

Effect of Entonox on reducing the need for Pethidine and the Relevant Fetal and Maternal Complications for Painless LaborAlireza Sharifian Attar¹, Atefe Shirinzadeh Feizabadi², Lida Jarahi³, Laya Shirinzadeh Feizabadi⁴, Shima Sheybani⁵

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Type of article: Original**Abstract**

Background: Pain relief during labour is one of the major concerns in obstetrics; severe labor pain causes fear of the next pregnancy, and interferes with the mother's family relationship.

Objective: The aim of this study was to evaluate the analgesic effects of Entonox during labor on reducing the need for pethidine (Meperidine) and fetal-maternal complications.

Methods: This double-blind randomized clinical trial was conducted on pregnant women who were candidates for vaginal delivery in Educational Hospitals of Mashhad University of Medical Sciences, Iran between January 2014 and November 2015. After entering into the inactive phase of labor, participants were randomly allocated to receive inhaled Entonox gas (n=200) or inhale Oxygen (n=200) as a control group. Mothers inhaled the gas at commencement of pain, and ceased as soon as the pain diminished, up to the end of the second stage of labor which was the neonate's birth. Main outcomes were pain score based on NRS (numerical rating scale), duration of delivery, required pethidine, maternal complications and satisfaction during labour. Chi-square and Independent T-test were used via SPSS for data analysis and P-value less than 0.05 was considered statistically significant.

Results: Four-hundred pregnant women with a mean age of 26.4±5.9 years were studied. Complications such as nausea, vomiting, dizziness, and drowsiness were reported in 25% of the Entonox group and 23% in the control group (p=0.640). Mean of pain severity score during labor in the Entonox and control groups was 4.5±1.2 and 5.2±1.4, respectively (p<0.001). Pethidine requirement, significantly was lower in the Entonox group (31.6±11.8 versus 35.7±12.4; p<0.001).

Conclusion: In our study, Entonox significantly reduced pain during delivery without significant increase in maternal and neonatal complications.

Trial registration: The trial is registered at the Iranian Clinical Trial Registry (IRCT.ir) with the IRCT identification number IRCT2015102713159N6.

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Keywords: Entonox, Analgesia, Obstetrical, Pethidine, Narcotics, Inhalation

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1. Introduction

Labour pain is one of the most painful experiences a human can endure. So much so, that fear of it has increased the rate of delivery by cesarean section, which is associated with particular problems and side effects when carried out without appropriate indication (1). The three basic principles in delivery are labor pain relief in midwifery, using an easy and safe method, and fetus homeostasis maintenance. Every mother who uses any form of painless delivery method should be precisely controlled and monitored (2). Entonox is a mixture of oxygen and nitrous oxide in equal proportions of 50-50 which its use is the highest among inhaled analgesics in the United States, and is used by 60% of women during labor (3). Due to easy use of Entonox, it can even be used at home with a mask (3-4). To gain the maximum analgesic benefits of this gas, the patient is required to be properly trained. Analgesia caused by inhaling Entonox is established within 30 seconds and the maximum effect is reached in about 2 minutes. Entonox affects the central nervous system and increases the secretion of endorphins leading to analgesia, relaxation and euphoria (4, 5). Since Entonox is quickly excreted within the respiratory system, it seems to have no effect on the fetus (6). Entonox can also be used in wound suturing, postoperative pain control, wound debridement and changing burns dressings. This analgesic in labor pain control leads to painless vaginal delivery (7). Use of Entonox, despite appropriate analgesic effect in various stages of delivery, has no effect on the neonate's Apgar score and postpartum hemorrhage (8). Given the high rate of cesareans in Iran and the fact that the fear of labor sometimes results in selection of cesarean section (9), it is recommended that methods in which vaginal delivery can be performed successfully without pain or complications are sought. One of the ways which helps us is to use Entonox which unfortunately is not routinely used, due to lack of knowledge about it. Entonox can reduce the pain of natural vaginal delivery, increase cases of vaginal delivery and reduce unnecessary caesarean sections and the need of pethidine. Therefore, according to the research priorities of painless delivery in our hospital, in addition to the evaluation of the effects of Entonox on labor pain intensity, the current study aimed to assess the effects of Entonox on mothers' hemodynamic, neonates' Apgar, blood oxygen saturation, umbilical cord PH after birth, and also need of pethidine, and finally the incidence of adverse effects such as nausea, vomiting, dizziness, and drowsiness.

2. Material and Methods

2.1. Research design and setting

This double-blind clinical trial study was performed on pregnant women who were candidates for vaginal delivery in three main referral teaching hospitals of Mashhad University of Medical Sciences, Mashhad, Iran between January 2014 and November 2015.

2.2. Sampling and sample size determination

The sample size was an estimated 210 patients for each group, considering $\text{Alfa} = 0.05$, $\text{Beta} = 0.2$, $Z_{1-\alpha/2} = 1.96$, $Z_{1-\beta} = 0.84$, $P_1 = 0.80$, $P_2 = 0.68$, $P = 0.74$. Based on aforementioned information the sample size was measured as 400 divided in two equal groups. Final samples were selected based on simple random sampling methods (Figure 1).

2.3. Randomization, allocation and blinding

By using random number tables, the mothers were randomly allocated to one of the two groups: Entonox: intervention group or Oxygen: control group. The surgeons were blind to the groups of intervention and just one research assistant was aware of precipitants group. Moreover, patients and statistician were also blind to the types of interventions.

2.4. Selection criteria

Nulliparous women aged 18-40 years, term pregnancy (37-42 weeks), singleton, normal fetus, no medical and midwifery complications of mother (heart problems or other internal diseases), no use of other anesthesia or analgesia drugs, cephalic presentation, no restrictions for Entonox gas inhalation (respiratory diseases, pneumothorax, history of head trauma), having a dilatation of 4 cm at the beginning of the active phase of delivery when entering into the study, and normal fetal heart pattern were included in this study, and patients with any complication during childbirth, lack of consent to enter the project, and those who required cesarean delivery were excluded from the study.

2.5. Data collection

A check list was used for data collection. At the beginning of admittance to the hospital, after the standard monitoring of mothers' vital signs including heart rate, pulse oximetry, blood pressure and respiratory rate, fetal heart rate was also measured and recorded in checklist as well as maternal primary vital signs.

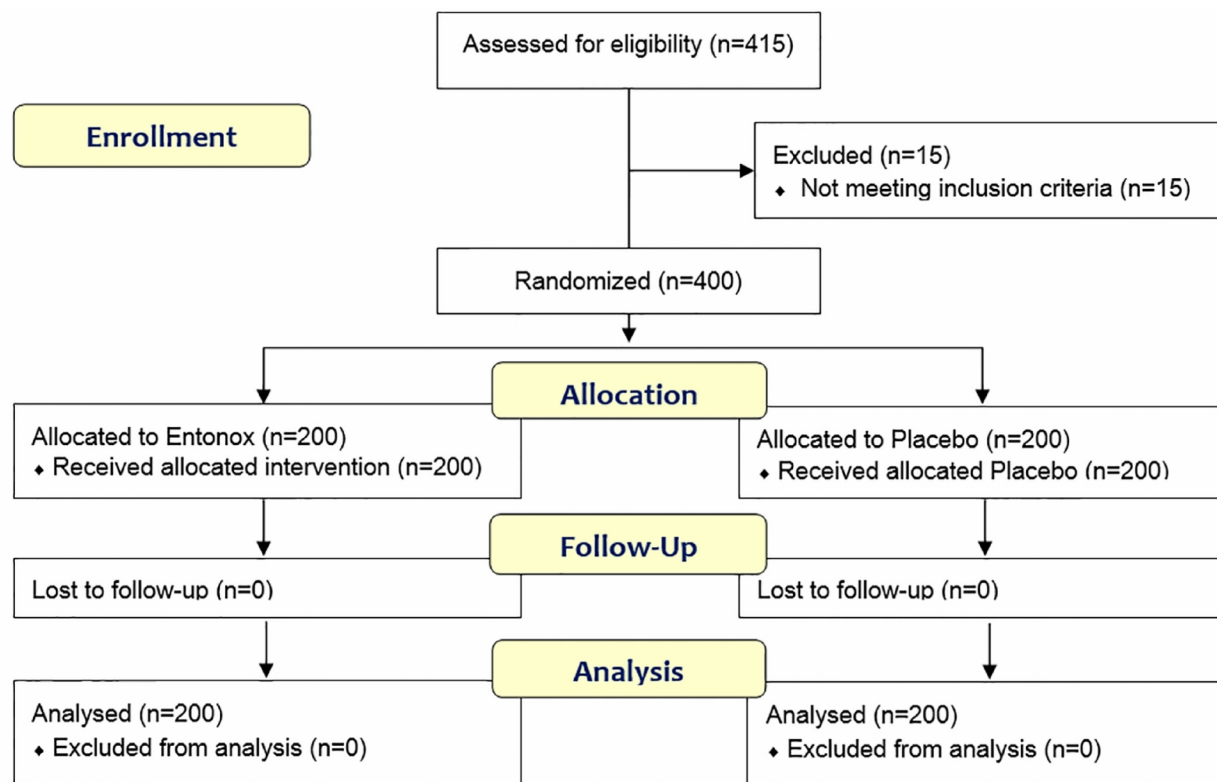


Figure 1. Follow-up diagram of patients (According to consort statement)

2.6. Interventions

The Entonox group received inhaled gas containing 50% oxygen and 50% nitric oxide and the Oxygen group received 4-6 lit/min oxygen only. After entering the active phase of labor (cervical dilatation of 4 cm), both groups were given the masks of which the intervention group inhaled Entonox and the control group inhaled oxygen. Mothers began inhaling through the masks at the beginning of pain, and as soon as the pain receded, the gas inhalation ended. Mothers would frequently receive gas up to the end of the second stage of labor which was neonate's birth. The patients were frequently controlled by an anesthesia assistant. If (NSR>4), 0.5 mg/kg, intravenous pethidine was administered for patients of the two groups in severe pain, and was recorded.

2.7. Outcomes

Pain intensity and maternal hemodynamics status (while receiving gas, and recorded every fifteen minutes), fetal heart rate, duration of the active phase and second stage of labor, 1 and 5 minutes Apgar score, infant's saturation (by pulse oximetry), and infant's cord pH (by arterial blood gas analysis after birth) was recorded and compared between the two groups. Also, the need for additional pethidine (in case of NSR >4) in both groups during childbirth was recorded. In addition, any adverse effects such as nausea, vomiting, dizziness, or drowsiness was mentioned in our check list and compared between the two groups.

2.7.1. Pain assessment

Pain assessment scale was numeric scale rating (NRS). Pain intensity was measured using the numbers of 0 to 10 that 0 represents complete analgesia and 10 represents the maximum pain that can be imagined.

2.7.2. Satisfaction

In our study, satisfaction level was studied in two main categories; complete satisfaction and relative satisfaction. Patients were assumed to be completely satisfied if there was no nausea, vomiting, dizziness drowsiness, or intolerance during and after interventions. On the other hand, they were assumed relatively satisfied, if there were any degree of the mentioned parameters.

2.8. Research ethics

After approval by the ethics committee of Mashhad University of Medical Sciences (Code: 966778) and registration in IRCT system (IRCT2015102713159N6) and obtaining the written consent of mothers, this study began in maternities of Mashhad University Educational Hospitals. In case of appearance of any gas inhalation

related complications, interventions were stopped and were recorded in the checklist, and then when the complication disappeared, the mask was again used, if it was needed.

2.9. Statistical analyses

Statistical analysis was performed using SPSS software version 16. For nominal variables, chi-square test was used and if needed, Fisher's exact test was performed. Kolmogorov-Simonov was used to determine normality of distribution. For comparative dependent data, paired T-test (parametric) and if non-parametric, Wilcoxon test were used. For comparing the independent data, independent-samples t-test (parametric) was used and if non-parametric, Mann-Whitney U test was used. In all measurements p-value less than 0.05 was considered statistically significant.

3. Results

In this study, 400 women with mean age of 26.4 ± 5.9 years, 200 in control (Oxygen) and 200 in intervention group (Entonox) were studied. The frequency of age groups <18 years, 18 to 30 years, and > 30 years was 3%, 72.2% and 24.8%, respectively. The mean gestational age was 38.7 ± 2.6 weeks. The mean of pain severity in total of patients when referring was 7.7 ± 1.7 . Two groups were homogenous according to maternal age, mother's pain severity and vital signs at the time of study entrance (Table 1). Results revealed that, patients in the Entonox group experienced less pain ($p = <0.001$) and they also had less duration of delivery in the first ($p = <0.001$) and second ($p = 0.004$) stage (Table 2). In addition, the required dosage of pethidine needed during labor was significantly lower in the Entonox group ($p = <0.001$) (Table 2). However, there was no significant difference between the two groups in terms of Neonate's Apgar scores and artery oxygen saturation (Table 2). The incidence of complications of nausea, vomiting, dizziness and drowsiness were observed in 24.5% of the Entonox group patients and 23% of Oxygen group patients, but the difference was not statistically significant ($p = 0.640$) (Table 3). In Table 3, the frequency of complications and maternal satisfaction of analgesia methods were compared.

Table 1. Comparison of baseline maternal characteristics between two groups of Entonox and Oxygen intervention

Variables, mean \pm SD	Oxygen (n = 200)	Entonox (n = 200)	p-value
Maternal age (year)	26.9 \pm 5.7	26 \pm 6	0.138
Pain severity when entering to the study (score)	7.74 \pm 1.7	7.76 \pm 1.7	0.089
Mother's systolic blood pressure (mmHg)	98.8 \pm 5.8	99.5 \pm 4.8	0.261
Mother's diastolic blood pressure (mmHg)	62.9 \pm 9	68.4 \pm 3.8	0.248
Maternal pulse rate (min)	86.3 \pm 8.1	86.9 \pm 8	0.663
Maternal respiratory rate (min)	13.9 \pm 3.2	14 \pm 1.1	0.678
Maternal artery oxygen saturation (%)	97.5 \pm 1.4	97.9 \pm 0.6	0.137

Table 2. Comparison of maternal and neonatal outcomes between two groups of Entonox and Oxygen intervention

Variables, mean \pm SD	Oxygen (n = 200)	Entonox (n = 200)	p-value
Pain severity during labor (score)	5.2 \pm 1.4	4.5 \pm 1.2	<0.001
Duration of delivery first stage (min)	150.5 \pm 69.2	103.4 \pm 56.6	<0.001
Duration of delivery second stage (min)	25 \pm 14.1	21.9 \pm 14	0.004
Needed pethidine during labor, mg/dl	35.7 \pm 12.4	31.6 \pm 11.8	<0.001
Neonate's first Apgar score	8.7 \pm 0.6	8.7 \pm 0.7	0.507
Neonate's fifth Apgar score	9.7 \pm 0.5	9.6 \pm 0.7	0.343
Neonate's cord Apgar score	7.32 \pm 0.77	7.33 \pm 0.076	0.116
Neonatal artery oxygen saturation (%)	96.5 \pm 2.9	96.4 \pm 2	0.133

Table 3. Comparison of the frequency of complications and maternal satisfaction of analgesia method

Variables, n (%)		Entonox (n = 200)	Oxygen (n = 200)	p-value
Nausea	Negative	192 (96)	183 (91.5)	0.097
	Positive	8 (4)	17 (8.5)	
Vomiting	Negative	194 (97)	195 (97.5)	0.999
	Positive	6 (3)	5 (2.5)	
Dizziness	Negative	182 (91)	181 (90.5)	0.999
	Positive	18 (9)	19 (9.5)	
Drowsiness	Negative	187 (93.5)	189 (94.5)	0.674
	Positive	13 (6.5)	11 (5.5)	
Satisfaction	Complete	134 (67)	155 (77.5)	0.019
	Relative	66 (33)	45 (22.5)	

4. Discussion

Pain relief is one of the main parts of midwifery, as one of the benefits of labor at the hospital is providing more technical pain relief. Severe labor pain can cause long-term emotional disturbance for a mother, and affects her mental health and has a negative impression on maternal-neonatal relationships in the first critical days after delivery. Moreover it might interfere with family relationships by causing fear of next pregnancy (10). Labor pain also reduces oxygenation of the fetus and subsequently leads to abnormal fetal heart rate patterns and decreased Apgar score, and this increases the need for obstetrical interventions and its relevant complications. Fear of labor pain is one of the main reasons of high demand for cesarean section (11). Due to the fact that delivery is a physiological process and promotion of natural vaginal delivery is considered as one of the principal policies of the health care systems, this important goal can be achieved by reducing labor pain. To reduce labor pain, we should resort to safe and secure methods for mother and fetus which, while are effective, do not cause interference with the labor process, maternal alertness or straining reflex and the mother's physiological functions (12). One of these methods is inhaled analgesia using Entonox gas (a mixture of 50% oxygen and 50% N₂O). The benefits of Entonox are that they are fast acting, give rapid clearance from the body, there is no need for sophisticated and expensive devices, no need for highly-skilled personnel, and finally mothers have greater tolerance (13-15). For nearly fifty years, Entonox has been approved for pain relief, and is used especially in England. Most studies in Europe and the United States have compared Entonox as a standard method with other relieving methods or medicines, rather than evaluate its effects on labor pain (16-18). In the present study, complications were observed in 24.5% of patients in the Entonox group and 23% of patients in the oxygen group, but the difference was not statistically significant (P=0.640). The most common side effects included nausea, vomiting, dizziness, and drowsiness that often make Entonox intolerable for parturient (16). In a review article, Entonox compared with other analgesia methods caused more nausea, vomiting, dizziness, and drowsiness (17). In the study of Rezaeipour, some possible side effects caused by inhaling Entonox, such as drowsiness and dry mouth were more commonly observed in the intervention group than the control group (P<0.001), but no statistically significant differences were observed in other complications (18). In our study, dizziness and drowsiness were slightly more common in patients of the Entonox group, but the difference was not statistically significant (P=0.744), and the most likely cause of these complications in the oxygen group was higher need to use pethidine. A study in 2011 showed that Entonox is safe for mothers and neonates, and people working in the environment if it is used with oxygen at a proportion of 50:50 (19). In the study of Pazande, Entonox had no negative effects on the mother and fetus (20). In our study, the hemodynamic changes in mother and infant during labor, were not significantly different between the two groups, which confirmed the safety of Entonox for mother and neonate. In the study of Zare, the mean length of first stage of delivery was shorter in the Entonox group than the control group, but the mean length of the second stage of delivery showed no significant difference between case and control groups (21). The study of Parashi showed that nitrous oxide reduces labor duration (22). In our study, the mean duration of the first and second stage was significantly lower in the Entonox group than the oxygen group. It seems that inhalation of Entonox to reduce labor pain, also decreases the labor duration. It is known that pain increases production of catecholamines and decreases blood supply to the uterus and uterine contractions. The subsequent weakness and ineffectiveness of these contractions result in inappropriate delivery progress. In the study of Pazande, the mean of pain intensity was significantly lower in the Entonox group than other methods (23). The study of Parashi showed that nitrous oxide reduces labor pain (24). In the study of Agah, pain severity was not significantly different in the groups of continuous and discontinuous use of Entonox gas (22). In our study also, the mean pain intensity during labor was 4.5 ± 1.2 in the Entonox group and 5.2 ± 1.4 in the oxygen group, and this difference was statistically significant. In our study, Entonox was administered as

discontinuous for the patients. Entonox gas has no effect on uterine contractions and does not cause malignant hyperthermia. Its side effects included nausea, vomiting, dizziness, and low reward. In terms of blood oxygen saturation for mothers and infants during delivery, the results of present study showed that SpO₂ was not less than 90% in any of the methods, and that is similar to the study of Masoudi (25). In our study, maternal hemodynamic findings were not significantly different between Entonox and oxygen groups. But in a study in Lorestan, hemodynamic findings were lower in the Entonox group than other groups (25). One of the complications of acute/severe pain caused by response of sympathetic nervous system, is increased pulse rate and blood pressure; the cause of difference between our study and other studies may be due to differences in the consumption of pethidine, because the oxygen group received pethidine during pain. In a study in Tehran, Iran, no statistically significant difference was observed between the two groups in first and fifth minute Apgar score (22). In our study, the mean first and fifth minute Apgar scores in the Entonox group were not statistically significant. Therefore, it seems that Entonox decreases maternal pain and severe anxiety and consequently reduces the incidence of abnormal fetal heart rate and leads to an improved Apgar score. In the study of Jafari, the use of Entonox increased maternal satisfaction (26). In our study, none of the patients were dissatisfied from the used analgesia methods. Full satisfaction was observed in 53.6% of the Entonox group and 46.4% of the oxygen group, and relative satisfaction in 40.5% of the Entonox group and 59.5% of the oxygen group was observed, and this difference was statistically significant. According to the study findings, it seems that the use of Entonox is an effective and safe method for labor pain relief which is associated with increased maternal satisfaction, therefore, delivery satisfaction has a direct relationship with pain relief and lack of severe side effects of Entonox. Several studies have indicated that 80% of patients tend to reuse Entonox in the next pregnancies (27-28). In order to reduce the rate of caesarean sections and encourage parturient women to vaginal delivery, it is recommended that the benefits of Entonox be provided in training sessions during pregnancy, for mothers or in the form of print material in doctors' offices and clinics; and this method might be an important step in improving the health of mothers and children. One of the minor limitations of this study was a short duration of study follow-up. It would be more advantageous if a follow-up of our patients could be carried out for at least one week after their discharge.

5. Conclusions

In our study, Entonox significantly improved labor pain during delivery without significantly increasing maternal complications. The three main principles of pain relief in obstetrics which are simplicity, safety and fetus homeostasis maintaining are considered. Since the use of Entonox, especially in intermittent form, reduces labor pain without causing complications for the mother, and also is associated with more maternal satisfaction, this gas can be used during labor in order to reduce the number of cesarean deliveries occurring due to labor pain and as a result, the complications of surgery and anesthesia and its high costs can be decreased.

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Trial registration:

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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