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Nitrous Oxide in Early Labor

Safety and Analgesic Efficacy Assessed by a Double-blind, Placebo-controlled Study

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Background: **Intermittent self-administered nitrous oxide has long had widespread use as an analgesic in labor, but its efficacy has not been adequately established. Questions about its effect on maternal oxygenation between labor contractions also have been raised.**

Methods: **Twenty-six women were recruited to participate in a randomized, double-blind, cross-over, placebo-controlled study to assess the effect of intermittent nitrous oxide inhalation on labor pain and maternal hemoglobin oxygen saturation (Sp_{O_2}) during the first stage of labor. Visual analog scale pain scores for each of five consecutive labor contractions were measured after administration of either nitrous oxide or compressed air.**

Results: **Mean visual analog scale pain scores for five contractions were 5.1, 5.2, 5.7, 5.2, and 5.6 (nitrous oxide) and 4.9, 5.2, 6.1, 5.6, and 5.7 (compressed air). There were no statistically significant differences in pain when nitrous oxide as compared with compressed air was administered. Pain scores did not differ significantly over time as a function of inhaled substance ($F = 0.41$, $P = 0.53$). The mean lowest Sp_{O_2} observed between these contractions after self-administration of nitrous oxide and air were 97, 97, 97, 97, and 97% (nitrous oxide) and 97, 96, 96, 96, and 96% (compressed air). Sp_{O_2} was significantly higher after nitrous oxide administration ($F = 8.8$, $P = 0.007$).**

Conclusion: **While intermittent self-administered 50% nitrous oxide in oxygen does not appear to predispose parturient women to hemoglobin oxygen desaturation, its analgesic effect has yet to be clearly demonstrated. (Key words: Analgesia: obstetric. Anesthetics, gases: nitrous oxide. Blood, hemoglobin: oxygen saturation. Measurement techniques: pulse oximetry.)**

ALTHOUGH nitrous oxide has been used for more than 100 yr[1] as an analgesic in labor, there is a paucity in the literature of well controlled trials evaluating its efficacy. Nevertheless, intermittent self-administered 50% nitrous oxide in oxygen is commonly offered as an analgesic to women in labor throughout the world. This administration is frequently accomplished by the use of a mask and demand-valve assembly connected to a regulator and a supply of nitrous oxide and oxygen. Use may be supervised by physicians, nurses, and midwives and is believed to be safe. However, questions have arisen in the literature recently about a possible deleterious effect on maternal hemoglobin oxygen saturation (Sp_{O_2}) between contractions when nitrous oxide is used in this manner.[2–5]

That nitrous oxide is in such common use led us to evaluate the quality of analgesia and safety in a double-blind, placebo-controlled manner. This study was designed to test the effects of nitrous oxide, as it is currently used, on the pain of labor contractions and on maternal Sp_{O_2} after labor contractions.

Materials and Methods

After obtaining institutional ethics committee approval, we recruited 29 women for participation in the

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study from among those admitted in labor to the delivery suite at the Toronto Hospital. Participants gave informed written consent. Exclusion criteria for entry into this study were age < 18 yr; maternal cardiorespiratory disease; any evidence of fetal distress or abnormal heart rate pattern; any condition affecting the accuracy of pulse oximetry (*e.g.*, low pulse volume, methemoglobinemia, and intravenous dyes); or the use of opioid or regional analgesia.

At the time of recruitment, after informed consent had been obtained, age and parity were recorded. Subjects were trained at this time in the use of a visual analog scale (VAS) to rate the pain of labor contractions.

Each trial began when a subject first requested analgesia. At this time, cervical dilation as measured by the most recent clinical examination was recorded. Duration of labor was defined as the time since the start of regular contractions and also was recorded. Subjects were instructed in the use of intermittent self-administered nitrous oxide analgesia. Continuous monitoring with a pulse oximeter (Nellcor N-100C and D-25 Oxisensor, Hayward, CA) was instituted. Subjects' ratings of the pain of two consecutive contractions were recorded as baseline values, as was the lowest Sp_{O_2} achieved after each of those contractions.

Subjects were assigned to two groups to randomize treatment order and control for the progress of labor. Before the start of the study, a random number table had been used to assign one of two treatment order instructions into numbered, sealed envelopes. In group 1, subjects self-administered a mixture of 50% nitrous oxide and oxygen (BOC Healthcare, Ohmeda Nitronox hospital model 91120053, Madison, WI) during each of five consecutive contractions. For the next five contractions, compressed air was self-administered *via* a hose and demand-valve assembly identical to that on the Nitronox machine. Subjects in group 2 received the gases in reverse order. The Nitronox machine and the compressed air tank and regulator were hidden from view throughout the trial, having been placed in position by the subject's nurse. The same nurse also opened the sealed envelope containing treatment order instructions and offered the appropriate mask to the subject.

VAS pain scores were obtained after each contraction, and the lowest Sp_{O_2} observed after a contraction was recorded. Because all participants received both nitrous oxide as well as compressed air as a placebo, each subject acted as her own control. At the end of each trial, after all data had been collected, subjects were asked to identify the order in which they had received the two gases, and this answer was recorded.

All recruitment, instruction, and data collection was carried out by two of the study's authors (JC and SL), who, along with the subjects, were blinded to the order in which the gases were given. Each subject's nurse remained present throughout the trial but had no involvement in the study other than as described above. The parturient woman's partner or labor coach also was permitted to be present. Trials were carried out in labor rooms where nitrous oxide is used in clinical practice, and after the trial, subjects were free to continue using the Nitronox. Subjects were encouraged to start inhalations as early as they could when they felt the start of a contraction. Thus, except for the use of pulse oximetry and the presence of an investigator, the clinical setting was made as close to that in which nitrous oxide analgesia is normally given to women in labor at the institution in which the study was carried out.

Data Analysis

VAS pain scores and Sp_{O_2} were analyzed by a three-factor (group by treatment by contraction) repeated-measures analysis of variance. Parity, cervical dilation, duration of labor, and ability correctly to identify the order of the gases in the two groups were compared using Student's t test or chi-squared analysis where appropriate. Significance was denoted by $P < 0.05$.

Results

Of the 29 women recruited, 3 were not able to complete their trials as set out by the protocol, and their results were excluded from data analysis. Two of these 3 subjects could not rate each of their contractions with a VAS, and in the case of the third, a protocol error occurred. Thus, 14 women remained in group 1 and 12 in group 2. No differences were found between groups in parity, duration of labor, cervical dilation, or baseline VAS and Sp_{O_2} values (table 1). It is noteworthy that 19 subjects asked for analgesia while still in early labor (cervical dilation ≤ 3 cm). Of the remaining 7, none had cervical dilation that had progressed to > 6 cm at the time of the first request.

Figure 1 shows mean VAS pain scores for each contraction during which nitrous oxide or air was used. Results of the analysis of variance showed no significant main effects. That is, neither the order in which the

Table 1. Demographic Data

	Group 1	Group 2
Age (yr)	31.1 ± 5.8	28.4 ± 5.0
Primiparity:multiparity	7:7	7:5
Cervical dilation (cm)	3 ± 1.4	3 ± 1.3
Duration of labor (h)	7.9 ± 3.8	7.6 ± 4.9
Baseline visual analog scale	5.6 ± 2.1	4.9 ± 2.5
(two contractions)	5.2 ± 2.2	5.8 ± 2.7
Baseline Sp_{O_2} (two contractions) (%)	97 ± 2.0	97 ± 2.0
	97 ± 2.0	96 ± 2.0

Values are mean ± SD.

two gases were administered, the nature of the treatment (i.e., self-administered nitrous oxide vs. compressed air), nor the progress of labor (contractions 1–5) significantly affected the VAS pain scores. Moreover, there were no significant interactions between these factors.

Figure 2 shows the means of the lowest Sp_{O_2} observed after each contraction. There was a statistically significant effect of treatment on Sp_{O_2}. After a contraction, Sp_{O_2} was greater if nitrous oxide had been self-administered. In only one subject was $Sp_{O_2} < 90\%$: 85% was recorded once after nitrous oxide, and 87% and 89% after air inhalation.

Twenty-one patients were able correctly to identify the order in which the gases had been administered. Three patients in group 1 and 2 patients in group 2 could not tell the difference between nitrous oxide and air; this difference was not significant.

A *post hoc* power analysis was performed on VAS pain scores (PC-Size 2.0 software for sample size determination) after all data had been collected and analyzed. The results showed that the current sample size of 26 would allow the detection of a 1.0-unit difference between VAS pain scores for air *versus* nitrous oxide with a power of 0.8 and an α of 0.05.

Discussion

The finding that nitrous oxide was no more effective than compressed air as an analgesic seems to contradict reports in the literature that first appeared over 100 yr ago.[1] This literature needs to be reviewed, however, before the current study's results can be put into context.

A review of 12 papers published since 1960 evaluating the use of nitrous oxide reveals methodological

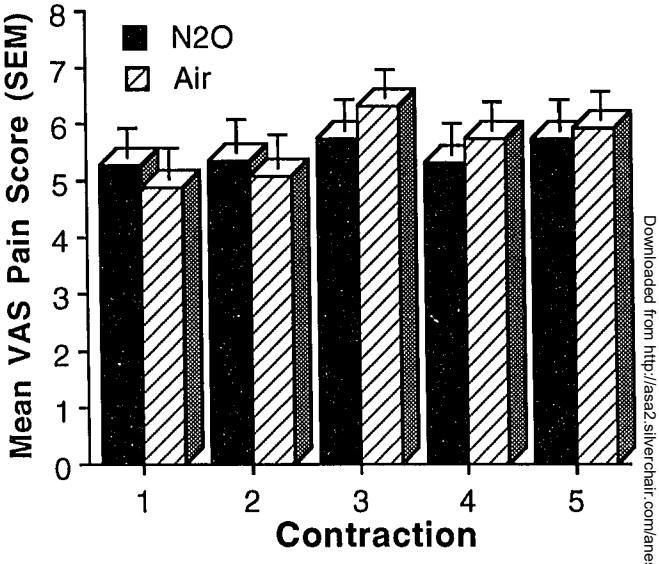

Fig. 1. Effect of nitrous oxide and air on visual analogue scale (VAS) pain scores during each uterine contraction. There was no difference in the VAS score between the patients receiving nitrous oxide or air for any contraction.

flaws that leave their conclusions open to question. One or more of the following weaknesses can be found in most of these studies: a lack of randomization; a lack of placebo or treatment controls; failure to control for

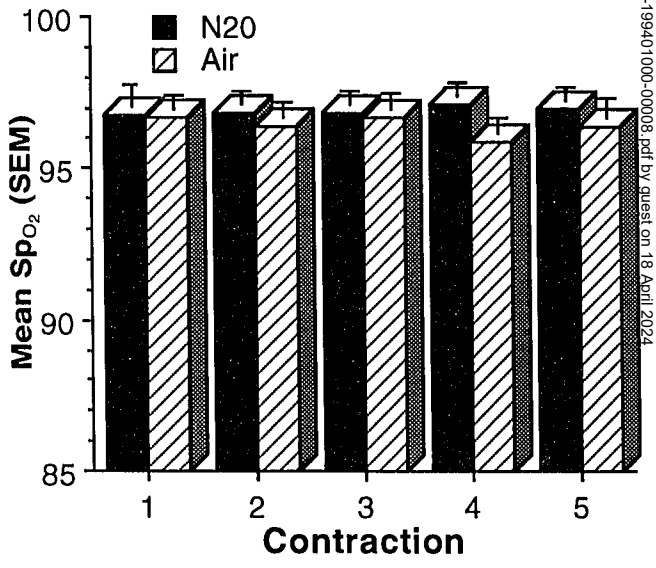

Fig. 2. Lowest hemoglobin oxygen saturation (Sp_{O_2}) recorded during a contraction. Patients using nitrous oxide had significantly higher Sp_{O_2} during a contraction than did patients using air.

the concomitant use of opioids; or failure to blind the investigators to the experimental conditions.[6-17] Another problem, particularly in reports published before 1980, is the method of measuring pain. In all but 3 papers,[13,16,17] investigators used four- or five-point scales for which no data exist on reliability or validity. Other studies failed to provide any statistical analysis comparing outcome after nitrous oxide *versus* no treatment[16] or comparison treatment.[11,14] Finally, only 2 reports controlled for the effect of the progress of labor itself on pain measurements.[16,17] Taken together, these weaknesses indicate that nitrous oxide has not been tested with the experimental rigor necessary to conclude that it is an effective analgesic when intermittently self-administered during labor.

In a well designed study on the effects of nitrous oxide on maternal circulation during labor, Westling *et al.*[17] were able to demonstrate that nitrous oxide inhalation led to lower VAS pain scores after labor contractions than did oxygen inhalation. Unfortunately, because not all contractions in the trial of each gas was measured, the study may have missed data that could have modified the results.

The results of the studies reviewed above indicate that the analgesic effects of intermittent self-administered nitrous oxide during labor are equivocal. The findings of the current study add to that uncertainty and raise several issues concerning the use and study of nitrous oxide analgesia.

First, concerning the extent to which results may be generalized, the sample of patients enrolled in the current study represents only a fraction of those whom the investigators attempted to recruit. These self-selected women may differ from the majority of women presenting in labor. The criticism that the results may not be broadly generalized can be applied to much research on analgesia in labor. Similarly, none of the subjects in this study was near the end of the first stage of labor, the time in the usual clinical situation when many parturient women who have not yet chosen any analgesia are given nitrous oxide. This difference also may have played a role in the negative results reported here.

Second, the manner in which nitrous oxide was administered, with patients told to start inhalations as soon as they suspected the onset of a contraction, is identical to the clinical procedure at the investigators' institution but may not be the most efficient method of use. Peak alveolar concentration of 50% nitrous oxide has been shown to occur 60 s after the start of inhalation.[18] Presumably, peak analgesia is not achieved until a contraction is almost over. A more thorough study, in which contractions are carefully timed, would allow the testing of the efficacy of nitrous oxide at its peak concentration.

Third, in the current study, VAS pain scores were used to assess the sensory intensity of pain.[19] Other important dimensions of the pain experience, such as affective experience or cognitive appraisal, were not measured. Although VAS pain scores were not different after nitrous oxide or compressed air, most subjects clearly differentiated the two gases and chose to continue nitrous oxide analgesia at least for a while. The cues that allowed these subjects to identify nitrous oxide are probably related to mild affective and cognitive changes (light-headedness and a sense of well-being), but it also is possible that the affective and cognitive dimensions of pain were affected.

Finally, the use of continuous nitrous oxide inhalation may be effective and safe, but there are few data in the literature to support or condemn its use. One study[20] investigated intermittent *versus* a combination of continuous and intermittent nitrous oxide, but without blinding subjects and investigators, without controlling the use of meperidine, and without applying any tests of significance to the results. Mean VAS scores for pain were 5.1 after continuous inhalation and 5.42 after intermittent inhalation. Further research must take into account the possible depressant effects of continuous nitrous oxide and the associated risk of aspiration.

The results of the current study also indicate that maternal oxygenation does not appear to be jeopardized by the use of intermittent self-administered nitrous oxide during labor. In fact, the argument can be made that oxygenation actually improves between contractions for which nitrous oxide and oxygen have been administered. Caution in that assertion is warranted, however, because it is doubtful that the observed small differences in oxygenation have any clinical significance despite their statistical significance.

This finding directly contradicts the conclusions drawn from the results of several published studies,[2-5] all of which invoke the mechanism of diffusion hypoxia to explain desaturation after nitrous oxide inhalation. This argument may be questionable on purely logical grounds. Analysis of the arterial blood of women breathing 50% nitrous oxide and oxygen intermittently has shown peak concentrations of nitrous oxide to be only 26%.[21] It is not clear that this concentration, diffusing rapidly into alveoli, would be adequate to dilute

alveolar oxygen to dangerous levels in someone who had been breathing 50% oxygen and nitrous oxide and who then begins to breathe room air.

Furthermore, all of the studies discussed above have methodological flaws that weaken their conclusions. In a recently published pilot study for the current investigation, desaturation was observed after nitrous oxide inhalation, but that was an nonblinded, uncontrolled trial.[2] Lin *et al.*[3] claimed to show conclusively the danger of nitrous oxide, although their study compared only four parturient women using 50% nitrous oxide with five who had received epidural analgesia and did not control for the progress of labor. Moreover, the use of epidural analgesia for a control condition is inappropriate. It has been demonstrated elsewhere[22] that epidural analgesia prevents the hyperventilation–hypoventilation phenomenon that may occur in normal labor and that can lead to significant desaturation between contractions regardless of the use of nitrous oxide.[23,24] Without data from a placebo group that involves inhalation or even from a no-treatment control group, it is impossible to conclude that nitrous oxide was responsible for the observed desaturation.

Deckardt *et al.*[4] stated that 50% nitrous oxide was responsible for desaturation in parturient women, even though the use of meperidine for analgesia was not controlled and thus confounds their results. Zelcer *et al.*[5] also warned against the use of nitrous oxide analgesia in any case in which there is a suspicion of decreased oxygen reserve in the mother, placenta, or fetus. Nevertheless, none of the subjects in the study by Zelcer *et al.* who used 50% nitrous oxide alone for analgesia demonstrated any desaturation, whereas those who had also received meperidine did.

The current study used an appropriate control for nitrous oxide inhalation: compressed air inhalation. Confounding variables were eliminated by excluding from the study all those who had received any drug that could affect oxygenation. It seems reasonable to conclude that there is little or no evidence to support the notion that intermittently self-administered nitrous oxide, in the absence of concomitantly administered opioids, poses any more of a threat to maternal oxygenation than does ordinary labor.

In conclusion, the results of this study support the safety of the use of intermittent self-administered nitrous oxide with regard to maternal oxygenation. However, the study failed to demonstrate that nitrous oxide, as it is used at the investigating institution, is any more effective as an analgesic than is compressed air. Further research is necessary before a conclusive statement about the efficacy of nitrous oxide in labor can be made. Particular issues that merit further attention include multidimensional pain assessment; the use of nitrous oxide at the end of the first stage or during the second stage of labor; administration of nitrous oxide in a manner ensuring that the peak analgesic effect of nitrous oxide coincides with contractions; and continuous nitrous oxide administration.

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