ORIGINAL RESEARCH

A Randomized Controlled Trial of Entonox and Oxygen in Labor Analgesia

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Abstract

Background and objectives: Labor pain is a severe form of pain experienced by a woman, leading to tremendous stress. Several routes for labor analgesia have been tried. Entonox is a premixed homogenous gas mixture of nitrous oxide and oxygen in the ratio of 50:50 providing conscious sedation in obstetrics during labor. It is a safe and effective analgesia for obstetrics use due to its properties of rapid onset, short half-life, and rapidly disappearing symptoms on withdrawal of the gas. Therefore, we aimed to evaluate the effect of Entonox on the severity and relief of labor pain during its various stages and its associated maternal or fetal side effects.

Materials and Methods: A prospective randomized controlled trial (RCT) of 200 term pregnant mothers reporting in labor over a period of 2 months who were randomized into Entonox group and placebo oxygen control group was included in the study. Administration of both gases was done, and the pain scoring was recorded. Maternal and fetal complications were noted.

Results: The intensity of labor pain was significantly lower in Entonox group as evident by lower pain scoring values. The mean duration of the active phase of labor in the Entonox group was comparable to the oxygen group. Maternal and fetal side effects were not significant in both groups. The mode of delivery is also comparable in both groups.

Conclusion: Entonox usage in labur analgesia is a safe, effective, and inexpensive method of relieving labor pain, achieving immense patient satisfaction and making labor a pleasurable experience.

Keywords: Entonox, Labor analgesia, Labor pain, Nitrous oxide.

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Introduction

Labor pain associated with childbirth is considered to be one of the life-changing experiences of a woman which she is usually told to accept as there seems to be no other option left but to bear the pain for the sake of her unborn child. Categorized at the top of the pain rating scale, being severe or intolerable, it leads to tremendous stress and anxiety to the mother. Labor pain has been described to be a complex interaction between physiological and psychological aspects, as well as excitatory and inhibitory aspects.[1] It has also been demonstrated to have some harmful effects on the mother and baby. It is accompanied in the mother by physiological stress, hyperventilation, and respiratory alkalosis, along with psychological effects like frustration and exhaustion. The release of catecholamines may lead to vasoconstriction and fetal distress.[2] There may be increasing demands for cesarean section on the pretext of inability to bear the pain. Several routes for labor analgesia have been tried, such as intravenous analgesics, inhalation therapy, acupuncture, pudendal nerve block, and epidural anesthesia.[3,4] However, all the methods should be safe for both the mother and the fetus. Of these, Entonox is an analgesia gas that is a premixed homogenous gas mixture of nitrous oxide and oxygen in the ratio of 50:50 compressed in a cylinder, and it is a noninvasive method of analgesia providing conscious sedation for obstetric purposes.

Historically in 1881, first invented by Klikovich,[5] nitrous oxide also known as laughing gas when mixed with oxygen forms a noninflammable, tasteless, odorless, and colorless gas that may be an ideal choice for pain during contractions as its inhalation can be synchronized with each contraction. Various studies have proved Entonox to be a safe and effective analgesia for use due to its properties of rapid onset, short half-life, and rapidly disappearing symptoms on withdrawal of the gas. It is a patient-friendly method, as the woman controls when and how much she inhales, with her mobility during labor not being compromised, along with the main benefit of relief of symptoms of pain. There are minimal systemic side effects that do not persist once gas inhalation is stopped. There is no major side effect on the fetus too. The main side effects in the mother may include excessive drowsiness, dizziness, nausea and vomiting, dry mouth, buzzing in the ears, rarely "pins and needles" or numbness, dreams, and a hazy memory of labor.[6,7]

The main mechanism of action is based on its analgesic and anxiolytic properties. The analgesic effect of nitrous oxide is similar to opioids, and, like morphine, may affect multiple spinal cord neuromodulators. Nitrous oxide also has anxiolytic effects similar to that of benzodiazepines involving the γ-amino butyric acid type A (GABAA) receptor. The anesthetic effect of nitrous oxide

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may be due to its actions at GABAA receptors and N-methyl-D-aspartate receptors.[8]

The use of Entonox may not remove pain totally but will reduce it to make labor pain bearable. Therefore, we aimed to evaluate the effect of Entonox on the relief of labor pain during its various stages along with its maternal or fetal side effects.

Materials and Methods

Study Design

This was a prospective randomized controlled trial (RCT). The trial group was of those receiving Entonox (group A), and the placebo control group was of those receiving oxygen (group B). It was a single-blinded trial with blinding of patients, and randomization was performed by tossing a coin, with each patient being handed sealed envelopes. Informed consent was obtained from the patients. The institutional ethical committee clearance was taken before beginning the trial. Number of sampling was determined by a confidence coefficient of 95% and power of 80%.

Study Period

The study was conducted over 2 months from May 1, 2020, to June 30, 2020, at a referral center.

Study Population

A total number of 200 women with term pregnancies were recruited and randomly divided into two groups—the trial and control, as per the inclusion and exclusion criteria.

Inclusion Criteria

- Term pregnancies from 37 to 41 weeks of period of gestation
- Singleton pregnancy
- No maternal or fetal high-risk factors.

Exclusion Criteria

- Multiple pregnancies.
- Pre-existing chronic illness in mother.
- Presence of meconium-stained liquor.
- Polyhydramnios or oligohydramnios.
- Macrosomia
- Maternal contracted pelvis
- Previous cesarean section
- Fetal heart rate (FHR) abnormalities
- Contraindications of Entonox usage, including head injury and severe asthma
- Inability or unwillingness of patients

Methodology

All antenatal cases meeting the inclusion criteria were approached for inclusion in the study. Patients giving consent for participation underwent randomization. In active phase of labor, pain intensity was analyzed using the WongBaker Faces Pain Rating Scale values. The Wong–Baker Faces Pain Rating Scale is a pain scoring system that was developed by Donna Wong and Connie Baker. The scale shows faces varying from a happy face at 0, which represents "without hurt," to a crying face at 10, which represents "hurts like the worst kind of pain." Based on the faces and written descriptions, the midwife chooses the face that best describes their level of pain.

In both groups, gas inhalations were introduced intermittently from the active phase of the first stage of labor (cervical dilatation of 4 cm and effacement of 40–50%) up to the delivery of the newborn. The cervical dilatation was measured by pervaginal examination every 2 hours. Entonox cylinder was made available in the labor room. The self-usage of Entonox gas was done via a univalved face mask. The Entonox administration began with the onset of the contraction pain and continued till the end of the contraction pain. The monitoring of contraction frequency and intensity, FHR, and mother's physical signs like blood pressure monitoring using a digital apparatus and SpO_2 using a pulse oxymeter were done as routine for both the groups by midwives. For the control group in the labor room, only oxygen inhalation was initiated at the onset of pain with each contraction. Women were unaware of the nature of the gas inhaled; however, the researcher was not blinded for the type of gas inhalation used. The midwives were trained earlier, filled up the questionnaire, and monitored the labor using a partograph. All these laboring patients were monitored using cardiotocography at the onset of the active phase of labor.

Method of Analysis

The present study was a prospective RCT. Data were compiled using Microsoft Excel and unpaired *t*-test to find the significance of study parameters between two groups. Finally, statistical analysis was performed by SPSS 17 software, unpaired t-test, and Chi-square test while $p < 0.05$ was considered significant.

Outcome Measures Noted

The parturients were assessed for the intensity of contraction pain by pain rating scale (numerical score 0–10) and side effects in mother or fetus every 10 minutes. Maternal parameters noted were noninvasive blood pressure, maternal heart rate (HR), and oxyhemoglobin saturation (SpO_2). Hypoxia and bradycardia were defined as SpO_2 <90% and HR <50, respectively. FHR and Apgar scores at 1 and 5 minutes in newborn were recorded. Apgar scores of <7 in 5 minutes were considered significant.

Results and Observations

In this study of 200 patients at term in labor, 59% of patients in the Entonox group (group A) were primigravidae and 41% multigravidae. In the oxygen group (group B), 58% were primigravidae and 42% were multigravidae. Out of these, most of the women (159 women) were in the age-group of 20 to 30 years as compared to the 41 women in the age-group of 30 to 40 years. After administering Entonox to laboring patients at various stages of cervical dilatation, the pain relief by WongBaker Faces Scale was charted.

The mean score at 4 cm dilatation in the Entonox group (A) was 6.85 as compared to 8.00 in the oxygen group (B) as depicted in Figure 1, which was not statistically significant. Hence, the pain relief in early active labor was not very evident (*p*-value of 0.1158).

The mean pain score at 6 cm of cervical dilatation in the Entonox group was 5.86 as compared to 8.64 in the oxygen group as depicted in Figure 2, which was statistically significant (*p*-value of 0.00 00).

Similarly, at 8 cm of cervical dilatation in the Entonox group, the mean score of pain was 4.99 as compared to 9.08 in the oxygen group, which showed significant relief in the late stages of the active phase of labor with the use of Entonox, as depicted in Figure 3 (*p*-value of 0.0000). During the second stage of labor, at

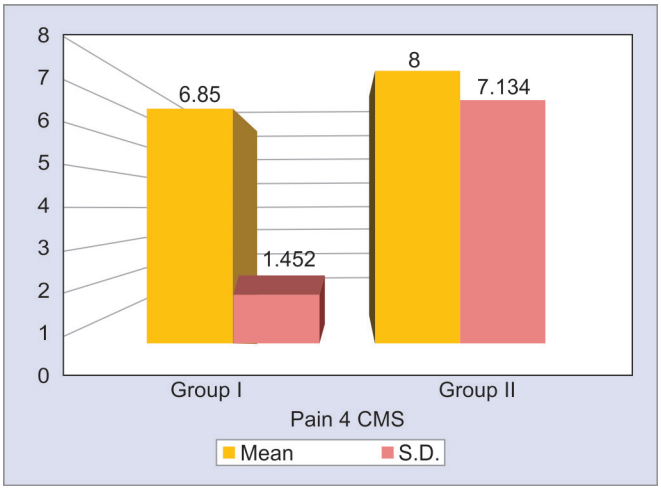

Fig. 1: Pain scoring at 4 cm of cervical dilatation

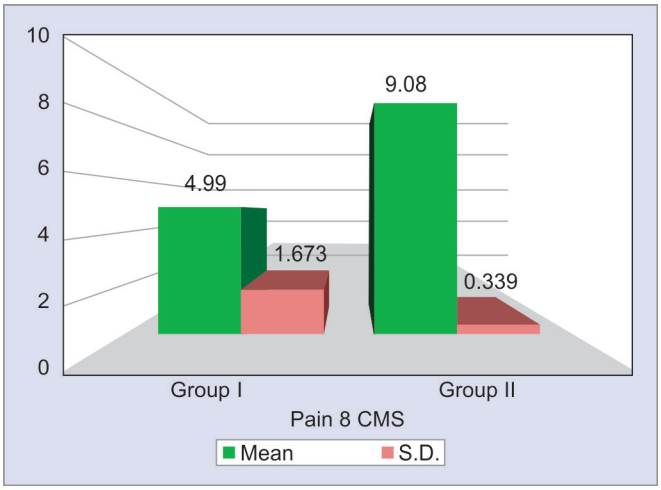

Fig. 3: Pain scoring at 8 cm of cervical dilatation

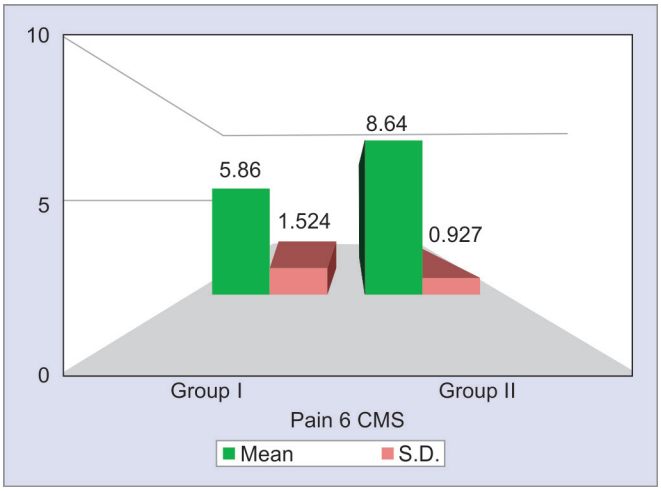

Fig. 2: Pain scoring at 6 cm of cervical dilatation

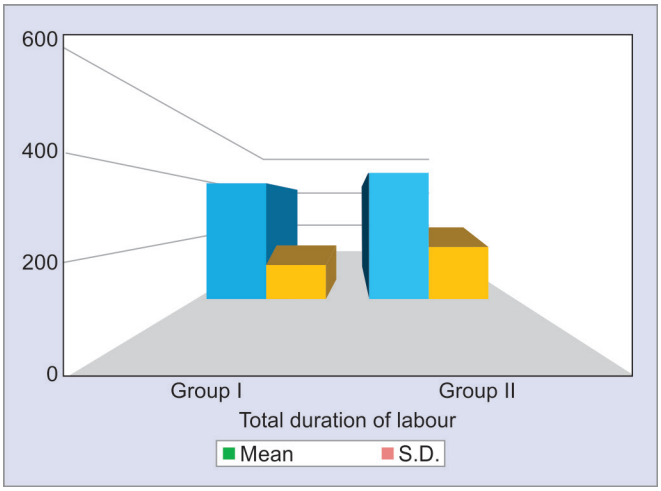

Fig. 4: Total duration of labor

full dilatation, the relief of pain was also significant in the Entonox group, mean score of 4.49 in Entonox versus 9.13 in oxygen.

The average pain scoring of less than or equal to 6, signifying better pain tolerance, was similar in the multigravidae versus primigravidae (56%vs 44%) at 4 cm dilatation, 17 versus 19% at 6 cm dilatation, 22 versus 17% at 8 cm dilatation, and 90 versus 89% at full dilatation with the use of Entonox. Hence, this shows that the pain relief with Entonox is better at the late stages of labor, and the pain relief is the same with primigravidae and multigravidae.

The result of our study showed that the mean duration of the active phase of labor was 389.09 minutes in the Entonox group and 413.52 minutes in the oxygen group, as depicted in Figure 4, and that the use of Entonox did not delay the progress of labor (*p*-value of 0.2555, not significant).

Around 88% in the Entonox group had vaginal normal delivery as compared to 90% in the oxygen group, and 12% in the Entonox group had either assisted instrumental delivery or cesarean section as compared to 10% in the oxygen group. This was not found to be statistically significant (*p*-value—3.651). Thus, there is no increased incidence of cesarean section with the use of Entonox.

Around 19% of the laboring patients in the Entonox group required augmentation with Pitocin as compared to 7% using oxygen. This difference was statistically not significant.

In our study, maternal side effects in the Entonox group were not very significant as compared to the oxygen group. As depicted in Table 1, the majority of our patients had no maternal symptoms in both groups. Three patients in the Entonox group had dizziness as compared to one patient in the oxygen group, which was not statistically significant. Three patients in the Entonox group showed symptoms of nausea. There was no abnormal maternal blood pressure, SpO_2 changes, or changes in the heart rate with the use of Entonox. There was no evidence of uterine atony and associated postpartum hemorrhage with the use of Entonox.

There were also no significant fetal side effects in the Entonox group as depicted in Table 1. One neonate in the Entonox group had birth asphyxia following shoulder dystocia requiring neonatal intensive care unit admission, two had a low Apgar score of less than

Table 1: Maternal and neonatal complications

Complications		*Entonox, %*	*Oxygen, %*
	Nil complications	94	97
Maternal	Dizziness	3	1
	Nausea	3	2
	Nil complications	97	97
Fetal	Birth asphyxia	1	0
	Low Apgar	2	3

7 at 5 minutes as compared to no neonate with birth asphyxia, and three with low Apgar score in the oxygen group.

Discussion

Pain tolerance is variable in most patients. It may be categorized into mild, tolerable, or intolerable depending on the pain perception of the woman.[9] Even the fear of having pain enhances the perception of pain.[10] Labor pain is one of the severe form of pain leading to tremendous physiological and psychological stresses to the woman. In spite of the number of techniques of available labor analgesia, none of them are being routinely used and some may not be as effective. Inhalation of gas is an old method applied in the 18th century that started to be often used for relieving pain since 1934. Entonox with a composition of 50% nitrous oxide and 50% oxygen packed in cylinders was commercially introduced in 1961. The major advantages of Entonox as an analgesic at the time of parturition are its favorable pharmacological profile (fast onset and fast washout of 30–50 seconds) and its ease of administration, as the patient herself controls the delivery.[11] All the relevant literature available shows that it has been widely used in the United Kingdom and the USA, but not regularly used in India. In India, epidural administration of local anesthetic agents and systemic (intravenous or intramuscular) administration of opioids are the two most frequently employed pharmacologic methods of analgesia. This study was done to evaluate the efficacy and safety of Entonox versus oxygen as a placebo such that more women may be made aware of this modality if it proved to be effective.

The current study showed that the intensity of labor pain measured by Wong-Baker Faces Pain score was significantly lower in the Entonox group than that in the oxygen group (p-value <0.001). Similar to our study, Richardson et al. found that among 264 laboring patients using Entonox exclusively, almost 238 women reported a high satisfaction score.[12] A meta-analysis by Sheyklo et al. showed that the satisfaction rate of the mothers in the Entonox group was 57.6% as compared to 21.3% of mothers in the oxygen group showing a high level of satisfaction.[13]

The duration of the active phase of labor in the Entonox group was comparable to the oxygen group in our study. Results of a study by Attar et al. revealed that patients in the Entonox group experienced less pain ($p \leq 0.001$) as compared to the oxygen group and also had less duration of delivery ($p \leq 0.001$).[14,16] Most of the parturients delivered vaginally with no additional requirement of augmentation with Pitocin in the Entonox group as also was noted in the study by Agah et al.[15]

In the present study, the majority of the laboring mother did not have any significant maternal side effects. Three patients in the Entonox group had nausea and dizziness as compared to one patient in the oxygen group who had dizziness. In a study by Naddoni et al.,[16] the subjects receiving Entonox experienced more adverse side effects compared to those receiving oxygen as follows: 61.63% of the participants felt sleepiness, 9.30% had dry mouth, 50% had lethargy, 26.74% had blurred vision, 30.23% felt tingling in their limbs, 36% faced vomiting, 23.26% had a headache, and finally, 31.40% had an uncomfortable feeling. In the study done by Foji et al.,[17] the most commonly observed side effect after receiving Entonox was lightheadedness 63.3%, nausea 13.3%, vomiting 1.7%, tiredness 28.3%, a dry mouth 17.7%, tingling of the fingers 5%, sleepiness 68.3%, and tinnitus 1.7%. Also in our study, there were no changes in maternal SpO_2 and heart rate with Entonox. This was similar to the research done by Parsa et al., where no significant variance was found between Entonox and oxygen groups, including the rate of the cesarean, maternal blood pressure, HR, FHR, and Apgar scores.[18]

The current study revealed no differences in 1- and 5-minute Apgar scores between groups. This same result was noted by Naddoni et al.[16] Hence, our study has revealed that inhaled Entonox may be beneficial for those women in labor who want to have pharmacological pain relief, without invasive methods, and has minimal to no effect on Apgar score of the newborn. With a shift in our thought processes of providing pain-free labor, we should propagate greater use of Entonox. Due to the small sample size of our study, a generalization cannot be made about the use of Entonox. Also, the nonavailability of pain perception data with respect to body mass index is a limitation. Hence, there is a requirement for a wider use of Entonox in the labor rooms to provide better data with regard to the efficacy of Entonox.

Conclusion

In our study, Entonox significantly provided labor pain relief without increasing maternal and fetal complications. Simplicity, safety, and maintaining fetal well-being, the three main principles of pain relief in obstetrics, were 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. More women should be educated about the use of Entonox as an option for pain relief in labor.

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