedback at every step of the process and from all involved participants was the last important key to success. As guidelines and policies were drafted, the input of key members of the patient care delivery team was necessary to continually make meaningful revisions. This feedback from key members at every step along the way in guideline and policy formation and implementation was a major contributing factor to the smooth transition from policy to practice.

Equipment

One major barrier to implementation of N₂O services in the United States has been the limited availability of N₂O delivery equipment. The device must be equipped with a demand valve capable of intermittent high-volume delivery capacity. Most commercially available N₂O analgesia systems, such as those used in the dental industry, employ continuous-flow low-volume systems and are unsuitable for intermittent use with laboring women. As previously mentioned, single-cylinder Entonox systems used in Europe have not been approved for use by the FDA and are not available for purchase in the United States. Currently, Nitronox is the only FDA-approved apparatus for the self-administration of N₂O. Matrix Medical (Orchard Park, NY), the initial manufacturer of Nitronox equipment, discontinued production several years ago, which made the purchase of new units impossible. Recently, however, the Porter Instrument Division of Parker Hannifin Corporation has secured the rights to manufacture the Nitronox apparatus, and have indicated that they intend to have a device on the market by the end of 2012 (M. Civitello, personal communication, June 2012). Reintroduction of Nitronox equipment will remove a major barrier to N₂O availability.

Conclusions

Inhaled N₂O has a long history of use in pregnancy, and provides a safe option for pain relief in labor. Currently, access to this therapy is limited in the United States, and a need for increased access has been proposed. We believe that a systematic approach, similar to that undertaken at VUMC, can lead to the introduction of N₂O delivery services for labor at many more institutions throughout the United States. The improved availability of N₂O for labor analgesia would increase options for pain management for laboring women.
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MAIN POINTS

• Nitrous oxide (N₂O) is a nonflammable, tasteless, odorless gas; it is commonly used as a labor analgesic in many Western countries, but is used infrequently in the United States.

• Anecdotal reports have noted patient report of greatest relief when the woman begins inhalation approximately 30 seconds prior to the start of her contraction. This pattern of inhalation allows for peak serum levels of N₂O to coincide with the peak of the uterine contraction.

• The use of N₂O as a labor analgesic in the United Kingdom has produced a long track record of safe outcomes for both mother and child. Although short duration and modest concentrations of such analgesics would be expected to have negligible effects, concentrations > 50% nitrous and 50% oxygen for prolonged periods may be deleterious.

• The improved availability of N₂O for labor analgesia would increase options for pain management for laboring women.


