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OBSTETRIC ANESTHESIA (LR LEFFERT, SECTION EDITOR)

Inhaled Nitrous Oxide Analgesia for Labor

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Abstract

Purpose of Review This paper reviews the history, efficacy, safety, and administrative concerns for nitrous oxide analgesia during labor.

Recent Findings While pain relief is inferior to that provided by neuraxial analgesia, maternal satisfaction is equivalent to that of neuraxial techniques, and better if analgesia is reported to be poor. A recent systematic review reports good safety for mother and child, that some women report excellent pain relief and others not, and that minor side effects are infrequent. Qualitative research summarizing patient comments on their experience suggests that numerous factors other than pain relief affect maternal satisfaction with their analgesia for labor. Only one study has examined patient factors that predict conversion from nitrous oxide to neuraxial analgesia for labor.

Summary Inhaled nitrous oxide offers a safe and effective means for labor analgesia for many women. Maternal satisfaction is not as dependent on effective pain relief as with neuraxial analgesia.

Keywords Labor analgesia · Inhalation analgesia · Nitrous oxide analgesia · Maternal satisfaction · Anesthetic toxicity

Introduction

The use of inhaled nitrous oxide for labor analgesia (N_2O) has become more widespread in the USA over the past decade. In 2011, only three US medical centers were known to offer it, but by late 2017, approximately 400 hospital delivery units and free-standing birthing centers reported its use [1]. The reasons for this dramatic increase are unclear, but the US midwives have long advocated its use as an alternative to neuraxial analgesia [2, 3]. Despite the widespread availability of epidural analgesia for labor in Western Europe, Australia, and New Zealand for decades, up to 66% of women in those countries choose to use N_2O for pain relief [3], despite offering inferior pain relief [4••]. Inhaled nitrous oxide has a long history of safety and benefit to laboring women in those countries [5]. Table 1 summarizes the advantages and disadvantages of its use during labor. Its availability increases the choices that laboring women have for analgesia during labor [6].

This review will summarize the pharmacology and efficacy of N_2O during labor, compare N_2O with other methods of pain relief, summarize its adverse effects, and discuss the considerations in establishing a clinical service for its use.

History of Nitrous Oxide Use During Labor

Caton's review of the history of pain relief during labor contains an excellent summary of the early development of the clinical use of N_2O [7]. The first device to administer a fixed ratio of nitrous to oxygen to laboring women was developed by Klikovich in 1881 [8]. The device was costly and unwieldy and the use of N_2O was minimal until the Minnitt apparatus was developed in 1933 [8]. This apparatus delivered a fixed 50% nitrous oxide in air mixture and its safety was certified by the Royal College of Obstetricians and Gynaecologists, which endorsed its administration by midwives in 1936 [8]. The use expanded greatly in the UK after Tunstall developed the Entonox® system, which mixed 50% NO in 50% oxygen in a single cylinder in 1965 [9]. This device is currently in widespread use there.

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Table 1 Advantages and disadvantages of nitrous oxide analgesia

Advantages	Disadvantages
Uses simple equipment	Side effects of nausea, dizziness, dysphoria
Patients can rapidly learn self-administration	Mask phobia
Rapid onset and offset allows titratability	Inferior pain relief to neuraxial blockade
Enhances maternal sense of control	Environmental pollution possible
Enhances maternal coping skills	
Can be used when neuraxial analgesia cannot	
Does not preclude other forms of analgesia	
Has no effect on the course of labor	

N_2O was often used for labor analgesia in the USA in the 1940s, but its popularity decreased rapidly over the next three decades as neuraxial techniques became more widely used [1, 7]. N_2O is currently administered frequently in dental offices where it provides minimal-to-moderate sedation when used in concentrations of 30–50%. The paucity of reports of significant misadventure from use in this environment, where monitoring often does not include hemodynamic measures or pulse oximetry, attests to its safety. A significant barrier to widespread administration for labor analgesia in the USA was overcome when Porter Nitronox® reintroduced the Nitronox® apparatus for use in 2013. The apparatus incorporates non-proprietary N_2O and oxygen cylinders and waste gas scavenging through stock vacuum systems. This device offers advantages of portability and minimal cost with reduced environmental pollution during clinical use [6].

Pharmacology

N_2O is a colorless, somewhat sweet-smelling gas of low anesthetic potency and low blood solubility, which is not metabolized to any significant extent. The low solubility allows for rapid onset and offset with peak brain concentration 60 s after inhalation without the risk of overdose if a non-hypoxic mixture is administered [9]. With proper patient instruction, the drug can be self-administered with a peak effect during the period of a routine labor contraction. The mechanism of action is complex, with central nervous system potassium channel inhibition, the release of endogenous opioids with k-receptor activation, and anxiolysis by GABA receptor activation; however, the inhibition of NMDA receptor activity is currently thought to mediate the primary analgesic effect [10]. The ability of the patient to self-titrate the drug to her level of pain, its low concentration relative to the concentration of oxygen, and its rapid offset are the primary pharmacokinetic characteristics that underlie its clinical safety.

Despite its low solubility, achieving analgesic end-tidal concentrations of N_2O may not be well synced with the onset and offset of contraction pain. Jones et al. [11] reported that the mean end-tidal concentration of N_2O needed for patients to self-report significant relief is 40% when continuously administered. During intermittent administration of a 50% concentration, end-tidal concentrations are only 7%, 30 s after the onset of administration [12]. At the end of inhalation, they do approach end-tidal levels associated with analgesia [12]. While some women will have significant pain relief with these levels of N_2O, many others will not.

Efficacy and Maternal Satisfaction

Clinical studies of N_2O analgesia have not been able to adequately quantify the amount of pain relief it affords. Two narrative reviews [5, 13] and two systematic reviews [14, 15••] of the safety and effectiveness of N_2O have been published over the past 20 years. Patient inclusion/exclusion criteria, patient randomization to treatment and control groups, and well-defined measures of analgesic effectiveness are missing from most studies. The 2002 systematic review by Rosen [14] included only 11 studies deemed adequate for review. Seven were published before 1985. Quantitating the degree of pain relief was difficult due to the heterogeneity between studies: the concentrations of inhaled N_2O varied from 30 to 70%, some involved continuous administration and others intermittent self-dosing, methods to assess analgesia varied, and most compared N_2O to other means of pain relief that are not currently in use and only two trials compared its use to a placebo The more recent review by Likis et al. [15••] identified only 12 trials, nine reviewed by Rosen, and added only one new study. The authors were unable to draw conclusions on the degree of pain relief afforded by N_2O.

The difficulty in evaluating pain relief with N_2O may in part be related to the challenges of evaluating labor analgesia efficacy in general. Studies are difficult to design as severe pain is experienced by most women at some point during labor, but the timing and the pain felt by women vary. Ethical issues make study design challenging as well. Pain typically increases during labor, but the correlation to the increases in cervical dilation is highly variable. In addition, a

women's pain experience depends on numerous psychosocial factors, which are difficult to measure. Measuring pain scores during labor is not often feasible, but studies that report assessments of labor pain 1–2 days post-delivery show these measures to vary greatly from those assessed during labor. Finally, randomized controlled trials to compare groups with pain relief to groups without it are unethical.

Despite the lack of many quality studies, a few small, well-designed ones included in the reviews mentioned above show modest analgesic effectiveness with the use of N_2O. As an example, Westling et al. [16] performed a well-designed crossover study involving 24 women in labor who had similar cervical dilations during the period of data gathering. Labor pain was assessed using at least five random sequences of 100% oxygen, 40 and 70% intermittent N_2O, and 40% continuous N_2O administration. A dose-dependent response was noted; intermittent dosing of 40% N_2O timed to uterine contractions reduced a visual analog pain score (VAS) by an average of 10 mm (from an average VAS of 81 to 71 mm), intermittent dosing of 70% reduced VAS by 18 mm, and 40% continuously administered N_2O reduced VAS by 27 mm.

For good effectiveness, many authors state that adequate patient instruction is needed for maximal effectiveness, but few studies note it as part of their methodology, and no study has expressly evaluated its effect on analgesia. As an example, a trial by Talebi et al. [17] noted that 50% nitrous oxide combined with patient instruction and coaching during reduced VAS scores 20 mm compared with a control group who received 50% oxygen and air and no instruction. Unfortunately, the benefit of rigorous instruction was not expressly evaluated.

Despite reporting modest or no reduction in average pain scores, most studies state that a significant portion of women have very good pain relief who state they would choose inhaled nitrous oxide during subsequent labors [11, 12, 13, 18–22, 23••]. In one trial comparing Entonox® with inhaled sevoflurane for labor, 42% of women reported N_2O to be very effective, although the average reduction in pain was of little clinical significance [18]. Another observational study of 800 women, who were interviewed before and after a pain relief intervention, reported the analgesic effectiveness of N_2O and epidural analgesia or after use of other non-neuraxial techniques. While approximately 95% of women reported good pain relief with an epidural and 28% reported poor analgesia with N_2O, one-third rated N_2O analgesia as good [19]. A study by Holdcroft and Morgan of 130 women noted that 31% reported no pain relief, but 47% of the women found nitrous oxide to be effective [20].

N_2O is effective for many women during labor as it may positively affect factors other than analgesia. A very recent study by Richardson et al. [4••] supports this. Among 6507 women in their sample who had labor, delivered vaginally, and received labor analgesia, 81% chose neuraxial analgesia and 19% chose N_2O. Of the women who received N_2O, 60% delivered with N_2O analgesia alone. While greater than 90% of women who received neuraxial analgesia reported good analgesia, only 50% of women who receive N_2O reported the same (Table 2). When maternal satisfaction was measured, women who reported poor analgesic effectiveness with N_2O were 2.5 times more likely to report good satisfaction with their anesthetic care, than those who reported poor analgesia with a neuraxial technique, and only 7% were dissatisfied with their care (Table 2). Clearly, factors other than analgesia are important to laboring women. One recent systematic review of factors that influence a women's satisfaction with childbirth include her personal expectations for pain relief, a positive relationship with caregivers, her perception of their support, and her involvement in care decisions [20].

Since a positive maternal experience for labor and delivery depends on many factors, measures of elements other than pain relief are necessary. Labor involves physical, social, and psychological processes unique to each person of which pain is only one component [21]. Coping composite scores which assess these other factors may be more meaningful measures of maternal relief from the pain and stress of labor [22]. A very recent qualitative study by Richardson et al. [23••] analyzed the content of comments made by women on the first post-delivery day who delivered with nitrous oxide analgesia. Many comments recorded that analgesia was incomplete, but that patient expectations were met. Many women stated that the technique enhanced their coping with labor by shifting attention and reducing anxiety. A significant minority said that it was consistent with their birth plan (some women noted that N_2O enhanced their "natural childbirth"). The side effects of nausea, dizziness, and vision changes were also commented upon. The availability of N_2O almost immediately, when parturients wished assistance, was noted by some as a significant advantage.

Many women will find N_2O inadequate for analgesia during labor. Only one study by Sutton et al. [24] has reported obstetric and patient factors that predict switching to a neuraxial technique after a trial of N_2O. Patients who converted were more likely to be English-speaking nulliparous women whose birth plan involved a preference for a medicated vs. non-medicated labor, who were undergoing labor with oxytocin augmentation, and who had lower pain scores and lower cervical dilation upon initiation of N_2O. A multivariate analysis indicated that only an induction of labor and augmentation with oxytocin were independently associated with conversion.

Comparison of Nitrous Oxide to Other Non-Neuraxial Analgesic Techniques of Labor Pain Management

There is only one study that compares N_2O with other non-pharmacologic analgesic methods. Harrison et al. [25]

Table 2 Proportion of parturients in three analgesic regimens who rated analgesic effectiveness and overall satisfaction as low (0–4), moderate (5–7), or high (8–10)

	N_2O only ($N = 678$)	N_2O and neuraxial block ($N = 461$)	Neuraxial block only ($N = 5103$)
Analgesic effectiveness			
Low (0–4)	21%	3%	2%
Moderate (5–7)	27%	5%	6%
High (8–10)	52%	92%	92%
Overall Satisfaction			
Low (0–4)	1%	0.7%	0.4%
Moderate (5–7)	6%	3%	3%
High (8–10)	93%	96%	97%

Data from reference [4••]

compared transcutaneous electrical nerve stimulation, Entonox®, intramuscular meperidine, and promazine with lumbar epidural analgesia for labor. This non-randomized, observational study demonstrated the superior analgesic benefit of epidural analgesia, reported that nearly half of the women received no relief from intramuscular narcotic, and reported that most women experienced some relief from the use of TENs and N_2O.

While the study cited above also confirmed the ineffectiveness of intramuscular narcotics found by others [26], the use of intravenous opioids has modest analgesic effectiveness, perhaps greater than that of N_2O, but significantly increases the risk for maternal respiratory depression [27]. Volmanen et al. [28] compared patient-controlled intravenous remifentanil with N_2O for labor analgesia and noted that the reduction in pain score was modestly higher with remifentanil, but with greater maternal sedation. A one-to-one nursing to patient ratio is probably necessary with this technique [27], as a significant incidence of maternal oxygen desaturation (25%) and more frequent periods of maternal apnea have been reported by others [29].

To summarize, there is a minimal work that compares nitrous oxide to non-pharmacologic techniques for labor analgesia, and while intravenous opioids offer modestly better analgesia, maternal sedation and desaturation are significant drawbacks not found with N_2O.

Adverse Effects

N_2O has been used in Europe for decades without major adverse effects on mother and child. While its use might increase the rate of maternal oxygen desaturation during labor as noted in the reviews by Rosen et al. [14] and Likis et al. [15••], the marked heterogeneity in studies looking for this adverse effect makes drawing a conclusion difficult. Maternal desaturation is noted during unmedicated labors [30] and it is difficult to say that the incidence increases with the use of N_2O [31]. However, the addition of systemic opioids will increase the incidence of respiratory depression [30] and thus N_2O use within 2 h of the administration of opioids is not recommended.

Rates of nausea and vomiting may be increased. An incidence of 0–45% was reported in the review by Likis et al. [15••], but whether the rates are increased compared with unmedicated labors is not clear [32]. Dizziness is reported in 0–23% of women who use it [12, 13], drowsiness in 0–24% [14, 15••], but unconsciousness is very rare [14, 15••, 32]. The excellent survey study by Peach noted an incidence of dizziness of 4% [32].

Adverse effects on the neonate have not been reported. The meta-analysis by Likis et al. [15••] did not find an effect on umbilical cord blood gases, Apgar score, and immediate neonatal behavior with nitrous oxide use in labor. While this information is reassuring, an editorial that accompanied its publication [33•] noted that the quality of the studies that report on the neonatal outcome is poor. Moreover, the long-term effects in human children of methionine synthetase inhibition [34] and the increased rates of neuroapoptosis reported in animal models [35] are unknown; thus, better data is required to judge long-term safety [33•]. Despite this, all these studies exposed animals to concentrations of N_2O and exposure durations that far exceed the amount a human fetus would receive during intermittent maternal self-administration.

Environmental pollution and health care worker exposure more than governmental limits are likely if unscavanged systems are used. The Occupational Safety and Health Administration (OSHA) has set a time-weighted average limit of 25 ppm for health care worker exposure [36]. However, this recommendation was not based on studies of the long-term effects on health care workers, but upon assessments of volunteer performance on audiovisual tests, which started to decline once exposure concentrations exceeded 50 ppm. The level at which long-term exposure creates deleterious effects is unknown [34] and thus a wide range of exposure limits is mandated by governmental agencies (25 ppm in the USA to

200 ppm in Germany). The use of N_2O administration equipment in ventilated labor delivery rooms is unlikely to lead to exposure that exceeds these limits. One study measured average values of 7.5 to 21 ppm when equipment with a demand valve and a scavenging system was used in ventilated labor and delivery rooms [37]. Several survey studies have reported an association between adverse reproductive outcomes and nitrous oxide exposure in the workplace among health care workers [38]. However, the relative risk of increased abortion [38, 39•] and neonatal congenital abnormality [38, 39•] is of marginal significance and may well be due to reporting bias and other confounding variables [38, 39•]. Moreover, worker exposure levels were many times greater than that found in ventilated labor and delivery rooms using scavenged nitrous oxide delivery systems.

Contraindications

Few contraindications exist to the use of N_2O. It should not be used in patients with a recent pneumothorax, pneumocephalus, retinal surgery, and middle ear or sinus infection due to its well-described tendency to increase pressure in gas-filled spaces. Careful assessment should occur prior to its administration in persons with congenital heart disease, increased pulmonary vascular resistance, or patients with pulmonary hypertension due to its effects on pulmonary vascular resistance. Caution is advised in patients with disorders of B_{12} or deficiency metabolism, or in patients with a deficiency of, or reduction in, methionine synthetase.

Some clinical situations might make N_2O analgesia for labor less attractive compared with the early use of epidural analgesia. Patients at high risk for emergent cesarean delivery, who are in very early labor and request pain relief, or in whom airway management may be difficult may benefit more from neuraxial analgesia than from N_2O. Patients in early spontaneous or induced labor, who have signs of fetal intolerance to same, might also be encouraged to choose neuraxial analgesia.

Clinical Use

In addition to labor analgesia, N_2O can be used for analgesia during post-delivery procedures such as repair of vaginal and cervical lacerations and intrauterine exploration for retained products of conception. N_2O administration in US institutions should follow the anesthesia and sedation policies of the individual institutions who participate in Medicare and Medicaid. These policies must comply with the Conditions of Participation (42 CFR 482.52) which have recently been undated by the Centers for Medicare and Medicaid Services. These rules direct each department of anesthesiology to develop and implement policies for sedation and analgesia and establish procedures for the credentialing of those who can administer the same. Since the American Society of Anesthesiologists classifies nitrous oxide analgesia as analgesia and minimal sedation, its administration does not require monitoring by anesthesia personnel unless other sedation is added [40]. Routine nurse to patient ratios need not be altered, in contrast to the use of patient-controlled intravenous opioids.

Adequate patient instruction and provider coaching are required for successful therapy. Intermittent use should start 45 s before the peak of a labor contraction and continue for 4–5 breaths. It may take several minutes for the patient to be able to recognize when to begin. A provider should observe the patient for several uterine contractions to assess timing, mask seal, and side effects.

Available equipment in Europe and in the UK most commonly consists of a single gas cylinder with a one/one mixture of N_2O in oxygen, attached to a circuit with a demand valve and scavenger. In the USA, the mixing valve draws form two gas sources, using most often an E cylinder with N_2O and either a wall source or E cylinder of oxygen. The cylinder with N_2O usually has the drug in the liquid phase, so the pressure will fall rapidly after the liquid is depleted. A sudden decrease in pain relief should alert to an empty cylinder as the cause. Although abuse by health care workers or persons other than the patient has not been reported, the apparatus should be stored securely when not in use.

The OSHA recommends that air sampling occurs every 6 months to check for environmental contamination [36]. Individual dosimeters that can be worn by health care providers are commercially available, but the OSHA has not calibrated them.

Conclusions

N_2O offers many women an effective alternative to neuraxial analgesia for the relief of pain during labor in those labor and delivery units who offer it. Most studies from the USA report that approximately 50% of women choose to use it as their sole method of pain relief, even when more effective means of pain relief are immediately available. Maternal satisfaction with its use is equivalent to that of epidural analgesia, even among women who report poor pain relief. Its use is very safe for the mother, fetus, and newborn. Further investigations should focus on how it improves the maternal labor experience unrelated to pain relief, better time administration with the onset of the pain of uterine activity, and addressing concerns of long-term effects on child development post-delivery. N_2O offers women a good alternative choice to neuraxial analgesia for labor.

Compliance with Ethical Standards

Conflict of Interest Curtis L. Baysinger declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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