ENTONOX VERSUS PETHIDINE FOR PAIN RELIEF DURING THE ACTIVE PHASE OF LABOR

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ABSTRACT

Background

Labour pain is one of the acute severe pains women suffer during their lives. Various methods have been tried to manage it.

Objectives

The aim was to compare analgesic effects and outcomes of Entonox versus Pethidine for labour pain.

Patients and Methods

The non-blinded Randomised clinical trial was performed on 221 pregnant women admitted to the Labor Ward of Sulaimani Maternity Teaching Hospital from January 2020 to January 2021. Women were randomly allocated the group I of 111 pregnant women who received Entonox and group II of 110 pregnant women who received 1 mg/kg of Pethidine. A visual analogue scale (VAS) pain score was used before 30 and 60 minutes after drug administration. In addition, a Neonatal Apgar score of one and five minutes was recorded.

Results

There were no significant demographic feature differences between both groups. Mean pain scores before drugs were 7.8±1.6 and 7.8±1.3 after 30 minutes were 4.6±1.6 and 5.7±1.6, and after 60 minutes were 3.8±1.5 and 3.9±1.6 for Entonox and pethidine groups, respectively. Entonox decreased pain score better than Pethidine after 30 minutes (p-value of <0.001); however, Pethidine decreased pain score better than Entonox after 60 minutes (p-value of <0.001). Mean Apgar scores in 1st minute were 8.6±.87 and 8.41±1.28, and in 5th minute was 9.84±.37 and 9.62±.82 for Entonox and pethidine groups, respectively. Significant association of drugs with Apgar score at 5th minute was found.

Conclusion

Entonox was better for acute pain management within 30 minutes; Pethidine was better for longer than 60 minutes.

Keywords: *Entonox; Labor Pain; Pain Relief; Pethidine; Sulaimani.*

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INTRODUCTION

Pain is one of the significant public health issues worldwide, and it represents significant social, economic, and clinical problems [1,2]. One of the severe acute pains in women during their lives is labour pain [3]. The psychological distress of severe pain should not be neglected because it is associated with adverse neonatal or maternal outcomes. Different pain management methods have been tried during labour with varying side effects and efficacies [4]. One of the methods is the inhalation of Nitrous oxide (N2O)/Oxygen (O2) mixtures which had been used in obstetrics for labour since 1880 [5].

The practice of gas inhalation analgesics was gradually developed into the self-administrable machine; Minnitt invented the self-administration machine in 1934 to inhale nitrous oxide [6]. The Entonox inhalation was composed of 50% Nitrous Oxide plus 50% Oxygen in a container [6]. The most suitable technique for Entonox usage is essential for achieving the inhalation method's maximal effect; Entonox must be inhaled 30-50 seconds before each contraction and ten breaths or inspiration for 50 seconds is adequate for analgesia [7].

Further, Entonox is a tasteless, colourless, and odourless gas that is cost-effective and easy to use with the advantages of rapid onset, short duration, minimal toxicity, and side effects to the mother and fetus and is filtered by the lungs [7,8]. The side effects of Entonox reverse after its discontinuation [9].

Entonox is not depressing respiration like opioids and has no effect on uterine contraction; thus, it increases Entonox usage [5]. Also, it does not affect maternal pushing during labour and labour length [10].

However, Pethidine is a synthetic opioid synthesised in 1932 [11]. After that, it was used widely worldwide as labour analgesia [6]. Intramuscular (IM) injection of Pethidine absorbs in about six hours, and the mean plasma concentration time is 24 minutes [6]. Therefore, Pethidine starts its effect in 10-20 minutes and lasts for two to four hours after its administration [6].

Although Pethidine can cause sedation and reduced pain, it develops complications in mothers and neonates [6]. Further, Pethidine binds to the mu receptor, an opioid receptor, and can lead to nausea, vomiting, euphoria, pruritis, urine retention, respiratory depression and hypoxia, sedation, and analgesia [12].

Pethidine affects neonatal circulation; it crosses the placenta by passive diffusion and becomes high in the fetus's plasma after two to three hours [7]. Due to the acidic environment of the neonatal circulation, it may cause maintain its high concentration more than the mother injected with IM pethidine [13]. Therefore, it may reduce Apgar score and cause respiratory distress to the baby [6]. The baby's liver metabolises the remaining dose of Pethidine after birth [14].

The visual analogue scale (VAS) was developed to assess pain severity [15]. The VAS consists of a line from "no pain" to "pain as bad as it could be" and numbers from 0-10 then put on that line to indicate the pain severity; zero means "no pain" and ten indicates "pain as severe as it could be" [15].

The study aimed to compare the analgesic effects and maternal and neonatal outcomes after using Entonox inhalation (50% nitrous oxide plus 50% oxygen) and 1 mg/kg IM Pethidine for labour pain management in our population.

PATIENTS AND METHODS

A randomised clinical trial (RCT) was performed on 221 pregnant women admitted to the Labor Room of the Sulaimani Maternity Teaching Hospital from January 2020 to January 2021. The pregnant women were non-blindly; however, randomly allocated into two groups. GroupI was 111 pregnant women who received Entonox, i.e., inhalation of 50% nitrous oxide plus 50% oxygen, continuously from four centimetres cervical dilatation onward. However, group II was 110 pregnant women who received a single dose IM injection of 1 mg/kg of meperidine (Pethidine) at four centimetres of cervical dilatation. Most women used oxytocin (Pitocin).

The Kurdistan Board of Medical Specialties (KBMS) approved the study proposal (No. 179, February 3, 2020), and a formal acceptance letter was obtained from Sulaimani Maternity Teaching Hospital before starting the study. In addition, written informed consent has been taken from the patients for their inclusion in the study.

The inclusion criteria included: Pregnant women with a singleton pregnancy. Vertex presentation.Term pregnancy in active labour.Patients who desired labour analgesia. Accept to participate and sign the written informed consent. The exclusion criteria included Antepartum haemorrhage and breech presentation—fetal distress.

Women with a prior history of significant diseases included valvular heart diseases, upper respiratory tract infection, asthma, chronic obstructive pulmonary disease (COPD), sinus obstruction, or diabetes mellitus (DM).Personality disorder.Contraindications to Entonox and Pethidine.Refusal to participate.

The demographic features were recorded, including maternal and gestational ages, residencies, education level, parity, and gravidity. The primary outcomes were the effect of both the drugs on labour, which included the severity of pain, duration of the active first and second stages of labour, and duration and contraction intervals. Further, cervical dilatations before initiating drugs and the time of the active first and second stages of labour were measured.

Delivery modes and, meconium's presence, the interval of contractions before and after interventions were measured. Pain score using VAS before administering the drugs and at 30 minutes and 60 minutes after administration of drugs was recorded. The secondary outcomes included maternal and neonatal complications were also recorded. The vital signs (heart rate, respiratory rate, and blood pressure) were recorded before, during one hour, and three hours after administering the drugs. Maternal side effects and neonatal Apgar scores were recorded at one and five minutes. The women were followed up by the researchers and the obstetricians on duty.

The "IBM SPSS Statistics version 25" software was used to analyse the data, and descriptive and inferential statistics were used. Further, a P-value of ≤ 0.05 was considered a statistically significant association. Also, Pearson Chi-Square was used to determine the significance of the association between categorical independent and dependent variable pairs. Finally, the student's T-Test (Paired-Samples T-Test) was used to compare numerical independent and dependent variables variable teams.

RESULTS

The mean±SD (standard deviation) of patients' ages were 27.05±6.18 years and 25.45±5.3, ranging from 17-43 years and 17-39 years in the Entonox and pethidine groups, respectively. On the other hand, the mean±SD of ages of all the patients was 26.25±5.79 years, ranging from 17-43 years. Further, the mean±SD of gestational ages were 39.04±0.97, 39.26±1.12, and 39.15±1.1 weeks, ranging from 37-41, 37-42, and 37-42 weeks, for the Entonox, and pethidine groups and all patients, respectively.

The gravidity and parity were the same in both the studied groups

Table 1. There have been no significant differences in patients' residencies, level of education, mode of delivery, and oxytocin usage in the groups, i.e., limited confounding factors.

Table 2. The pethidine group's blood pressure (BP) became slightly higher than the BP in the Entonox group, which stayed nearly the same after three hours of the medications. However, other vital signs were almost the same. Table 3. The cervical dilatation before commencing the medications, duration and interval of contraction before and after drug administrations, time of the active first stage, and duration of the second stage remained unchanged. Table 4. The mean±SD of pain scores before medication were 7.8±1.6 and 7.8±1.3, ranging from 4-10 and 4-10 for Entonox and pethidine groups, respectively. Further, the mean±SD pain scores after 30 minutes from drug administration were 4.6±1.6 and 5.7±1.6, ranging from 2-8 and 2-8, for Entonox and pethidine groups, respectively. Also, the mean±SD pain scores after 60 minutes from drug administration were 3.8±1.5 and 3.9±1.6, ranging from 2-6 and 2-8 for Entonox and pethidine groups, respectively.

The analgesics statistically significantly decreased the patients' pain score after 30 minutes from administering the anaesthetics; Entonox decreased the pain score better than Pethidine after 30 minutes, Table 5. The analgesics statistically significantly decreased the patients' pain score after 60 minutes from administering the anaesthetics; Pethidine decreased the pain score better than Entonox after 60 minutes, Table 6. Thus, Entonox was better for acute pain management; Pethidine was better for a longer duration, Tables 5,6. There was a statistically significant association of painkillers with the dizziness side effect; Entonox caused more dizziness than Pethidine. However, there were no differences among the groups for nausea and vomiting side effects,

Table 7. The mean±SD of Apgar scores in the 1st minute was 8.6±.87 and 8.41±1.28, ranging from 5-10 and 2-10, for Entonox and pethidine groups, respectively. However, the mean±SD of Apgar scores in the 5th minute was 9.84±.37 and 9.62±.82, ranging from 9-10 and 3-10, for Entonox and pethidine groups, respectively. There was a statistically significant association of the

types of analgesics with the neonatal Apgar score at five minutes post-delivery; Entonox was better, Table 8. Further, 3.2% of the patients had thick meconium-stained amniotic fluid; all were thick meconium in the pethidine group. However, 5% of the patients had thin meconium-stained amniotic fluid; 3.6% in the Entonox group and 1.4% in the pethidine group. However, meconium-stained amniotic fluid was not significantly different among both groups, Table 9. The association of maternal complications (vital sign abnormalities) and neonatal complications (admission to neonatal intensive care unit) with the types of painkillers were statistically non-significant, Table 10.

Table 1. Obstetrical history of both the studied groups.

Obstetrical history		Painkillers	
		Entonox	Pethidine
Gravida	mean±SD (range)	2.39±1.6 (1-9)	1.82±1.4 (1-8)
parity	mean±SD (range)	1.06±1.23 (0-5)	0.61±1.1 (0-5)
abortus	mean±SD (range)	1.5±1.18 (1-5)	1.27±.46 (1-2)
dead babies	mean±SD (range)	1±0 (1-1)	0±0 (0-0)

SD = standard deviation

Table 2. Association of some essential characteristics of the patients in both studied groups.

Variables		Painkillers (%)		Total (%)	p values
		Entonox	Pethidine		
Residency	Urban	68 (30.8)	76 (34.4)	143 (64.7)	0.203
	Rural	43 (19.5)	34 (15.4)	77 (34.9)	
Level of education	Illiterate	11 (5)	12 (5.4)	23 (10.4)	
	Primary school	30 (13.6)	36 (16.3)	66 (29.9)	0.456
	Secondary school	49 (22.2)	37 (16.7)	86 (38.9)	
	Institute or university degree	21 (9.5)	25 (11.3)	46 (20.8)	
Mode of delivery	NVD	105 (47.5)	100 (45.2)	205 (92.8)	0.290
	C/S	6 (2.7)	10 (4.5)	16 (7.2)	
Oxytocin used?	Yes	83 (37.6)	89 (40.3)	172 (77.8)	0.272
	No	28 (12.7)	21 (9.5)	49 (22.2)	
Total		**111 (50.2)**	**110 (49.8)**	**221 (100)**	—

C/S = cesarean section; NVD = normal vaginal delivery.

Table 3. Distribution of vital signs among both studied groups.

Variables		Mean±SD	Range
BP (before drug administration) (mmHg)	Entonox	107 ±10.8/ 69.53±8.4	90-130/45-90
	Pethidine	107.3±11.14/70.27±7.4	90-140/60-90
BP after 1 hour (mmHg)	Entonox	106 ±9.8/68.6±7.3	90-130/50-80
	Pethidine	109 ±10.7/71.2±7.5	90-14/60-100
BP (mmHg) after 3 hours	Entonox	106.7±8.8/69.09±6.7	90-130/50-90
	Pethidine	110.7±9.9/72.09±7.3	90-135/45-90
PR (before drug administration) (b/m)	Entonox	86.6±8.6	70-120
	Pethidine	83.8±8.3	69-99
PR (b/m) after 1 hour	Entonox	86 ±7.45	71-105
	Pethidine	85.7 ±8.19	70-102
PR (b/m) after 3 hours	Entonox	88 ±7.8	70-110
	Pethidine	87 ±7.5	73-102
RR (before drug administration) (CPM)	Entonox	16.2 ±1.7	12-20
	Pethidine	16.3 ±1.6	13-21
RR (CPM) after 1 hour	Entonox	16 ±1.5	13-20
	Pethidine	16.6±1.3	13-20
RR (CPM) after 3 hours	Entonox	16.7 ±1.4	14-21
	Pethidine	16.9 ±1.5	12-22

BP = blood pressure; b/m = beat per minute; cpm = cycle per minute; mmHg = millimeters of mercury; PR = pulse rate; RR = respiratory rate; SD = standard deviation

Table 4. Distribution of delivery parameters in both the studied groups.

Variables		Mean±SD	Range
Cervical dilatation before initiation of drugs (cm)	Entonox	4.5±0.5	4-5
	Pethidine	4.16±0.37	4-5
Duration and interval of contraction (before drugs)	Entonox	3.93±0.6 contractions 41.9±5.7 sec.	3-5 contractions 30-55 sec.
	Pethidine	4.08±0.53 contractions 43.2±4.9 sec.	3-5 contractions 35-50 sec.
Duration and interval of contraction (after drugs)	Entonox	3.89±0.4 contractions 41.9±4.8 sec.	3-5 contractions 30-55 sec.
	Pethidine	4.03±0.41 contractions 44.3±4.99 sec.	3-5 contractions 30-55 sec.
Duration of the active first stage (hour)	Entonox	3.62±1.98	0.83-11
	Pethidine	3.46±1.9	0.67-9
Duration of the second stage (minute)	Entonox	23.36±19.05	2-90
	Pethidine	28.73±18.5	2-90
The total duration of labour (hour)	Entonox	**3.99±2.12**	**0.88-12**
	Pethidine	**3.91±2**	**0.86-10.5**

b/m = beat per minute; BP = blood pressure; cm = centimeter; cpm = cycle per minute; PR = pulse rate; RR = respiratory rate; SD = standard deviation

Table 5. Association of painkillers and the degree of pain score after 30 minutes from the painkiller administration.

Painkiller			Pain score after 30 minutes (%)			Total (%)	p-value
			Mild pain (1-3)	Moderate pain (4-6)	Severe pain (7-10)		
Entonox	Pain score before medication	Moderate pain (4-6)	8 (7.2)	24 (21.6)	0 (0)	32 (28.8)	
		Severe pain (7-10)	9 (8.1)	64 (57.7)	6 (5.4)	79 (71.2)	
	Total		17 (15.3)	88 (79.3)	6 (5.4)	111 (100)	
Pethidine	Pain score before medication	Moderate pain (4-6)	6 (5.5)	22 (20)	0 (0)	28 (25.5)	
		Severe pain (7-10)	2 (1.8)	59 (53.6)	21 (19.1)	82 (74.5)	<0.001
	Total		8 (7.3)	81 (73.6)	21 (19.1)	110 (100)	
Total	Pain score before medication	Moderate pain (4-6)	14 (6.3)	46 (20.8)	0 (0)	60 (27.1)	
		Severe pain (7-10)	11 (5)	123 (55.7)	27 (12.2)	161 (72.9)	
	Total		25 (11.3)	169 (76.5)	27 (12.2)	221 (100)	

Table 6. Association of analgesics and the degree of pain score after 60 minutes from the administration of the analgesic.

Analgesic			Pain score after 60 minutes (%)			Total (%)	p-value
			Mild pain (1-3)	Moderate pain (4-6)	Severe pain (7-10)		
Entonox	Pain score before medication	Moderate pain (4-6)	18 (16.2)	14 (12.6)	0 (0)	32 (28.8)	
		Severe pain (7-10)	20 (18)	59 (53.2)	0 (0)	79 (71.2)	
	Total		38 (34.2)	73 (65.8)	0 (0)	111 (100)	
Pethidine	Pain score before medication	Moderate pain (4-6)	16 (14.5)	12 (10.9)	0 (0)	28 (25.5)	
		Severe pain (7-10)	21 (19.1)	60 (54.5)	1 (0.9)	82 (74.5)	<0.001
	Total		37 (33.6)	72 (65.5)	1 (0.9)	110 (100)	
Total	Pain score before medication	Moderate pain (4-6)	34 (15.4)	26 (11.8)	0 (0)	60 (27.1)	
		Severe pain (7-10)	41 (18.6)	119 (53.8)	1 (0.5)	161 (72.9)	
	Total		75 (33.9)	145 (65.6)	1 (0.5)	221 (100)	

Table 7. Association of painkillers with their side effects among the groups.

Side effects		Painkillers (%)		Total (%)	p values
		Entonox	Pethidine		
Nausea	Yes	25 (11.3)	29 (13.1)	54 (24.4)	0.51
	No	86 (38.9)	81 (36.7)	167 (75.6)	
Vomiting	Yes	7 (3.2)	9 (4.1)	16 (7.2)	0.59
	No	104 (47.1)	101 (45.7)	205 (92.8)	
Dizziness	Yes	93 (42.1)	65 (29.4)	158 (71.5)	<0.001
	No	18 (8.1)	45 (20.4)	63 (28.5)	
Total		**111 (50.2)**	**110 (49.8)**	**221 (100)**	—

Table 8. Association of analgesic and neonatal Apgar score at five minutes.

Apgar score		Painkillers (%)		Total (%)	p values
		Entonox	Pethidine		
1st minute	2	0 (0)	1 (0.5)	1 (0.5)	0.48
	4	0 (0)	1 (0.5)	1 (0.5)	
	5	1 (0.5)	1 (0.5)	2 (0.9)	
	6	2 (0.9)	5 (2.3)	7 (3.2)	
	7	4 (1.8)	9 (4.1)	13 (5.9)	
	8	33 (14.9)	31 (14)	64 (29)	
	9	58 (26.2)	47 (21.3)	105 (47.5)	
	10	13 (5.9)	15 (6.8)	28 (12.7)	
5th minutes	3	0 (0)	1 (0.5)	1 (0.5)	0.04
	8	0 (0)	3 (1.4)	3 (1.4)	
	9	18 (8.1)	29 (13.1)	47 (21.3)	
	10	93 (42.1)	77 (34.8)	170 (76.9)	
Total		**111 (50.2)**	**110 (49.8)**	**221 (100)**	—

Table 9. Distribution of meconium among both the groups.

Painkiller			Thick meconium (%)		Total (%)	p-value
			Yes	No		
Entonox	Thin meconium	Yes	0 (0)	8 (7.2)	8 (7.2)	0.54
		No	2 (1.8)	101 (91)	103 (92.8)	
	Total		2 (1.8)	109 (98.2)	111 (100)	
Pethidine	Thin meconium	Yes	0 (0)	3 (2.7)	3 (2.7)	
		No	5 (4.5)	102 (92.7)	107 (97.3)	
	Total		5 (4.5)	105 (95.5)	110 (100)	
Total	Thin meconium	Yes	0 (0)	11 (5)	11 (5)	
		No	7 (3.2)	203 (91.9)	210 (95)	
	Total		7 (3.2)	214 (96.8)	221 (100)	

Table10. Association of painkillers with maternal and neonatal complications.

Outcomes		Analgesic (%)		Total (%)	p values
		Entonox	Pethidine		
Maternal complication	Yes	0 (0)	2 (0.9)	2 (0.9)	0.15
	No	111 (50.2)	108 (48.9)	219 (99.1)	
Neonatal complication	Yes	2 (0.9)	2 (0.9)	4 (1.8)	0.99
	No	109 (49.3)	108 (48.9)	217 (98.2)	
Neonatal heart abnormality	Yes	5 (2.3)	8 (3.6)	13 (5.9)	0.38
	No	106 (48)	102 (46.2)	208 (94.1)	
Total		111 (50.2)	110 (49.8)	221 (100)	—

DISCUSSION

The current study showed that Entonox was better for acute pain management in less than half an hour; however, Pethidine was better for pain management that lasted more than an hour. The current study's findings were about the same as the previous literature in that Entonox was better for labour pain but a shorter period [12,16]. However, Mobaraki et al. [4] found no difference between Entonox and pethidine groups after 60 minutes. This difference in the current study's findings from the study of Mobaraki et al. [4] may be that they used 0.5 mg/kg of Pethidine; however, we used 1 mg/kg of Pethidine.

A mixture of 50% nitrous oxide and 50% oxygen, i.e., Entonox, is usually prepared in a single container and is a patient-controlled analgesia inhaler [17]. Entonox is transported without binding to the proteins in the blood; it has low blood solubilities [17]. Also, Entonox diffuses rapidly via the alveolar-arteriolar membrane and excretes through the lung without changes [9]. Therefore, it is quickly reversible when discontinued, and recovery from its sedative effects is quicker than intravenous analgesia [9]. Due to these fast onset and rapid reversibility effects, Entonox can be given throughout the labour without being afraid of its impact on the baby [9]. Although it is not a potent analgesic, the highest efficacy of Entonox is at 70% concentration, which can relieve pain during labour in nearly two-thirds of the parturients [16].

Various analgesic inhalators had been tried for labour pain relief; however, Entonox was accepted to a greater extent [16]. Further, Entonox can be used continuously throughout the labour, same as the findings of this study, or intermittently with the onset of each uterine contraction and stopped when the contraction stops [16].

There is a 50 seconds delay after Entonox administration before its analgesic effect occurs; therefore, it is problematic to use intermittent administration [9]. Thence, if intermittent administration of Entonox is used, it is better to start the administration about 30-50 seconds before beginning each contraction, which is also problematic (9). In addition, although side effects such as nausea, vomiting, dizziness, and drying of the mouth due to the dry gas inhalation, can occur [12,18], they are quickly reversible after its discontinuation [9].

One common opioid used for labour pain is IM pethidine [4]. However, Pethidine has frequent side effects on both the mother and the baby, which make it less favourable for labour pain management; it can cause dysphoria, vomiting, nausea, and all opioids can cross the placenta; thus, Pethidine causes decreased neonatal heart rates and respiratory depression [3]. Nevertheless, Pethidine is readily available and cheap; therefore, it is widely used in most obstetrical units worldwide [18].

In this study, Entonox was used continuously for the parturients; therefore, it may cause a high frequency of dizziness side effects among them. However, it had better results for managing acute labour pain of less than half an hour. Further, IM pethidine was better for controlling labour pain for a more extended period, i.e., more than an hour.

In conclusion, the Entonox was better for managing acute labour pain for half an hour; Pethidine was better for extended labour pain management of more than an hour. No significant differences in the side effects of both the drugs were found except for dizziness which was more frequent among parturients who used Entonox.

Our study included both primigravida and multigravida, which may be a limitation. Therefore, we recommend conducting future research on the same topic with the same study design; however, we should choose only primigravida or multigravida to limit confounding factors.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Imani F, Safari S. "Pain Relief is an Essential Human Right", We Should be Concerned about It. Anesthesiol Pain Med. 2011;1(2):55–7.

2. Phillips CJ. Economic burden of chronic pain. Expert Rev Pharmacoeconomics Outcomes Res. 2006;6(5):591–601.

3. Wee MYK, Tuckey JP, Thomas P, Burnard S. The IDvIP Trial: A two-centre randomised, double-blind controlled trial comparing intramuscular diamorphine and intramuscular Pethidine for labour analgesia. BMC Pregnancy Childbirth. 2011;11:51.

4. Mobaraki N, Yousefian M, Seifi S, Sakaki M. A randomised controlled trial comparing Entonox with Pethidine for pain relief in primigravid women during the active phase of labour. Anesthesiol Pain Med. 2016;6(4):e37420.

5. Rosen MA. Nitrous oxide for relief of labour pain: A systematic review. Am J Obstet Gynecol. 2002;186:S110–26.

6. Subasinghe T. The Effectiveness of Entonox Compared to Pethidine for Labor Pain: A Systematic Review. Proceeding 5th Int Conf Public Heal. 2019;5(2019):8–18.

7. JP R. Safety and Risks of Nitrous Oxide Labor Analgesia: A Review. J Midwifery Women's Heal. 2011;56:557–65.

8. King TL, Wong CA. Nitrous oxide for labour pain: Is it a laughing matter? Anesth Analg. 2014;118(1):12–4.

9. Bishop JT. Administration of Nitrous Oxide in Labor: Expanding the Options for Women. J Midwifery Women's Heal. 2007;52:308–9.

10. Collins MR, Starr SA, Bishop JT, Baysinger CL. Nitrous oxide for labour analgesia: expanding analgesic options for women in the United States. Rev Obstet Gynecol. 2012;5(3):126–31.

11. Manouchehrian N, Bakhshaei MH. Nitrous oxide relieves anxiety and pain in parturients under spinal anaesthesia for caesarean section. Anesthesiol Pain Med. 2014;4(2):e16662.

12. Anderson D. A Review of Systemic Opioids Commonly Used for Labor Pain Relief. J Midwifery Women's Heal. 2011;56:222–39.

13. Sosa CG, Buekens P, Hughes JM, Balaguer E, Sotero G, Panizza R, et al. Pethidine's effect during the first labour stage on the acid-base status at birth. Eur J Obstet Gynecol Reprod Biol. 2006;129:135–9.

14. Goodson C, Martis R. Pethidine: to prescribe or not to prescribe? A discussion surrounds Pethidine's place in midwifery practice and New Zealand prescribing legislation. New Zeal Coll Midwives J. 2014;49:24.

15. Haefeli M, Elfering A. Pain assessment. Eur Spine J. 2006;15(SUPPL. 1):17–24.

16. Rooks JP. Nitrous oxide for pain in labour - Why not in the United States? Birth. 2007;34(1):3–5.

17. addy SC, Garlick SR. A systematic review of the safety of analgesia with 50% nitrous oxide: Can lay responders use analgesic gases in the prehospital setting? Emerg Med J. 2005;22(12):901–6.

18. Teimoori B, Sakhavar N, Mirteimoori M. Nitrous Oxide versus Pethidine with Promethazine for Reducing Labor Pain. Gynecol Obstet. 2011;01(01):1–4.