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Research Article

Comparing the Effect of Entonox With and Without Spinal Analgesia in Labor: A Randomized Clinical Trial

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Running title: Entonox With Spinal Analgesia in Labor

ABSTRACT

Background: Combined nitrous oxide - spinal analgesia has been used less for labor pain. It is cost benefits and is a relatively easy in low resource setting.

Objective: This study conducted to determine the effects of combined nitrous oxide-spinal analgesia on delivery outcomes.

Method and Materials: One hundred parturients with pregnancy ≥37 weeks gestation, in the active phase of labor and cervical dilation of 3-4 cm participated in this study. After obtaining informed consent randomly divided equally into two groups. One group received combined intermittent Entonox (nitrous oxide 50%, oxygen 50%) with spinal analgesia (IESA) and the other group received intermittent Entonox (IE). Duration of the first, second and third stage of the labor was recorded. Pruritus, Nausea, Dizziness, Drowsiness and headache were recorded during the labor. The intensity of pain was assessed with using Visual Analogue Scale (VAS) and Apgar score was recorded after delivery.

Results: Duration of first and second stage of the labor was higher in the EISA group compare to the IE women but was not significant. The mean number of cesarean section increased significantly in the IESA group compare to the IE women **(**P<0.001). There was no statistical significant difference in the first and five min Apgar scores between two groups. The mean pain were 0.06±0.02 for Entonox with spinal analgesia groups and 5.6±1.1 for the Entonox women at 135 minutes after delivery (P<0.001).

Conclusion: Entonox with SA is safe option and provided the sufficient pain relief during labor with no serious risks for mother or neonate.

Keywords: Apgar score, Entonox, Labor, Pain, Obstetrical analgesia
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1. INTRODUCTION

Severe pain during labor may be associated with risks to the mother and neonate and control of pain is necessary for their health (1). Pain relief during the labor has improved psychological effects for mother, breastfeeding and relationship between mother and infant (2). In development country more than 85 % of pregnant women have demand labor analgesia and only 40 % of them received labor analgesia (3). Among the different techniques, epidural and spinal analgesic methods are the most well-known and are considered the most effective technique for pain management during labor (4). These methods may be accompanied by increased of instrumental vaginal delivery and caesarean section (5). Further, facilities for epidural analgesia is limited in the under development countries (3). So, the simple and cost-benefit method is necessary in small and less resource centers.

Inhaled analgesia gas such as Entonox (low-dose nitrous oxide/oxygen combination 50% N2O/O2) appears to be safe, helps women relax, is effective to pain relief during the first stage or all time of labor (6). The analgesic effect of nitrous oxide could be due to release of endogenous dopamine, endorphins and enkephalins from the brain neurons cells which in turn modulates pain by corticospinal pathway (7,8) and decrease of cortisol that is produced in response to stress (9). Parturients women could control the how long use of Entonox by self-administered and inhale the gas during uterine contractions. Although, the nitrous oxide passes through the placenta and reaches the fetus during the labor it has no side effect on fetal heart rate and is eliminated by the neonate's with the onset of breathing (10).

Spinal analgesia is another method that can be alternative for epidural analgesia in small and low facility delivery center (11). Spinal analgesia is a central nerve blockade method and is more reliable for pain relief in the entire duration of the labor (12). It could block impulses from the sensory nerve by blocking sodium channels in nerve cell membranes after 10 to 20 minutes of administration (13). It has been reported the effective time of labor analgesia in single- low dose intrathecal analgesia is limited compared to the epidural analgesia (14). So to keep the pain management during the labor, we hypothesized the use of Entonox in the first phase of labor and continuing with spinal analgesia would provide effective pain managements without serious side effects on mother and neonate. Most studies have been done on epidural or spinal–epidural analgesia (SEA) in labor, as far as we know there is no specific clinical trial research that focuses the effect of Entonox with spinal analgesia on labor.

2. OBJECTIVES

So, this study conducted to determine the effect of the Entonox inhalation with and without spinal analgesia during labor on maternal and neonatal outcomes.

3. MATERIALS AND METHODS

3.1. Ethical considerations

This study was a randomized clinical trial that was approved by biomedical research ethics committees in Yasuj University of Medical Science (ir.yums.REC.1394.34) and written informed consent was obtained from parturients before treatment. This study was registered in the Iranian registry of clinical trials (http://irct.ir) with IRCT No: IRCT201111218109N2.

3.2. Participants and groups

A total of 100 pregnant women participated in this study who referred to Imam Sajad Hospital Labor Ward for vaginal delivery in 2014-2015 in Yasuj-Iran. After obtaining informed consent the women randomly divided into 2 groups of 50. Some demographic characteristics of the pregnant women including age, weight, height, history of labor analgesia, Gestational age, gravid, parity was recorded by an interviewer. After obtaining informed consent, they examined by a midwife in the ward to confirm they were in the first phase of labor. Inclusion criteria included if the pregnant women were aged between 18 and 35, with pregnancy ≥37 weeks gestation, in the active phase of labor with cervical dilation of 3-4 cm.

The exclusion criteria were for any participant with contraindication for vaginal delivery or spinal analgesia, uterine abnormalities, use of sedative drugs, pregnancy related disease and malpresentation.

The sample size (a total of 100 parturients) randomly divided into 2 groups of 50 participant including combined intermittent Entonox (nitrous oxide 50%, oxygen 50%) with spinal analgesia (IESA) group and intermittent Entonox (IE) group without spinal analgesia.

3.3. Inhalation of Entonox and Spinal analgesia procedures

The parturients were trained to self-administration by breathing deep and calm in mask whenever she touched or feel uterine contractions by put their hand on abdomen and cut it between uterine contractions. In IE groups women used of Entonox with cervix dilatation 3-4cm and effacement ≥40% and cut at 8 cm dilatation with effacement ≥80%.

In EISA group the Entonox self-administration inhalation gas was started by commencement of active phase with cervix dilatation 3-4cm and effacement ≥40%. The Entonox cut and put aside with progress of labor to reach dilatation 5-6cm and effacement 60-70% with fetal head had descended to station -1 and then they received spinal analgesia.

For achieving the spinal analgesia, the parturients received 500 ml ringer lactate and placed in the sitting position. The intervertebral space of L4-L5 was identified and a pencil-point 25-G spinal needle placed in the intervertebral ligament after aseptic precautions. These ligaments have high degree while epidural space has a low resistance to needle penetration. So, with suddenly decrease of resistance the anesthesiologist recognize the needle enter the epidural space. Then, spinal needle was entered into the subarachnoid space with observation of backflow of cerebrospinal fluid (CSF). Next, a third of an intrathecal mixture contained 25 µg of fentanyl, 2.5 mg of bupivacaine and 0.2 mg of morphine with 0.2 ml of backflow of CSF was injected in the subarachnoid space and two-thirds of this dose was administered 2 minutes after the first injection. Then, the parturient was placed left lateral with the head end of the bed elevated to 30°

3.4. Measures

The use of instrumental vaginal delivery or caesarean section were recorded in two groups.Vital sign of all parturients were recorded before delivery and in each 15 minutes in the first and second stage of labor.

Based the management protocol, vaginal examination was performed to record duration of first, second and third stage in labor room by a midwife for different groups. Pruritus, nausea, dizziness, drowsiness and headache were assessed hourly during the labor based on Bromage scale (15).

The intensity of pain was assessed with using Visual Analogue Scale (VAS), score ranging from 0, indicating painless to 11 intolerable pain. The pain score was measured before and 45, 90 and 135 minutes after the administration of Entonox in both groups (16). As previously described, a questionnaire was designed to assess the satisfaction of the pain management on a 5-point scale from very satisfied to very dissatisfied for both groups one hour after delivery in postpartum (17). Apgar score was recorded in first minute and five minute after delivery.

3.5. Statistical analysis

Statistical calculation was performed by using SPSS. The Student's t test were used to analyses continues data and Mann-Whitney U test were used to non-continues data. Data are expressed as mean ± SD; the significance level was set up at *P* less than 0.05.

4. RESULT

During the study, 3 women from the IESA and 4 women from the IE groups had no willingness to cooperate and they were excluded from the study. Data was collected from 93 pregnant women who participated in this study and referred to Imam Sajad Hospital Labor Ward for vaginal delivery. There were no significant differences in age, body mass index (BMI), gestational age and cervical

dilation at induction of analgesia between two groups (Table 1).

As shown in Table 2, duration of first and second stage of labor increased in the EISA group compare to the IE women but this difference was not significant. There was no difference in the duration of third stage of labor between two groups (P>0.101). The mean number of cesarean section increased significantly in the IESA group compare to the IE women **(**P<0.001).

Neonatal outcomes demonstrated that there was no statistical significant difference in the first and five min Apgar scores and in birth weight between two groups (Table 2).

The mean (Mean±SD) pain severity were 7.9±2.6 and 8.1±0.6 before administration for IE and IESA groups, respectively. The mean pain did not significant before and at 45 minutes post administration between two groups. As shown in table 3, the increase of mean pain in the Entonox group had statistically significant difference compared to Entonox with spinal analgesia groups at 90 and 135 minutes post administration (P<0.001).

Result showed there was a statistical significance of satisfaction of women who received the combined Entonox-spinal analgesia compared the Entonox group (table 3).

As shown in the table 4, the increase number of nausea in the IESA group was 4.4% higher than IE group, this difference did not reach statistical significance (p>0.206). The mean of pruritus, dizziness and headache increased significant in women who received the Entonox with spinal analgesia compared to the women who received the Entonox (table 4).

5. DISCUSSION

This study demonstrated the combined Entonox with single-dose of spinal analgesia is safe and effective in pain management comparison to the group that received the Entonox alone. Result of this study showed the slight increase in the mean duration of first stage of labor in parturient who received EISA with 454 min was not significantly compared in IE group who received IE with 412 min. In our study, the mean duration of the second stage of labor increased in the EISA women 13 min compare to the IE group and this difference between the two groups did not reach statistical significance. However, in our study 10.6% percent (5 of 47) of parturient in the EISP were received instrumental assisted delivery compared with 2.17 percent (1 of 46) of women who experience the Entonox alone. Spinal analgesia has advantage of faster onset of analgesia, decrease of instrumental delivery with preserve of mobility and improving of parturient satisfaction with labor compare to the epidural analgesia (18). The possibility of spinal anesthesia is more convenient and cost benefit and did not accompanying with sever limited ambulation in the women (3). In our study, Entonox was used at the beginning of the active phase with cervix dilatation 3-4cm until 5-8cm with a mean time of 47 minutes of total labor time. Our study confirm the results of other studies that demonstrated the nitrous oxide in the early stage of pain in emergency medicine is simple, non-invasive with few side effect (19). The effective and benefits of intermittent Entonox for management the pain have been proved in different studies (20). Entonox did not blockade the sensory or motor nerve during the labor, supported the maternal ambulation and decreases anxious in young pediatric patients (21). Although Entonox is not effective for pain management the same as epidural or spinal analgesia it is suitable when parturient prefer to delay use of regional analgesia until subsequent in delivery, when there is severe pain and unbearable (22).

Entonox have different mechanism to control labor pain compared spinal analgesia and perhaps can not be compared with each other on pain management. However, in our study 80.85 percent (38 of 47) of parturient in the EISP group were very satisfied with pain management compared with 60.86 percent (28 of 46) of women who experience the Entonox alone. In a prospective study 66% of women believed that Entonox was suitable for pain relief compared 89% who prefer the epidural analgesia during labor (23). In a cross-sectional, 50% of women who treated with

Entonox, were agreed that the inhaled of Entonox is appropriate pain relief compared with 22% of women who received the pethidine (24). In one study, based on questionnaire that responding by 2482 women two months after delivery the epidural analgesia with 84% has the most effective pain labor followed by Entonox with 49% and pethidine with 41% (25). In another study, Entonox has more satisfactory with 46% compared pethidine with 22% on labor pain relief (26).

It has been shown 8.4% of women who received the Entonox as sole agent with face mask had nausea and vomiting has seen (27). In our study 12.8% of women who received combined Entonox-spinal had nausea compared 17.4% of women who received Entonox. In one cross-sectional study the rate of nausea was similar in Entonox with 13% compared epidural with 14% (28). In this study the mean of headache increase in the IESA group significantly compare to the IE group. Other study showed the incidence of headache was 3.6% in women that using regional analgesia compared none incidence in women with nitrous oxide (29). The pruritus in this study was 57.4% in the IESA group which other study showed the intrathecal fentanyl could induced pruritus 95% during labor (30). Our result confirm other studies which found the Apgar scores in neonates that their mother received Entonox was not significantly differences with no analgesia, paracervical block or pethidine (23). Whereas, Intramuscular meperidine injection alone (50 mg) in the healthy parturients with singleton term pregnancy has deleterious effects on fetal heart rate (31). In consistence with this results, Sheybani et al demonstrated that Entonox could significantly decreased the pain during labor and reduced the consumption of the Pethidine during the delivery (32).

5.1. CONCLUSIONS

Women in the under development country have less option for analgesia labor than development countries (3). The inhaled N2O in the first stage of labor follow by an intrathecal dose including 25 µg of fentanyl, 2.5 mg of bupivacaine and 0.2 mg of morphine is an appropriate option for the Labouring parturients who is close to delivery. Entonox with SA is safe option and provided the sufficient pain relief during labor with no serious risks for mother or neonate. Entonox alone or combine with SA is simple to use and cost-effective procedure in a small town with limited facilities, few anesthesiologist and high number of parturients with demand for analgesia. However, more study are needed to detect the appropriate dose for spinal analgesia that provide the enough time and sufficient analgesia with minimal side effect.

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Competing interests

The authors declare that they have no competing interests.

Footnotes

Authors' contributions: PR conceived, collected the data and helped in drafting the manuscript, performed the statistical analysis and drafted the manuscript. HH designed and implemented the study protocol, provided materials for the research and interpreted the data. HD design the study, collected of the data, interpreted the data, drafted the manuscript and supervised the research. SA participated in the design of the study and drafted the manuscript and coordination. All authors read and approved the final manuscript.

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Table 1. parturients demographic in both groups

parturients demographic	IESA group (n=50)	IE group (n=50)	P-value
Maternal age (Years)	27.4±2.7	26.9±3.1	0.179
Body Mass index (kg/m^2)	25.9±1.4	26.2±2.2	0.326
Gestational age (weeks)	38.9±1.4	39.2±2.1	0.201
primipara	17 (68%)	15 (60%)	0.122
multipara	8 (32%)	10 (40%)	0.132
Cervical dilation pre-administration (cm)	3.94+2.1	3.88+ 1.4	0.431

The Student's t test were used for comparison of parturients demographic, Values are (Mean±S.D)

Table 2. Maternal and Neonatal outcomes in different groups (Mean±S.D)

Delivery characteristics	IESA group (n=47)	IE group (n=46)	P-value
Duration of 1th stage (h)	7.34±4.27	6.52±32.1	0.139
Duration of 2th stage (min)	52.33±7.33	39.21±3.1	0.101
Duration of 3th (min)	7.52±4.02	8.9±1.6	0.321
Receiving oxytocin	45%	51%	0.942
Caesarean section	5 (10.6%)*	1(2.17%)	0.001
1st min Apgar scores	8.14±1.21	8.23±2.20	0.631
5st min Apgar scores	8.85±3.11	9.33±1.16	0.401
Birth weight (g)	3241±253.43	3211±503.28	0.228

*The Student's t test showed statistically significant difference between two groups.

Table 3. Satisfaction with pain management one hour in postpartum

Scale	IESA group (n=47)	IE group (n=46)	P-value
Very satisfied	38 (80.85%)*	28 (60.86%)	0.001
Quite satisfied	4 (8.51%)	6 (13.04%)	0.204
Neutral	2 (4.25%)	5 (10.86%)	0.124
Quite dissatisfied	1 (2.12%)	2 (4.34%)	0.441
Very dissatisfied	3 (6.38%)	5 (10.86%)	0.203

Data were summarized as number (percentage),* Mann-Whitney U test showed statistically significant difference between groups.

Table 4. Maternal adverse effects of Entonox with spinal analgesia or Entonox alone

Measures	IESA group (n=47)	IE group (n=46)	P-value
Nausea	6 (12.8%)	8 (17.4%)	0.079
Pruritus	27 (57.4%)*	1 (1.17%)	0.001
Dizziness	17 (36.9%)*	9 (19.1%)	0.001
headache	8 (12.7%)*	1 (2.1%)	0.001

Data were summarized as number (percentage),* Mann-Whitney U test showed statistically significant difference between groups.