American Society of Anesthesiologists®

Nitrous Oxide

ASA Committee on Obstetric Anesthesia Working Group

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Introduction

Inhaled nitrous oxide (N_2O) was first used for labor analgesia in the 1880s in the United Kingdom. Its routine use became more widely available after an apparatus for self-administration was developed in 1934, which was certified as safe by the Royal College of Obstetricians and Gynecologists in 1936.(1-3) Overall, countries with high maternal safety standards including the United Kingdom, Scandinavia, Canada and Australia have allowed the use of an inhaled mixture of N_2O in oxygen for decades and have utilization rates greater than 50% for laboring women.(4,5) In these countries, the use of N_2O for labor analgesia is supervised by physicians, nurses or midwives, with no widespread safety concerns for mother or child documented.(6) In the United States, N_2O was originally administered in the 1930s using concentrations as high as 80%. It was also frequently

combined with other sedating medications including opioids, barbiturates, benzodiazepines and scopolamine in order to produce a "twilight sleep."(7) The combination of N_2O with these sedating medications resulted in significant peripartum risks and complications. With the rise in neuraxial labor analgesia during the 1940s-1950s, use of N_2O continually decreased in the United States until a recent resurgence in popularity following a 2010 published statement encouraging increased availability of N_2O for labor analgesia by the American College of Nurse-Midwives(8) and approval of a delivery system by the Food and Drug Administration (FDA) in 2012.(9)

Analgesic Efficacy and Maternal Satisfaction

N_2O has properties that are desirable for labor analgesia. Its low blood solubility and minimal metabolism (<1%) allow for a rapid effect and low tissue absorption. Despite decades of use, the evidence that N_2O provides effective labor analgesia is still limited. A 2014 systemic review found a total of 58 publications that evaluated N_2O in labor, however only two studies were of good quality, 11 fair quality and 46 poor quality.(4) Prior studies on the efficacy of N_2O labor analgesia are confounded by variable concentrations (30-70%) of N_2O studied, small sample sizes, heterogeneous study methodologies, numerous comparator modalities and different effectiveness assessments.(2,4,10) Systematic reviews have concluded that the strength of evidence of the effectiveness of N_2O for labor analgesia is insufficient(2,4,10), and results should be interpreted with caution because of the numbers and the size of studies, risk of bias and poor methodological quality of studies to date.(11)

Studies comparing N_2O to non-active control (air/oxygen) or no intervention reported limited analgesic benefit with the administration of N_2O during labor. A 2012 Cochrane review examining the role of inhaled analgesia for labor analgesia reported that N_2O offered a small analgesic effect compared to placebo or no treatment (average risk reduction [RR] 0.06, 95% CI 0.01 to 0.34, two studies, 310 women; mean difference [MD] -3.50, 95% CI -3.75 to -3.25, one study, 509 women).(12) Westling et al. reported a moderate decrease in visual analog pain scores (from 8 out of 10 to 6 out of 10) with varying concentration of inspired N_2O 40-70%.(13) Carstoniu et al. comparing 50% N_2O to compressed air found no statistically significant differences in the mean visual analogue pain scores; however, many of the women in that study wished to continue its use after the study period.(14) Talebi et. al.'s study of 523 parturients receiving either N_2O(50% N_2O/50% O_2) or 50% oxygen found moderately lower visual analogue pain scores in the N_2O group.(15)

Pain relief is, however, only one component of women's labor experience, and although effective pain relief does influence satisfaction with labor analgesia, a sense of control and the ability to cope with pain may be more important determinants.(16) Nitrous oxide also produces feelings of euphoria and dissociation. Therefore, N_2O administration in labor may provide benefits beyond

pain relief and may improve women's perceptions of their labor experience. For example, in a recent study evaluating N_2O for labor analgesia women reported poor analgesic efficacy but still provided high satisfaction ratings with their analgesic care.(17) Several studies have similarly reported improved maternal satisfaction with the use of N_2O during labor; however, the quality and heterogeneity amongst the studies evaluating women's satisfaction with their birth experience make evaluation of this outcome difficult to assess.(4) Further studies indicate that despite reported lack of analgesic efficacy, most would choose N_2O as a form of pain relief for subsequent labors.(2,4,18) The primary beneficial effects of N_2O in labor may be due its anxiolytic effect and impact on the woman's sense of control with self-administration.(11)

Comparison of Efficacy with Other Methods of Labor Analgesia

Many studies have compared N_2O to both pharmacological and non-pharmacological labor analgesic options. However, the majority of studies are of poor quality, have small sample sizes and use heterogeneous study methodologies.(2,4,10) Therefore, the strength of evidence for comparison of efficacy of N_2O with other methods of labor analgesia is weak, and results should be interpreted with caution.(4,11)

A 2012 Cochrane review found that flurane derivatives (sevoflurane, desflurane, isoflurane, halothane, enflurane and methoxyflurane) offered moderately better pain relief than N_2O in first stage of labor.(12) Using a Visual Analogue Scale from 0 to 100, a lower pain intensity score (average MD 14.39, 95% CI 4.41 to 24.37, three studies, 70 women), and a higher pain relief score were seen with flurane derivatives compared with N_2O (average MD -16.32, 95% CI -26.85 to -5.79, two studies, 70 women). Additionally, more nausea was found with N_2O compared with the flurane derivatives group (RR 6.60 95% CI 1.85 to 23.52, two studies, 98 women). However, substantial heterogeneity and poor methodical study designs should caution these conclusions. Additionally, barriers to routine use of flurane derivatives for labor analgesia include the need for specialized vaporizers and unwanted side effects.(12)

Studies comparing N_2O with systemic opioids for labor analgesia are few and of poor quality.(4) Studies that compared N_2O with meperidine and diamorphine found similar and minimal reductions in pain scores with either technique.(4) Remifentanil (0.4 µg/kg patient-controlled intravenous analgesia) was found to provide more effective analgesia compared to N_2O (mean visual analog pain score reduction of 1.5 points on a 0–10 scale with remifentanil compared to mean pain score reduction of 0.5 points with N_2O).(19) However, remifentanil resulted in more sedation and opioid-related side effects.

Several studies have compared N_2O to epidurals for labor analgesia.(4,10,11) The majority of studies show that epidural analgesia provides significantly more effective pain relief than N_2O. A

2019 European Society of Anaesthesiology Task Force on Nitrous Oxide recommends that N_2O is a good option for analgesia during labor provided that adequate boundary conditions are provided and the parturient is not willing or able to receive more effective invasive interventions such as epidural analgesia.(11) A contemporary evaluation in a tertiary center in the United States following the introduction of N_2O for labor analgesia found that the conversion rate to neuraxial blockade was 63% in women selecting N_2O compared to an institutional epidural rate of 85%.(20) Factors associated with conversion from N_2O to neuraxial blockade were labor induction (adjusted RR=2.0, 95% CI 1.2–3.3) and labor augmentation (adjusted RR = 1.7, 95% CI 1.0–2.9). Additionally, a retrospective study examining the impact of implementing the availability of N_2O for labor analgesia found no difference in the use of neuraxial analgesia after N_2O implementation compared to the period before N_2O was available.(9) Future studies are required to better predict which women will or will not need to convert from N_2O to epidural analgesia.

N_2O Use on Labor and Delivery beyond Labor Analgesia

The use of N_2O during other procedures performed on labor and delivery units includes external cephalic version (ECV), manual removal of the placenta, postpartum perineal wound repair, intravenous starts, placement of urinary catheters, intracervical Foley bulb insertions and neuraxial anesthesia placement.(21) A few small studies have been published regarding efficacy in its use for ECV and postpartum perineal wound repair. One prospective comparative cohort study randomized 300 women to either inhaled N_2O or no analgesia for ECV. The authors found that while the success rate of ECV was similar, the median level of reported pain was significantly lower in the N_2O group ($p < 0.01$) with a 49% decrease in severe pain.(22) They also reported no complications with N_2O use.

In postpartum perineal wound repair, patient self-administered N_2O appears at least as effective in reducing pain as local anesthesia infiltration in women without epidural labor analgesia. One study randomized 120 women to receive either 5 mL of 2% lidocaine infiltrated into the perineal wound versus inhaled N_2O beginning two minutes before starting episiotomy repair and continuing until the end of the procedure.(23) Nine (15%) participants in the N_2O group and 23 (38%) in the lidocaine group had moderate, severe or extremely severe pain ($P = 0.005$). There was no significant difference in satisfaction level between the two groups ($P = 0.713$). Another study randomized 100 women to receive 1% prilocaine infiltration versus N_2O during postpartum perineal suturing after birth injury or episiotomy and found that there were no significant differences in pain or satisfaction between the groups.(24) Additionally, pain and satisfaction with wound repair might have been further improved if both local infiltration and N_2O were administered. None of these studies reported adverse patient events.

Adverse Maternal and Fetal/Neonatal Effects

N_2O has a long safety record of use in labor when used at a 50% N_2O/50% O_2 concentration and not used in combination with other sedating agents.(16) Nausea is one of the most common side effects women describe with the use of N_2O for labor analgesia, with an incidence of reported nausea between 0 and 45% and of vomiting between 0 and 16%.(4) In comparison to the use of halogenated inhalation agents, N_2O has a lower incidence of nausea, yet when compared to placebo there is a significant increase in the incidence of nausea.(12) The incidence of nausea is believed to be greater when other agents such as systemic opioids are co-administered with N_2O. Dizziness, drowsiness and dysphoria are also commonly reported side effects with rates typically < 5%.(2,4,10) N_2O administration does not affect uterine activity and thus would not be expected to affect the course of the first and second stages of labor and mode of delivery.(3) Studies have failed to show significant adverse fetal or neonatal effects measured by fetal heart rate, Apgar score, or umbilical artery and vein blood gases.(2,4,10)

Concern has been raised that N_2O could theoretically increase the rate of maternal oxygen desaturation by direct respiratory depression or diffusion hypoxia (when the laboring patient stops inhaling 50% N_2O/50% O_2).(2) Small, well-conducted studies have failed to show a significant decrease in oxygen saturation between contractions(14) and noted no significant hypoxemia during N_2O labor analgesia.(25,26) A small study comparing inhaled N_2O (50% N_2O/50% O_2) to epidural labor analgesia reported that while the number of women who experienced at least one episode of hypoxia (saturation <90%) was equal, the number of maternal desaturation episodes was higher and of greater duration in the N_2O group compared to the epidural analgesia group.(27) Of note, neither group demonstrated saturations less than 84%, and typical desaturation episodes were < 30 seconds in duration. It is important to note that the addition of systemic opioids to N_2O analgesia appears to increase the likelihood of maternal hypoxemic episodes.(26,28,29) As a result, the co-administration of systemic opioids and inhaled N_2O labor analgesia is not recommended.

Practice Management

Practice management remains an important aspect of daily patient care. This section will address aspects of implementation and staffing requirements with the use of N_2O for labor analgesia in an effort provide guidance and address potential misconceptions.

Implementation

Procedures for the administration of inhaled N_2O for labor analgesia must comply with sedation policies developed within each institution's Department of Anesthesiology. These policies should be in accordance with Centers for Medicare and Medicaid Services (CMS) guidelines for anesthesia

care. The administration of N_2O should be performed in health care facilities with written protocols for its use and where pulse oximetry and gas scavenging systems are available.

The safe and proper use of N_2O for labor analgesia requires multi-disciplinary involvement (anesthesiology, obstetrics, neonatology, nursing, risk management, facilities management, etc.).(30,31) Success increases when all stakeholders are involved in the discussion and development of local policy and protocol. However, CMS designates the Chief of Anesthesiology as ultimately responsible for all anesthesia/sedation policies, and thus requires their final approval. Local policy or protocol development may allow for labor nurse or midwife initiated N_2O for labor analgesia with obstetric provider orders (50% N_2O without co-administration of other analgesic/sedative agents typically produces an effect, defined as normal response to verbal stimulation, that qualifies as minimal sedation).(32)

N_2O delivery systems include both wall-mounted internally piped labor room systems and portable devices that use blended gas from individual oxygen and N_2O cylinders. The proper equipment for delivering N_2O for labor analgesia should include a negative pressure opening demand valve, a 50% N_2O /50% O_2 fixed ratio, face mask and scavenging system. The N_2O should be delivered via patient-controlled facemask. The mask should not be held in place by straps or other individuals. This provides optimal safety, as the demand valve only opens to provide N_2O when the laboring patient seals the mask to her face and exerts a negative inspiratory pressure. A patient education component should be included. Efficacy and maternal satisfaction are increased if the patient is educated to begin inhaling N_2O approximately 30 seconds prior to the anticipated contraction.(3,13) Additionally, a scavenging system should be connected to mask and is most effective when the patient is instructed to exhale directly into the mask. Only the women (not partners or health care providers) are allowed to hold the mask to provide additional safety. The rooms where N_2O will be utilized must have proper ventilation, waste gas scavenging, hazard communication and training for staff, secure equipment storage areas and a plan for servicing equipment and checking the efficacy of N_2O scavenging.(3,13,16,31) Documentation regarding patients qualifying for N_2O self-administration for labor analgesia per local policy should be entered in their medical records. Contraindications include known significant vitamin B12 deficiency, pernicious anemia, impaired consciousness, inability to hold face mask and concern for expansion of gas in an enclosed space (e.g., tension pneumothorax).

Informed consent should be obtained from the patient and they should be educated regarding its proper use. The risks and benefits of N_2O should be discussed relative to each patient's medical history and relative contraindications. Informed consent should include a discussion of possible risks for expectant mothers and their newborn. It is important to let patients know data is lacking

regarding potential effects from fetal exposure despite decades of worldwide experience of N_2O use during labor.(33) Maternal consent for N_2O might include the following statement

> … I understand that nitrous oxide has been used throughout the world for labor pain control for many decades and is considered safe. However, some animal studies have shown effects on newborns, and it is not known if in the future there may be some negative affect on human babies proven. I understand there could be theoretical risks to N_2O as well as most other pain relieving medications use during pregnancy.(33).

Staffing

Use of 50% N_2O for labor analgesia as the sole agent with no other sedative or analgesic medications should produce an effect that is designated as "minimal sedation," and administration does not require patient oversight by an anesthesiologist.(34) Labor and delivery staff need training and education on N_2O use, knowledge of their local policies, proper administration, importance of scavenging, patient monitoring, and potential for exposure of health care workers.(35) Some hospitals require 1:1 nursing/midwife care:patient staffing for N_2O usage, while others allow the labor nurse to leave after the first 15 minutes of 1:1 supervision. N_2O dosimetry badges may or may not be required for staff and local policy determines how environmental exposure will be monitored (compliance with National Institute for Occupational Safety and Health limits, see below).

Potential Concerns of N_2O

Fetal Neurotoxicity, Neuroapoptosis, and Methionine Synthase Activity

The mechanism of N_2O is not fully understood.(2,31) N_2O acts as an N-methyl-D-aspartate (NMDA) antagonist and theoretically could inhibit synaptogenesis and cause neuroapoptosis and neurotoxicity.(36) Anesthetic drugs that block N-methyl-D-aspartate (NMDA) receptors and drugs that potentiate GABA receptors can trigger widespread neuroapoptosis.(37-40) The exposure period on the developing brain for neuronal synaptogenesis occurs from the third trimester until 3 years of age.

The FDA Drug Safety Communication alerts(37) warn against repeated or lengthy use of general anesthetic and sedation drugs including NMDA antagonists on the brain during surgeries or procedures in children less than 3 years or in pregnant women in their third trimester. This warning is based on concern that anesthetic or sedation drugs could result in long-term effects on children's learning and behavior. The FDA warning resulted in a labeling change for 11 common general anesthetics and sedative agents that bind to GABA or NMDA receptors, including all halogenated anesthetic gases. Following the review of all anesthetic agents, the FDA did not include N_2O in its warning, primarily as a result of the current lack of compelling clinical evidence suggesting any significant detrimental effects to either the mother or fetus. Recent human infant observational

studies and interventional trials suggest that short-duration, single-agent fetal anesthetic exposure is likely safe.(41) Additionally, there is no evidence of cognitive differences between large populations with low (United States) and very high (Australia, Canada, Scandinavia and United Kingdom) rates of fetal N_2O exposure during labor.(35)

N_2O rapidly crosses the placenta. A 1 to 3-hour N_2O exposure inactivates methionine synthase in both the mother and fetus.(42,43) Human placental methionine synthase activity decreases in laboring women inhaling N_2O after minutes to hours, with a faster decrease in women with lower vitamin B12 levels.(44) Over 20% of pregnant women may be deficient in vitamin B12 at term, which could further exacerbate the adverse effects of N_2O exposure.(43) Given the high rate of N_2O use in many countries for decades, it is uncertain if this potential 20% maternal vitamin B12 deficiency is of clinical significance. The neonatal effects of decreases in methionine synthase activity as well as the neonatal effects of in-utero exposure to N_2O are unknown. Additionally, with the limited and intermittent use of 50% N_2O used for the provision of labor analgesia, the total human and fetal exposure would be expected to be considerably less than if inhaling N_2O continually over the same period.

N_2O Occupational Exposure Safety Limits

Chronic long-term occupational exposure to N_2O may cause spontaneous abortions and reduced fertility.(11,45) Recent studies find that scavenging systems and negative pressure demand valves effectively decrease occupational exposure to levels below the occupational exposure limits.(11,46) In order to provide occupational safety and health protection from unacceptable levels of N_2O, the National Institute of Occupational Safety and Health (NIOSH) in 1977 and again in 1994 reiterated these limits, recommending a maximal time-weighted average level of N_2O exposure to 25 ppm per procedure over an 8-hour period.(47,48) European countries have similar or higher N_2O exposure limits, ranging from 25 ppm (France), 50 ppm (Italy, Belgium) to 100 ppm (Germany, Sweden, United Kingdom).(6)

Potential for Abuse and Diversion

Other public health risks include potential diversion or abuse, including health care professionals who have access and are familiar with its clinical use.(49) Although N_2O is a weak anesthetic, it has some abuse potential. N_2O is also available from other sources including as a propellant for pressurized cans (e.g., whipped cream). Acute inspiration of 100% N_2O can lead to addiction, cerebral hypoxemia, asphyxiation and death.(11) Repeated chronic abuse over several months to years can lead to irreversible peripheral myeloneuropathy with the potential for permanent neurologic disability.(48,49) In a 2016 literature review(50), nitrous oxide abuse strongly correlated with low vitamin B12 and included 72 cases of neurologic sequelae including myeloneuropathy or

subacute combined degeneration and 29 cases of death due to nitrous abuse. Because of the potential for abuse, the delivery system should be regulated in a controlled environment and stored appropriately.(48)

Environmental Concerns

Larger public health aspects of N_2O use during labor should also be considered, such as N_2O emission and its effect on global warming. Almost all climate scientists agree the main cause of the current global warming trend is human expansion of the greenhouse effect.(51,52) There are multiple gases that contribute to the greenhouse effect including carbon dioxide, methane, chlorofluorocarbons and N_2O. Nitrous oxide is one of the six main greenhouse gases regulated by the Kyoto Protocol.(53) The largest human source of N_2O emissions into the atmosphere comes from agriculture (67%), followed by fossil fuel combustion and industrial processes (10%), biomass burning (10%), atmospheric deposition (9%), and human sewage (3%).(51) The total greenhouse gas effect of N_2O atmospheric emissions is estimated to contribute less than 0.1%.(51) Although limited data is available on N_2O's emissions from anesthetic practices, efforts to reduce even this small contribution are being encouraged.(54,55) Currently we are unaware of commercially available methods to reduce N_2O emissions from the health care sector.

Conclusion

Inhaled N_2O for labor analgesia is offered in many countries and is a valuable analgesic alternative option for women who may not desire neuraxial analgesia. Women should be informed of the risks and benefits of this option and be confident that it is administered in a safe manner. Although N_2O has a significant safety record over many decades across the globe, continued research is needed to better understand its efficacy in labor and potential adverse effects.

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