

<http://www.pjbs.org>

**PJBS**

ISSN 1028-8880

**Pakistan  
Journal of Biological Sciences**

**ANSI***net*

Asian Network for Scientific Information  
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

## Entonox for Labor Pain: A Randomized Placebo Controlled Trial

<sup>1</sup>H. Talebi, <sup>1</sup>A. Nourozi, <sup>2</sup>M. Jamilian, <sup>3</sup>N. Baharfar and <sup>4</sup>P. Eghtesadi-Araghi

<sup>1</sup>Department of Anesthesiology, Arak University of Medical Sciences, Arak, Iran

<sup>2</sup>Department of Obstetrics and Gynecology, Arak University of Medical Sciences, Arak, Iran

<sup>3</sup>Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>4</sup>Department of Anesthesiology, Parsteb Pajouheshyar Medical Sciences Research Institute, Tehran, Iran

**Abstract:** This study aims to investigate the effectiveness of nitrous oxide on pain of labor contractions and on maternal SaO<sub>2</sub>. The patients were randomized to receive either a pre-prepared mixture of 50% nitrous oxide and oxygen or 50% oxygen by a coin. Study drugs started as early as the onset of pain with each contraction. The patient herself administered gases via a facemask connected to the uni-directional valve which enables the patients to breathe fresh gas in each inspiration. The gas administration was continued to the end of contraction pain at which the patient breathed the room air. Variables such as SaO<sub>2</sub>, blood pressure, pain and side effects were recorded. 534 ASA I and II parturients, aged from 16 to 35 years, scheduled for elective labor from September 2004 to 2006 were evaluated. Four patients were lost from the study. The mean age of patients was 25.5±4.3 years. During the first three measurements, the SaO<sub>2</sub> was significantly higher in control group. In addition, the mean arterial pressure was comparable between groups except two first measurements in which the control group was higher. All the Visual Analogue Scale (VAS) values were significantly lower in nitrous oxide group. There were no significant differences in 1st and 5th min apgar scores between groups. All of the side effects were significantly higher among patients in nitrous oxide. In conclusion, our data indicate that using nitrous oxide 50% provides significant pain relief. Nonetheless, it is associated with few side effects, nitrous oxide can be quickly implemented during advanced painful labor.

**Key words:** Entonox, labor pain, randomized controlled trial

### INTRODUCTION

Despite nitrous oxide has been used for more than 100 years as an analgesic in labor, there is paucity of well controlled trials evaluating its efficacy in the literature (Carstoniu *et al.*, 1994). In a systematic review, Rosen (2002) assessed the studies which were conducted to determine the efficacy and safety of nitrous oxide for labor analgesia, only found eleven randomized controlled trials with adequate control groups and outcome assessment. Taken together, these studies do not provide clear, quantitative, objective evidence of the analgesic efficacy of nitrous oxide for relief of labor pain (Irestedt, 1994).

In the only placebo controlled crossover study conducted by Carstoniu *et al.* (1994), intermittent self-administration of 50% nitrous oxide in oxygen was compared with compressed air in 26 women. They found no differences in visual analogue pain scores over 5 successive contractions between the 2 gas mixtures, yet most subjects were able to distinguish nitrous oxide and chose to continue using it. However, there were several

limitations in this study. In the first place, many women who agreed to participate in the study were in early labour with fairly low pain scores with limited potential for differentiating an analgesic effect. Secondly, intermittent self-administration of the mixture, might not met the synchronization with peak nitrous oxide concentrations with the peak of the pain of contraction, which is essential for effective use. Nevertheless, most women differentiated the mixtures and chose to continue the use of nitrous oxide.

Furthermore, there is a lack of reports comparing nitrous oxide with control group who received placebo. In brief, although 50% nitrous oxide/oxygen mixture is widely used to alleviate labor pain (Bishop, 2007; Onody *et al.*, 2006), there are just evidence level B (systematic review of lower quality studies) to support efficacy and safety of this mixture (Leeman *et al.*, 2003) in labor pain. Thus, it seems that performing more randomized placebo controlled trials is necessary to test efficacy and safety of nitrous oxide in alleviating labor pain. The goal of this study was to investigate the effectiveness of nitrous oxide on pain of labor contractions and on maternal SpO<sub>2</sub>

in a single blinded, placebo-controlled manner. We hypothesized that administration of the nitrous oxide and oxygen mixture during labor by the patients herself will reduce labor pain, while it is associated with low rate of side effects.

## MATERIALS AND METHODS

Following approval of Institutional Review Board of Arak University of Medical Sciences (Arak, Iran) and written consent, 534 ASA I and II parturients, aged from 16 to 35 years, scheduled for elective labor from September 2004 to 2006 were evaluated. Term (38 to 42 weeks), primigravid or second gravid parturients who were in active phase of labor (dilatation more than 4 cm) were enrolled. Patients with any evidence of fetal distress or abnormal heart rate pattern, gestational age of less than 37 weeks or more than 42 weeks, maternal cardiorespiratory disease or any condition affecting the accuracy of pulse oximetry (e.g., low pulse volume, methemoglobinemia and intravenous dyes) or history of taking opioids or administration of sedatives or regional analgesia (e.g., pudendal blocks and local infiltration) were excluded from the study. Patients who did not tolerate Entonox were also excluded. At the time of recruitment, gestational age and parity were recorded.

Each trial began when a subject first requested analgesia. At this time, the patients were randomized to receive either a pre-prepared mixture of 50% nitrous oxide and oxygen (Carstoniu *et al.*, 1994) (Darman Gaz Co. Tehran/Iran) (Nitrous oxide group) or 50% oxygen (Control group) by a coin. Study drugs started as early as the onset of pain with each contraction. The patient herself administered gases via a facemask connected to the uni-directional valve which enables the patients to breathe fresh gas in each inspiration. The gas administration was continued to the end of contraction pain at which the patient breathed the room air.

Patients whom underwent caesarean section (e.g., descent arrest) or needed forceps for any reason during delivery were excluded from the study.

The Visual Analog Scale (VAS) was utilized to rate the pain of labor contractions by which the zero denotes no pain and 10 was considered as the most aggressive pain that the patient has ever experienced (Goodman *et al.*, 2009) Subjects were instructed how to use VAS before the study.

Furthermore, continuous monitoring of SpO<sub>2</sub> with a pulse oximeter (Oxyplat Nova Matrix, USA), blood pressure (Riester, Germany) and fetal heart rate (Sonictae, Toitu Co, Ltd. Japan) were instituted. At the start of active phase (time 0) and every hour (times 1 to 5), a single

assistant who was blind to the group of patients recorded subjects' ratings of the pain of consecutive contractions, as was the lowest SpO<sub>2</sub> and the mean arterial pressure achieved after each of those contractions. The 1st and 5th minutes apgar scores of infant were recorded as well. Side effects like nausea, vomiting, dizziness, dry mouth from breathing dry gas, pins and needles or numbness and drowsiness were measured at the end of the study.

**Sample size:** Some studies have documented that utilizing nitrous oxide resulted 30% reduction in women's assessment of labor pain (Jones *et al.*, 1969a). Respecting these studies, a sample size of 250 patients was deemed to be sufficient to detect a 30% reduction in labor pain, using  $\alpha = 0.05$  and  $\beta = 0.1$ .

**Statistical analysis:** Data were expressed as simple count, or Mean±SD and were compared by Student's t-test, Fisher's exact test, or Chi square test where appropriate. Statistical calculations were performed using SPSS version 12.0. Significance was denoted by  $p < 0.05$ .

## RESULTS

There were 523 parturient. Four patients were lost from the study. The mean age of patients was 25.5±4.3 years. Some of the clinical variables were compared between groups in Table 1.

During the first three measurements, the SaO<sub>2</sub> was significantly higher in control group compared with nitrous oxide group; yet, there were not difference among groups in the next measurements (Fig. 1, 2). Also, the mean arterial pressure was comparable between groups except two first measurements in which the control group

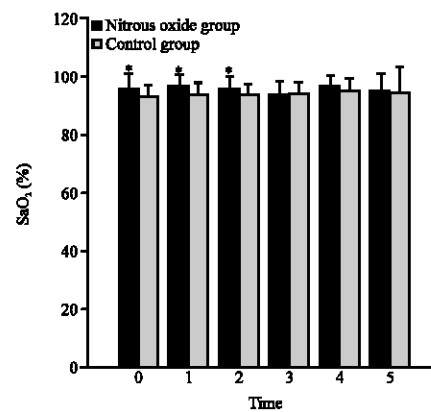


Fig. 1: Comparison of SaO<sub>2</sub> (%) between nitrous oxide and control groups. Values are expressed as Mean±SD. \*Significant difference (Independent samples t-test)

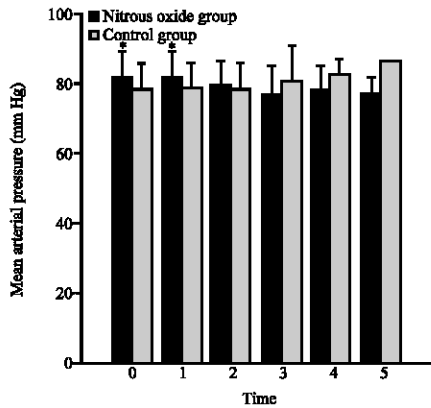


Fig. 2: Comparison of mean arterial pressure (mmHg) between nitrous oxide and control groups. Values are expressed as Mean±SD. \*Significant difference (Independent samples t-test)

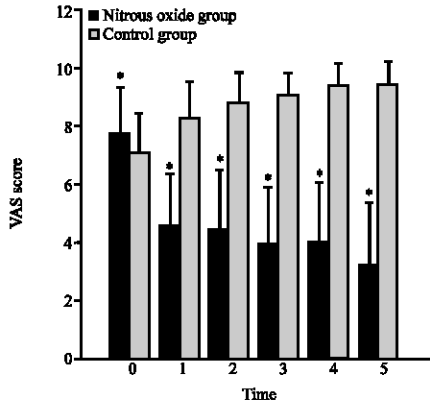


Fig. 3: Comparison of pain according to VAS score between nitrous oxide and control groups. Values are expressed as Mean±SD. \*Significant difference (Independent samples t-test)

Table 1: Subjects' demographic and clinical data

Variables	Nitrous oxide group	Control group	p-value
Age (year)	24.2±4.0	24.9±4.7	0.100
Gravid (Prime/Multi)	163/97	126/123	0.007
Gestational age (weeks)	39.9±0.5	39.8±0.5	0.120
Apgar score (1st min)	8.5±0.9	8.5±0.8	0.760
Apgar score (5th min)	9.5±0.8	9.5±0.7	0.860
<b>Side effects</b>			
Nausea	8.40%	0%	0.001
Vomiting	2.30%	0%	0.030
Dizziness	22.60%	0%	0.001
Dry mouth	8.30%	0%	0.001
Pins and needles or numbness	4.10%	0%	0.001
Drowsiness	15.40%	0%	0.001

Note: Data are represented as Mean±SD, numbers or percentages

was higher. Furthermore, throughout the study measurements, all the VAS values were significantly lower in nitrous oxide group compared with control group

(Fig. 3). There were no significant differences in 1st and 5th apgar scores between groups. All of the side effects were significantly higher among patients in nitrous oxide (Table 1).

## DISCUSSION

This study compared to the previous studies, included much higher number of participants which differs our study from the previous ones. The results of current study showed that when nitrous oxide was compared to the placebo, the labor pain was significantly lower, while changes in the SaO<sub>2</sub> or MAP were comparable in most of times and no difference between 1st and 5th min apgar scores were revealed.

It is in concordance with the results of other studies. It has been shown that using nitrous oxide significantly reduces women's concurrent assessment of labor pain with that 2 to 3 days later (Jones *et al.*, 1969a, b). Jones *et al.* (1969a) studied 48 women randomized to receive either continuous nitrous oxide in oxygen or methoxyflurane in air. In nitrous oxide group patients reported considerable or complete pain relief with nitrous oxide. In a companion study, Jones *et al.* (1969b) revealed that women in Entonox group considered pain relief as complete or considerable. Stefani *et al.* (1982) reported that 73% of the women who received nitrous oxide described the second stage as very little pain or no pain. The median pain score with Entonox reduced to 52/100 mm (range 29 to 70) in the McGuinness and Rosen (1984) study. In the literature, there are other evidences that nitrous oxide provided benefit to the parturient woman (Bergsjö and Lindbaek, 1971; McLeod *et al.*, 1985; Stefani *et al.*, 1982). In many of these studies, women describe significant analgesia with nitrous oxide use (Abboud *et al.*, 1995; Bergsjö and Lindbaek, 1971; Jones *et al.*, 1969a, b; McLeod *et al.*, 1985; Stefani *et al.*, 1982) many chose to continue its use after the study period ended and many would choose it again. In a study where nitrous oxide was not demonstrated to provide benefit for labor analgesia compared with compressed air, most subjects chose to continue using it after the study period was over (Carstoniu *et al.*, 1994).

**Cardiovascular effects of nitrous oxide:** In consistence with the results of this study, in one study, it has been shown that an increasing concentration of nitrous oxide produced better analgesia and was associated with a diminished cardiovascular response to painful contractions. Continuous breathing of 40% nitrous oxide minimized the increased maternal blood pressure and pulse associated with pain (Westling *et al.*, 1992).

**Maternal oxygen saturation:** Both diffusion hypoxia and direct respiratory depressant effects of nitrous oxide have been suggested as a potential cause for maternal oxygen desaturation between painful uterine contractions. It can occur as a result of the outpouring of large volumes of nitrous oxide from the body that may directly affect oxygenation by displacing oxygen in the lungs (alveolar oxygen) or by diluting lung (alveolar) carbon dioxide, which controls respiratory drive (Rosen, 2002). In a nonrandomized study, Zelcer *et al.* (1989) examining the maximum and minimum oxygen saturation showed that nitrous oxide alone did not result in lower minimum oxygen saturation compared with that of a group of women who labored without analgesia. Like the results of the present study, Carstoniu *et al.* (1994) found that mean oxygen saturations after contractions with administration of compressed air are lower than after contractions with nitrous oxide. Arfeen *et al.* (1994) also found no significant difference between episodes of desaturation among the women receiving nitrous oxide and epidurals. Einarsson *et al.* (1996) showed that during nitrous oxide administration, episodes of hypoventilation were rare and diffusion hypoxia was not found to be important.

**Neonatal outcome:** The current study revealed no differences in 1st and 5th apgar scores between groups. It was in concordance with previous reports that found no effect of nitrous oxide administration on neonatal's Apgar scores (Anonymous, 1970; Abboud *et al.*, 1981; Amiel-Tison *et al.*, 1982; McAneny *et al.*, 1963; Scanlon *et al.*, 1974; Stefani *et al.*, 1982).

**Side effects:** Nausea and vomiting have been reported in nitrous oxide studies, ranging from 5 to 36% (Arthurs and Rosen, 1979; Bergsjö and Lindbaek, 1971; Jones *et al.*, 1969a, b; McAneny and Doughty, 1963; McGuinness and Rosen, 1984) In the present study we found a rate of 8.4% of nausea and 2.3% of vomiting among patients in nitrous oxide group which was significantly higher than control group. Dreams or drowsiness, ranging from 0 to 24%, have been reported. We found this side effect in 15.4% of patients receiving nitrous oxide (Anonymous, 1970; Jones *et al.*, 1969a, b; McAneny and Doughty, 1963; Wee *et al.*, 1993). Other low incidence side effects including dry mouth and pins and needles or numbness were found in 8.3 and 4.1% of cases respectively. Another side effect that has low incidence in other studies (Bergsjö and Lindbaek, 1971; Jones *et al.*, 1969a; McGuinness and Rosen, 1984) was dizziness which was suprisingly high in our series (22.6%). All of these side effects occurred higher in nitrous oxide group.

In this study, we selected the intermittent technique for nitrous oxide administration, because the continuous level of sedation can be dysphoric. Without the pain of contraction, the woman may experience the central nervous system effects of nitrous oxide as excessive drowsiness, dizziness, or lightheadedness (Rosen, 2002). However, the use of an intermittent technique with initiation at the onset of contraction is problematic. The time lag of approximately 50 sec after the onset of administration before the full analgesic effect is anticipated. This requires careful attention to contraction timing and intervals to allow onset of administration of nitrous oxide in anticipation of the onset of the next contraction rather than at the onset of contraction pain, which is difficult for many parturient women to do (Rosen, 2002). It is probably a poorly controlled aspect of this model.

This study has other limitations. For instance, we did not evaluate the patients' assessment of pain relief during delivery and 36 to 48 h later. Furthermore,

## CONCLUSION

In conclusion, present data indicate that using nitrous oxide 50% provides significant pain relief. Nonetheless, it is associated with few side effects; nitrous oxide can be quickly implemented during advanced painful labor.

## REFERENCES

- Abboud, T.K., S.M. Shnider, R.G. Wright, S.H. Rolbin and J.B. Craft *et al.*, 1981. Enflurane analgesia in obstetrics. *Anesth. Analg.*, 60: 133-137.
- Abboud, T.K., F. Swart, J. Zhu, M.M. Donovan, E. Peres Da Silva and K. Yakal, 1995. Desflurane analgesia for vaginal delivery. *Acta Anaesthesiol Scand*, 39: 259-261.
- Amiel-Tison, C., G. Barrier, S.M. Shnider, G. Levinson, S.C. Hughes and S.J. Stefani, 1982. A new neurologic and adaptive capacity scoring system for evaluating obstetric medications in full-term newborns. *Anesthesiology*, 56: 340-350.
- Anonymous, 1970. Clinical trials of different concentrations of oxygen and nitrous oxide for obstetric analgesia. Report to the medical research council of the committee on nitrous oxide and oxygen analgesia in midwifery. *Br. Med. J.*, 1: 709-713.
- Arfeen, Z., P.J. Armstrong and A. Whitfield, 1994. The effects of Entonox and epidural analgesia on arterial oxygen saturation of women in labour. *Anaesthesia*, 49: 32-34.

- Arthurs, G.J. and M. Rosen, 1979. Self-administered intermittent nitrous oxide analgesia for labour. Enhancement of effect with continuous nasal inhalation of 50 per cent nitrous oxide (Entonox). *Anaesthesia*, 34: 301-309.
- Bergsjö, P. and E. Lindbaek, 1971. Comparison between nitrous oxide and methoxyflurane for obstetrical analgesia. *Acta Obstet Gynecol Scand*, 50: 285-290.
- Bishop, J.T., 2007. Administration of nitrous oxide in labor: expanding the options for women. *J. Midwifery Womens Health*, 52: 308-309.
- Carstoniu, J., S. Levytam, P. Norman, D. Daley, J. Katz and A.N. Sandler, 1994. Nitrous oxide in early labor. Safety and analgesic efficacy assessed by a double-blind, placebo-controlled study. *Anesthesiology*, 80: 30-35.
- Einarsson, S., O. Stenqvist, A. Bengtsson, H. Noren and J.P. Bengtson, 1996. Gas kinetics during nitrous oxide analgesia for labour. *Anaesthesia*, 51: 449-452.
- Goodman, S.R., R.M. Smiley, M.A. Negron, P.A. Freedman and R. Landau, 2009. A randomized trial of breakthrough pain during combined spinal-epidural versus epidural labor analgesia in parous women. *Anesth. Analg.*, 108: 246-251.
- Irestedt, L., 1994. Current status of nitrous oxide for obstetric pain relief. *Acta Anaesthesiol Scand*, 38: 771-772.
- Jones, P.L., M. Rosen, W.W. Mushin and E.V. Jones, 1969a. Methoxyflurane and nitrous oxide as obstetric analgesics. I. A comparison by continuous administration. *Br. Med. J.*, 3: 255-259.
- Jones, P.L., M. Rosen, W.W. Mushin and E.V. Jones, 1969b. Methoxyflurane and nitrous oxide as obstetric analgesics. II. A comparison by self-administered intermittent inhalation. *Br. Med. J.*, 3: 259-262.
- Leeman, L., P. Fontaine, V. King, M.C. Klein and S. Ratcliffe, 2003. The nature and management of labor pain: Part II. Pharmacologic pain relief. *Am. Fam. Phys.*, 68: 1115-1120.
- McAneny, T. and A. Doughty, 1963. Self-administration of nitrous oxide/oxygen in obstetrics. *Anaesthesia*, 18: 488-497.
- McGuinness, C. and M. Rosen, 1984. Enflurane as an analgesic in labour. *Anaesthesia*, 39: 24-26.
- McLeod, D.D., G.P. Ramayya and M.E. Tunstall, 1985. Self-administered isoflurane in labour. A comparative study with entonox. *Anaesthesia*, 40: 424-426.
- Onody, P., P. Gil and M. Hennequin, 2006. Safety of inhalation of a 50% nitrous oxide/oxygen premix: A prospective survey of 35 828 administrations. *Drug Saf.*, 29: 633-640.
- Rosen, M.A., 2002. Nitrous oxide for relief of labor pain: A systematic review. *Am. J. Obstet Gynecol*, 186: S110-126.
- Scanlon, J.W., W.U. Brown, Jr., J.B. Weiss and M.H. Alper, 1974. Neurobehavioral responses of newborn infants after maternal epidural anesthesia. *Anesthesiology*, 40: 121-128.
- Stefani, S.J., S.C. Hughes, S.M. Schnider, G. Levinson and T.K. Abboud *et al.*, 1982. Neonatal neurobehavioral effects of inhalation analgesia for vaginal delivery. *Anesthesiology*, 56: 351-355.
- Wee, M.Y., M.A. Hasan and T.A. Thomas, 1993. Isoflurane in labour. *Anaesthesia*, 48: 369-372.
- Westling, F., I. Milsom, H. Zetterstrom and B. Ekstrom-Jodal, 1992. Effects of nitrous oxide/oxygen inhalation on the maternal circulation during vaginal delivery. *Acta Anaesthesiol Scand*, 36: 175-178.
- Zelcer, J., H. Owers and J.D. Paull, 1989. A controlled oximetric evaluation of inhalational, opioid and epidural analgesia in labour. *Anaesth Intensive Care*, 17: 418-421.