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A Randomized Controlled Trial Comparing Use of Enthonox With Pethidine for Pain Relief in Primigravid Women During the Active Phase of Labor

Noshin Mobaraki,[1] Mahzad Yousefian,[2,*] Solmaz Seifi,[1] and Mehran Sakaki[3]

[1]Department of Obstetrics and Gynecology, Ardabil University of Medical Sciences, Ardabil, Iran
[2]Department of Anesthesiology, Ardabil University of Medical Sciences, Ardabil, Iran
[3]Department of Pathology, Ardabil University of Medical Sciences, Ardabil, Iran

[*] *Corresponding author*: Mahzad Yousefian, Department of Anesthesiology, Ardabil University of Medical Sciences, Ardabil, Iran. E-mail: dr_mahzad@yahoo.com

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Abstract

Background: The use of pain-relieving drugs during labor is now part of standard care in many countries throughout the world. Each method of pain relief has its own risks and benefits, variations in effectiveness, and availability and acceptability.
Objectives: This study aimed to assess the efficacy and safety of intramuscular pethidine as an analgesic during labor by comparing it to inhaled 50% nitrous oxide (Entonox).
Methods: In this clinical trial study, 100 women who expected to have a natural childbirth were observed. The inclusion criteria for this study were the commencement of spontaneous labor pain along with appropriate maternal and fetal indications for vaginal delivery. By using random numbers, each subject was randomly allocated to one of two groups, with one group using Entonox and the other receiving an intramuscular injection of 0.5 mg/kg of pethidine for pain relief. The intensity of labor pain experienced by the subjects and the outcomes of the deliveries were collected with questionnaires.
Results: The average pain scores in the Entonox and pethidine groups were 3.94 ± 1.4 and 5.6 ± 1.1, respectively, 30 minutes after intervention ($P = 0.001$), but there was not a significant difference in the severity of the pain (5.06 ± 1.4 and 4.7 ± 1.1 for the Entonox and pethidine groups, respectively) between the subjects in each group 60 minutes after the intervention ($P = 0.592$). No significant differences were seen in the duration and interval of uterine contractions, maternal complications, Apgar scores, and the duration of the first and second stage of labor between the two studied groups ($P > 0.05$). An analysis of the pooled risk differences showed that none of the side effects investigated were significantly different between the two groups except for mouth dryness, which was significantly higher in nitrous oxide users ($P = 0.044$).
Conclusions: Inhaled nitrous oxide seems to give better pain relief in the short term compared to a single dose of pethidine. Entonox, which is more convenient to administer than an intramuscular injection of pethidine, is also regarded as safe both for mothers and neonates.

Keywords: Entonox, Labor Pain, Pethidine

1. Background

Pain is a major public health issue throughout the world and represents a major clinical, social, and economic problem (1, 2). Labor pain is one of the most acute pains that women experience during their lives (3). The psychological effects of severe pain should not be ignored, especially when they are associated with adverse maternal or fetal outcomes.

There are different methods of pain relief used during labor with different side effects and efficacies. One of the most common methods is the inhalation of 50% nitrous oxide (4, 5). Nitrous oxide is an odorless, tasteless, inhaled analgesic (6) that has been found to be an effective analgesic for many women that is safe for both mothers and babies (4). Use of nitrous oxide during labor began in the late 1800s, and Minnitt in England introduced equipment for self-administration in 1934. Nitrous oxide is usually run through a mouth mask intermittently, starting about 30 seconds before each contraction (7, 8). Inhalation of 50% nitrous oxide can significantly decrease anxiety without clinically significant side effects, and its effects are quickly reversible upon discontinuation of inhalation (8, 9).

Pethidine or meperidine hydrochloride was the first synthetic opioid, synthesized in 1932 (9). Systemic pethidine is routinely used throughout the UK for labor analgesia (10, 11). However, systemic opioids lead to some complications for mothers (12, 13) and babies (14). Since pethidine passes through the placenta, pethidine may accumulate in the fetal circulation (8), causing early neonatal respiratory depression and behavioral and feeding problems for up to

six weeks after delivery (14).

2. Objectives

In present study, we aimed to assess the safety of using inhaled 50% nitrous oxide as an analgesic during labor in comparison to intramuscular pethidine among women undergoing normal vaginal delivery.

3. Methods

This study was a randomized clinical trial conducted in Alavi hospital (Ardabil, Iran) in 2015. One hundred pregnant women who were in the initial phase of labor were enrolled in study. The sample size was calculated with a confidence of 95% and a power of 80%.

3.1. Patient Selection

The inclusion criteria for this study were the commencement of spontaneous labor pain along with appropriate maternal and fetal indications for vaginal delivery. The exclusion criteria were the presence of a personality disorder, an addiction, a complicated pregnancy, diabetes mellitus, macrosomia, chronic obstructive pulmonary disease, an unconfident fetal heart rate, valvular heart disease, an upper respiratory tract infection or sinus obstruction, a history of asthma, and contraindications for Entonox and pethidine usage.

By using random numbers, the subjects were randomly allocated into two groups, with one group using Entonox and the other receiving an intramuscular injection of 0.5 mg/kg of pethidine for pain relief.

3.2. Ethics Declaration

The study was reviewed and approved by the Ardabil University of Medical Science Ethics Committee. Information about the study was given comprehensively to all patients. Informed consent was obtained from all patients according to the University Ethical Committee. This study has been registered at www.irct.ir with the code IRCT 201503244256N6.

3.3. Data Collection

A questionnaire to collect information about the patients' demographic characteristics, their severity of pain, the duration of the first and second stage of labor, the duration and interval of uterine contractions, any neonatal and maternal complications, and the side effects of drugs was completed by the researcher through the intervention.

Patients were taught to use an Entonox face mask at the beginning of uterine contractions and to continue deep inspirations at times when there was pain and cramps. Use of Entonox could be started or cut at any moment during labor according to the needs and preferences of the woman.

The pethidine group received an intramuscular injection of 0.5 mg/kg of pethidine. If a patient's pain rated higher than 5 VAS, 0.25 mg/kg of pethidine was injected.

Each patient's parturient pain scored was evaluated according to their VAS score, which was graded from 0 to 10 (0 = no pain and 10 = severe and intolerable pain) once before any analgesic administrations and twice at 30 and 60 minutes after analgesic administration using a structured questionnaire and a subjective labor pain scale (visual-analogue scale).

The vital signs of all parturient were monitored. The main outcomes (pain score, duration of the first and second phase of the labor, and Apgar scores at one and five minutes) were recorded prospectively by one person with one technique. For comparison studies between the two groups, a cervical dilatation of four to five cm was considered the signal of the start of the active phase of labor.

3.4. Statistical Analysis

The results were reported as mean $\pm$ standard deviation (SD) for the quantitative variables and percentages for the categorical variables. The groups were compared using a t-test for the continuous variables and a chi-squared test for the categorical variables. A P value $\leq$ 0.05 was considered to be statistically significant. All the statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) for windows.

4. Results

Of the 107 pregnant women were enrolled in this study, seven were excluded by the exclusion criteria.

The majority of women in this study were in the 21 - 30-year age range. The mean maternal age was 26.2 and 27.2 in the Entonox and pethidine groups, respectively. The demographic data of the participants is summarized in Table 1.

The average pain scores 30 minutes after intervention in the Entonox and pethidine groups were 3.94 $\pm$ 1.4 and 5.6 $\pm$ 1.1, respectively, (P = 0.001), but there was not a significant difference in the severity of the pain between the two groups 60 minutes after intervention (P > 0.05). No significant differences were seen in the duration and interval of uterine contractions, maternal complications, Apgar score, and in the duration of the first and second stage of labor between the two studied groups (P > 0.05). An

Table 1. The Frequency Distribution of the Demographic Characteristics of the Pregnant Women in the Intervention Groups[a]

Characteristics	Entonox (n = 50)	Pethidine (n = 50)	Total Number	P Value
Age, y				
< 20	16 (32)	9 (18)	4 (4)	
21 - 30	29 (58)	34 (68)	63 (63)	
31 - 40	5 (10)	7 (14)	12 (12)	
Habitant				0.099
Village	13 (26)	16 (32)	29 (29)	
City	37 (74)	34 (68)	71 (71)	
Level of Education				0.002
Illiterate	1 (2)	1 (2)	2 (2)	
Junior and Senior High School	27 (54)	29 (58)	56 (56)	
Diploma and University	22 (44)	20 (40)	42 (42)	
Gestation (weeks), mean ± SD	38.86 ± 2.95	38.36 ± 2.11		NS

[a]Values are expressed as No. (%) unless otherwise indicated.

analysis of the pooled risk differences showed that none of the side effects investigated were significantly different between the two groups except for mouth dryness, which was significantly higher in the nitrous oxide users (P = 0.044) (Table 2).

5. Discussion

Nitrous oxide has low solubility in blood and is transported in a solution without binding to protein. Nitrous oxide takes effect rapidly (15) because it spreads rapidly through the lining of the arterial alveolar membrane and is excreted unchanged mainly through the lungs (6). As a result, the effects of nitrous oxide are quickly reversible upon the discontinuation of therapy (16). The recovery time from the effects of nitrous oxide sedation is faster than that of intravenous analgesia (6).

The analgesic effect of pethidine starts within 10 - 20 minutes and lasts two to four hours after being administered intramuscularly (17). The rate of use of parental opioids was between 39% and 56% in various hospital obstetrics units in the United States (10). However, many studies have suggested that intramuscular pethidine may be ineffective at relieving labor pain and that their use may even be unethical and medically incorrect (18, 19).

In this study, pain severity, which was defined according to a patient's VAS score, was significantly lower in patients who received nitrous oxide 30 minutes after intervention, but there was not a significant difference in the severity of pain between the patients in the two groups 60 minutes after intervention.

Research has shown that 80% or more of a 100-mg dose of pethidine administered intramuscularly is absorbed over six hours with a mean time of maximum plasma concentration of approximately 24 minutes. With intramuscularly administered pethidine, analgesia may persist for two to four hours following intramuscular, intravenous, or subcutaneous administration (12).

With an intramuscular pethidine injection, appropriate levels of pethidine still exist in the plasma 60 minutes after intervention. In contrast, Entonox consumption requires more cooperation from patients. With the progression of labor and the exacerbation of pain, participants' cooperation with Entonox use decreases, which might increase a patient's 60-minute pain score compared to their 30-minute score.

No significant changes in the maternal cardiorespiratory parameters were noted with either of the two analgesics. Associated factors and transplacental transmission of the analgesic from mother to fetus can affect the Apgar scores of the babies at birth. The ideal analgesic is one that has no adverse effect on the fetus. In our study, the Apgar scores of the babies at birth were satisfactory, and no significant difference was observed between infant complications and Apgar scores in the two groups.

Abdollahi et al. concluded that intravenous paracetamol was more effective than intramuscular pethidine at relieving labor pain in normal vaginal deliveries (19).

Pasha et al. showed that the use of 50% nitrous oxide caused less labor pain, favorable expectations and experiences, and also greater maternal satisfaction compared with a control group that did not receive gas (20).

Table 2. Descriptive Data of the Entonox and Pethidine Subjects

Characteristics	Entonox	Pethidine	P Value
Duration			
First stage, hour	3.15 ± 1.65	3.65 ± 1.76	0.124
Second stage, minute	33.7 ± 13.2	31.6 ± 7.5	0.124
VAS mean score			
Before analgesia	7.38 ± 2	7.3 ± 1.1	0.812
30 minutes after analgesia	3.94 ± 1.4	5.6 ± 1.1	0.044
60 minutes after analgesia	5.06 ± 1.4	4.7 ± 1.1	0.592
Systolic blood pressure			
Before analgesia	113.33 ± 12.64	114.32 ± 8.52	0.185
After analgesia	115.67 ± 9.12	114.39 ± 8.21	0.067
Duration of uterine contractions			
Before analgesia	39.32 ± 9.12	38.82 ± 7.21	0.12
After analgesia	40.32 ± 6.12	41.32 ± 5.45	0.08
Interval of uterine contractions			
Before analgesia	120.72 ± 32.61	129.35 ± 8.66	0.34
After analgesia	123.37 ± 46.47	118.39 ± 3.67	0.09
Apgar score			
First minute	9 ± 0.1	8 ± 9	0.465
Fifth minute	9.91 ± 0.4	9.88 ± 0.2	0.598

An analysis of the pooled risk differences showed that none of the side effects investigated were significantly different between the two groups except mouth dryness, which was significantly higher in nitrous oxide users.

As a result, inhaled nitrous oxide seems to give better pain relief in the short term compared to a single dose of pethidine. Since Entonox is more convenient to administer, it is also regarded as safe for both mothers and neonates.

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Footnotes

Authors' Contribution: Noshin Mobaraki conducted the study and supervised the project, Mahzad Yousefian supervised the project and wrote the thesis and manuscript, Solmaz Seifi collected the study data, and Mehran Sakaki contributed to the study design.

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