Journal of Midwifery & Reproductive Health

JMRH.mums.ac.ir

Effects of Entonox in Comparison with Lidocaine on Pain Severity during Episiotomy Incision in Nulliparous Women: A Randomized Control Trial

Azam Honarmandpour (MSc)[1], Zahra Abbaspour(PhD)[2], Sara Ziagham (BSc)[3], Nahid Javadifar (PhD)[4]*

[1] Nursing & Midwifery School, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[2] Assistant Professor, Reproductive Health Promotion Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[3] Department of Midwifery, Shushtar Faculty of Medical Sciences, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[4] Assistant Professor, Reproductive Health Promotion Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

ARTICLEINFO

Article type:
Original article

Article History:
Received: 12-Dec-2015
Accepted: 11-Apr-2016

Key words:
Entonox
Episiotomy
Lidocaine
Pain intensity

ABSTRACT

Background & aim: Episiotomy is one of the most common surgical procedures in obstetrics, which requires analgesia. Entonox gas is known to have analgesic and sedative properties. However, no studies have been found on the analgesic effects of Entonox on episiotomy incision. Therefore, this study aimed to compare the effects of Entonox and lidocaine on pain intensity during episiotomy incision in nulliparous women.

Methods: This randomized controlled trial was conducted on 120 term nulliparous women, who met the inclusion criteria. Subjects were selected by randomized sampling and equally divided into two groups of intervention and control (n=60). In the intervention group, Entonox gas was applied two minutes before episiotomy incision until the end of the procedure. On the other hand, the control group received 5 ml of lidocaine 2% as routine care before episiotomy incision. Data were collected using visual analogue scale to compare the study groups in terms of pain intensity. In addition, patient satisfaction with pain management technique during episiotomy and side effects of Entonox were assessed. Data analysis was performed in SPSS version 22 using Mann-Whitney U and Chi-square tests, and P value of less than 0.05 was considered statistically significant.

Results: In this study, no significant difference was observed between the intervention and control groups regarding pain intensity (P=0.52). Moreover, no significant difference was observed in the satisfaction level of the two groups (P=0.70).

Conclusion: According to the results of this study, Entonox could be used as an effective and noninvasive alternative to lidocaine to reduce pain during episiotomy incision without significant side effects.

► *Please cite this paper as*:
Honarmandpour A, Abbaspour Z, Ziagham S, Javadifar N. Effects of Entonox in Comparison with Lidocaine on Pain Severity during Episiotomy Incision in Nulliparous Women: A Randomized Control Trial. Journal of Midwifery and Reproductive Health. 2017; 5(1): 791-799. DOI: 10.22038/jmrh.2016.7965

Introduction

Episiotomy is usually performed with scissors before fetal head crowning, when the perineum is sufficiently distended and stretched, to prevent severe spontaneous perineal tears, facilitate delivery and reduce the time of baby's exit from the womb (1). Despite the decreased rate of episiotomy in developed countries during the past years, total rate of trauma and injury to the genital tract after vaginal delivery is still high (2). This rate has been reported to be 8% in the Netherlands, 20% in England, 50% in the United States, 28% in Argentina, 40.6% in Australia and 54% in North America.

While there is no comprehensive statistics about episiotomy in Iran, its prevalence might be

* *Corresponding author:* Nahid Javadifar, Reproductive Health Promotion Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. Email: Nahidjavadifar_341@yahoo.com

on the rise due to the high fertility rate in our country (3). In this regard, Khajavi et al. (2009) reported the prevalence of episiotomy in Iran to be 97.3% in nulliparous women (4). Although the routine use of episiotomy has declined in developed countries, episiotomy is still practiced in Asian countries due to the high susceptibility of Asian women with short perineum and strong tissue to extensive perineal tears (5).

Pain is a common phenomenon, regarded as an inevitable part of delivery and postpartum process (6). Injection of lidocaine is one of the usual pain relief methods in small operations (e.g., episiotomy) (7). Despite the benefits of this technique, exceeding the maximum dose of lidocaine could be associated with considerable side effects. However, these important complications are not common and often occur due to the accidental intravascular injection of local anesthetics during nerve block.

Neurotoxicity could lead to fidgeting, dizziness, tinnitus, slurred speech, and tonic and colonic seizures. Seizure is associated with the weakening of the central nervous system (CNS), apnea, vascular hypoxia and metabolic acidosis, which occur quickly and cause death in some cases. Despite the fact that cardiovascular system is resistant to the toxic effects of local analgesics, high plasma concentrations of analgesics can cause arteriolar smooth muscle relaxation, direct weakening of myocardia and severe hypotension (8).

Labor pain management encompasses the use of analgesics and anesthetics with minimum side effects. Lidocaine is currently used as a pain-relieving agent during episiotomy; however, it is associated with various side effects that cannot be controlled by the therapist. In addition, accidental intravascular injection of lidocaine could lead to the mentioned complications (9). Today, non-injection methods for analgesia have opened a new horizon in medicine, among which Entonox is considered the most important compound. Entonox is a weak inorganic gas consisting of 50% nitrous oxide and 50% oxygen. It is odorless and colorless, which serves as an effective inhaled analgesic (10).

Studies have shown that Entonox gas can be used as an analgesic in surgeries, such as colonoscopy and liver biopsy (11, 12). Furthermore, it has been declared that this gas can reduce the pain of joint dislocation along with other analgesics; this effect could be exerted independently or in combination with other analgesics in childbirth and sigmoidoscopy (13-15). Entonox can also be applied along with other analgesics to decrease the pain and discomfort caused by intra-articular injection of drugs, ophthalmologic surgeries, cancer treatment, peripheral vein cannulation and biopsy (16-20). However, independent use of this compound might be insufficient in some cases, such as the alleviation of the pain caused by shoulder dislocation (21).

On this theme, Becker (2008) has reported the analgesic effects of morphine at the dosage of 15 mg (22). In addition, Rosen (2003) evaluated labor pain and reported that the analgesic effects of nitrous oxide are more significant compared to opioids. Moreover, he compared this drug with paracervical block, revealing the short-term pain relief by Entonox, which was associated with lower anxiety and pain (23).

Entonox rapidly diffuses through the walls of the alveoli and is transported in the plasma as a solution without binding to hemoglobin (10). Due to its very low solubility in blood, it is transferred to the brain and spinal cord about 15 seconds after inhalation with appropriate concentration and effective pressure (24). As an anesthetic gas, Entonox weakens the CNS non-specifically.

According to the results obtained by Gilman, Entonox particularly acts through interactions with endogenous opioids system. In addition, its functionality is mostly observed in the areas of the brain and spinal cord with many morphine-sensitized cells (25). Side effects of Entonox start within 30 seconds after administration and maximize within two minutes (10). Oxygen in Entonox prevents the risk of hypoxia in patients (26).

Entonox could be easily administered and used as a simple and safe method with fast analgesic effects and quick returns (27). Moreover, Entonox has a short half-life without the need for sophisticated devices (10). This gas has glancing effects due to the rapid excretion from the lungs, while it has no significant impact on maternal cardiovascular, respiratory and nervous systems (28).

According to the American Gynecological and Obstetrical Society (AGOS), progress of pain

management programs in different countries could improve the quality of obstetric care and promote normal vaginal delivery by proposing new pain-reliving methods, which ultimately reduces the rate of elective caesarean section. While it is recommended that episiotomy be applied in emergency cases only, application of this technique for many pregnant women, especially nulliparous women, is still inevitable. Moreover, pain relief is considered as one of the pillars of care during childbirth and thereafter.

Several studies have been performed in Iran, focusing on the effect of Entonox on labor pain (9, 29-31); nevertheless, no studies are found on the effect of Entonox on pain intensity during episiotomy. With this background in mind, this study aimed to compare the effects of Entonox and lidocaine on pain intensity during episiotomy incision in nulliparous women.

Materials and Methods

This clinical trial was conducted on 120 nulliparous women referring to Alhadi Hospital of Shushtar, Iran in 2015. Inclusion criteria were pregnant women with gestational age of 39-42 weeks (based on first-trimester ultrasound or first day of last menstruation), age range of 18-35 years, singleton pregnancy, nulliparous women, cephalic presentation and body mass index (BMI) of 19.8-30 kg/m^2 during the first trimester of pregnancy.

Exclusion criteria were the presence of respiratory, hepatic, renal, cardiovascular, and gastrointestinal tract diseases, hypertension, autoimmune diseases, diabetes, placental abruption, placenta previa, multiple pregnancy, pelvic stenosis, allergy to local analgesia or Entonox gas, prolonged delivery, and stopping the active phase and the second stage of labor. After obtaining the necessary approval from hospital authorities, study objectives were explained to the subjects and they were assured of confidentiality terms regarding their personal information. In addition, written informed consent was obtained prior to the study.

Sample size was estimated at 60 cases per group, and the participants were randomly assigned to two groups of intervention (Entonox) and control (lidocaine). The first and second subjects in each group were selected by coin flip and the following participants entered as just one amongjthat one subject was allocated to the intervention group and the next subject was assigned to the control group.

At the beginning of the study, the researcher explained about the research procedures, labor stages and visual analogue scale (VAS). VAS is a standard method to measure pain intensity, the reliability of which has been confirmed in numerous studies (32). Feting et al. (1992) used the test-retest method at intervals of 10-15 minutes to determine the validity of VAS. According to the results, coefficient of this scale was r=0.85, and VAS was introduced as a standard procedure to determine pain intensity (33). According to VAS, pain intensity is classified as none (score zero), mild (scores 1-3), moderate (scores 4-6), severe (scores 7-9) and very severe (score 10) (30).

Demographic questionnaires were completed by the researcher, and content validity was used to determine the scientific validity of this questionnaire and prepared checklists. To do so, the researcher used books, articles, scientific resources and numerous publications to codify the check-lists. The validity of the questionnaire was confirmed by 10 faculty members. Simultaneously, to determine the scientific reliability of data collection checklists, they were completed for 10 participants by a co-researcher midwife and another midwife, who were at the same level. Afterwards, the results were compared using Pearson's correlation coefficient (0.8) and scientific reliability of tools was measured.

In order to synchronize the confounding variables (e.g., length and type of incision), vaginal examinations, which could interfere with the process of the study, were conducted by the researcher, who acted as a delivery agent and performed all incision and internal examinations. However, data collection and analysis was performed by a midwife, who was a co-researcher and blinded to the method of pain relief in the delivery room. After admission, mothers were transferred to the labor unit and monitored until the time of fetal head crowning and transfer to the delivery room.

In the control group, 5 ml of 2% lidocaine was injected to the perineum or entry of vagina by the researcher at seven, eight and nine h before the episiotomy incision. In the intervention group, Entonox gas was administered two minutes before the episiotomy procedure. Entonox cylinders should be stored at above 10°C for 24 hours prior to use. After the admission of mothers, they were trained how to inhale Entonox through deep and calm breaths. During episiotomy, Entonox was inhaled through face masks by the participants, and they were encouraged to take deep and slow breaths. Before the intervention, breathing techniques "deep breath, pause at the end of each breath, exhale slowly, rest" were taught to mothers and they were allowed to use Entonox gas at any time.

Changes in heart rate, blood pressure and oxyhemoglobin saturation were recorded through a pulse oximetry test from the beginning of Entonox inhalation to the end of the incision. In addition, side effects of Entonox were recorded by midwife on duty during the inhalation period. To avoid bias, mother's satisfaction with both analgesic methods was recorded using the "completely satisfied, satisfied, dissatisfied, completely dissatisfied" options after completing the repair of episiotomy and leaving the delivery room by the researcher. Moreover, pain intensity was measured in both groups using VAS (10 cm) in the delivery room by a midwife and score of five was considered as moderate pain.

This study was approved by the Ethics Committee of Ahvaz University of Medical Sciences, Ahvaz, Iran with the ethical code of IR.AJUMS.REC.1394.151, funded by the university.

Data analysis was performed in SPSS version 22 using Mann-Whitney U and Chi-square tests. In addition, P-value of less than 0.05 was considered statistically significant.

Results

In this study, the intervention and control groups were homogenous regarding demographic characteristics (e.g., age, educational level, place of residence, income status, occupational status, BMI and maternal factors, including gestational age, severity and duration of contractions at the second phase, duration of the second phase, need for and rate of induction, participation in labor preparation classes, prenatal exercises and perineal exercises during the last month of pregnancy) (P<0.05) (Tables 1-3).

Table 1. Frequency distribution and comparison of demographics of subjects in intervention (Entonox) and control (lidocaine) groups

Variables	Control (lidocaine) group(n=60)	Intervention (Entonox) group(n=60)	P-value
Maternal age	23.25±4.28	23±4.26	*0.74
BMI in the first trimester (kg/m^2)	23.62±2.99	23.08±3.68	**0.89
Educational level			*0.12
Illiterate	3 (5%)	1 (1.7%)	
Below diploma	31 (51.7%)	31 (51.7%)	
Diploma	11 (18.3%)	20 (33.3%)	
College	15 (25%)	8 (13.3%)	
Place of residence			*0.99
City	27 (45%)	27 (45%)	
Village	33 (55%)	33 (55%)	
Income status			*0.48
Favorable	2 (3.3%)	2 (3.3%)	
Adequate	50 (83.3%)	45 (75%)	
Inadequate	8 (13.3%)	13 (21.7%)	
Occupational status			*0.24
Employed	3 (5%)	0 (0)	
Housewife	57 (95%)	60 (100%)	

Quantitative variables presented as Mean±standard deviation; qualitative variables presented as percentage. * Chi-square, **Mann-Whitney U

Table 2. Comparison of frequency distribution of delivery characteristics and maternal factors in intervention (Entonox) and control (lidocaine) groups

Variables	Control (lidocaine) group (n=60)	Intervention (Entonox) group (n=60)	P-value
Classic induction			*0.70
Yes	23 (38.3%)	21 (35%)	
No	37 (61.7%)	39 (65%)	
Severity of contractions at the second phase			*0.99
Moderate	7 (11.7%)	6 (10%)	
Severe	53 (88.3%)	54 (90%)	
Participation in labor preparation classes			*0.43
Yes	5 (8.3%)	2 (3.3%)	
No	55 (91.7%)	58 (96.7%)	
Prenatal exercise			*0.17
Yes	4 (6.7%)	1 (1.7%)	
No	56 (93.3%)	59 (98.3%)	
Perineal exercises during the last month of pregnancy			*0.49
Yes	2 (3.3%)	0 (0%)	
No	58 (96.7%)	60 (100%)	

Qualitative variables presented as percentage.*Chi-square test

Table 3. Comparison of mean and standard deviation of delivery characteristics and maternal factors in intervention (Entonox) and control (lidocaine) groups

Variables	Control (lidocaine) group (n=60)	Intervention (Entonox) group (n=60)	P-value
Rate of classic induction (cc)	68.54±34.99	73.09±36.62	**0.65
Duration of contractions at the second phase (sec)	56.66±6.92	56.25±6.14	**0.93
Duration of the second phase of delivery (min)	46.50±33.05	39.50±25.47	**0.30
Gestational age based on the last menstrual period	40.21±0.80	40.25±0.77	**0.99
Gestational age based on sonography	40.25±0.72	40.20±0.65	**0.69

Quantitative variables presented as mean and standard deviation. *Mann-Whitney U

None of the patients in the intervention group required lidocaine administration along with Entonox for pain relief during episiotomy. Furthermore, all these subjects recommended Entonox gas as an analgesic method during episiotomy incision.

Evaluation of the transient side effects observed in the intervention group revealed that 20 patients (33.3%) had no specific side effects, 26 (43.3%) cases had dizziness, seven (11.7%) individuals had dry mouth and seven (11.7%) participants had increased drowsiness. In this study, the most common observed side effect was dizziness. All the side effects were transient and were eliminated after the inhalation period.

Pain intensity during the episiotomy incision was estimated by the VAS ruler and no significant difference was observed between the two groups (P=0.52). Moreover, there were no cases of very severe pain in the groups. After the comparison of maternal satisfaction, no statistically significant difference was observed between the intervention and control groups (P=0.70). It is noteworthy that no cases of completely dissatisfied were observed in the study groups (Table 4).

Discussion

According to the results of the current research, no significant difference was observed between the intervention and control groups regarding pain intensity during episiotomy (P=0.52). Therefore, Entonox, which is a non-injection method, can be used as an alternative to lidocaine, which is the standard method of pain

Table 4. Frequency distribution and comparison of pain intensity and satisfaction with the method of pain relief during episiotomy in intervention (Entonox) and control (lidocaine) groups

Variables	Control (lidocaine) group (n=60)	Intervention (Entonox) group (n=60)	P-value
Pain intensity during episiotomy			*0.52
Mild	44 (73.3%)	48 (80%)	
Moderate	15 (25%)	10 (16.7%)	
Severe	1 (1.7%)	2 (3.3%)	
Satisfaction with the pain relief method during episiotomy			*0.70
Dissatisfied	1 (1.7%)	0 (0%)	
Satisfied	21 (35%)	19 (31.7%)	
Completely satisfied	38 (63.3%)	41 (63.3%)	

Qualitative variables presented as percentage.*Chi-square test

relief during episiotomy. On this note, a study by Meskine et al. (2011) was conducted to evaluate the analgesic effect of a mixture of oxygen and nitrous oxide (immuno) inhaled during biopsy during percutaneous biopsy of the liverin patients with liver lesions. According to the results, a reduction was observed in pain level of the group receiving immuno, compared to the placebo group. Moreover, the number of patients who were willing to receive additional liver biopsy in this condition was higher in the immuno group, compared to the placebo group. There was a significant relief of pain in patients treated with immuno, compared to those administered with placebo (12), which is consistent with our findings.

In a study by Navarro et al. (2003), it was concluded that a mixture of sevoflurane with Entonox gas is more effective, compared to the use of thiopental-fentanyl for anesthesia in small surgeries of women. In addition, this study focused on the reduction of pain score using Entonox (34). In another study by Young et al. (2012), pain intensity significantly reduced in the group receiving Entonox, compared to the oxygen group in the diagnostic and therapeutic procedures for urology outpatients (35). Manikandan et al. (2003) suggested no significant difference between the lidocaine and Entonox groups regarding the score of pain during prostate biopsy (36).

Results obtained by Sullivan et al. (2007) were indicative of a significant decrease in verbal scores of pain and VAS during cystoscopy in the Entonox group (26). On this theme, Mazdak (2007) marked a significant reduction in the pethidine and Entonox groups in terms of pain in patients undergoing the removal of stones through extracorporeal shock wave lithotripsy (Eswl). According to the results of the mentioned study, no significant difference was found between intravenous pethidine and Entonox groups regarding pain reduction (37). Although in all the mentioned studies Entonox was used for purposes other than incision to relieve pain, their results regarding its analgesic effects were in line with those of the present study.

In a study by Mahshidfar et al. (2009), Entonox gas was not suitable to relieve the pain of a dislocated shoulder, which is inconsistent with our findings (21). Findings of the mentioned research were indicative of higher pain reduction, greater patient satisfaction and shorter duration of surgery in the group receiving midazolam and fentanyl; however, length of recovery was shorter in the Entonox group. This discrepancy could be due to no limitations in age and gender, differences in how to use Entonox and the initiation time of Entonox use.

Bruce et al. (2006), conducted a study to evaluate the effect of independent use of morphine or Entonox as an analgesic to relieve pain. According to the results, independent use of the mentioned compounds had no significant impact on children with chest drain undergoing a surgery (38). Moreover, in a study by YauKan (2006), no significant difference was observed between inhaled Entonox gas and oxygen to relief pain during abortion suction evacuation at the first trimester. According to the results, Entonox had no significant effect as an analgesic method during abortion suction evacuation at

the first trimester. This inconsistency between the results could be due to the differences in age, gestational age and route of administration of Entonox gas (39). In the mentioned study, subjects inhaled Entonox gas simultaneous with the onset of pain, whereas Entonox gas inhalation started two minutes prior to the start of episiotomy in the present study. In another study by Sewell (2014), Entonox is recommended as a pain relief method used in all women referred for intrauterine device insertion (40).

In the present study, satisfaction with the used pain relief methods during episiotomy was not significantly different between the two groups. Berlit performed a study in Germany (2013) and suggested no significant difference between Entonox and lidocaine groups in terms of satisfaction with genital laceration repair (2), which is consistent with the results of the present study. However, it is worth mentioning that the technique was used in the study by Berlit to repair genital laceration.

Results obtained by YauKan (2006) revealed no significant difference between the Entonox and oxygen inhalation groups regarding patient satisfaction with pain relief during abortion suction evacuation at the first trimester (39). This consistency between the two groups could be due to the ineffectiveness of Entonox as an analgesic during abortion suction evacuation at the first trimester.

In a study by Salehian et al. (2009), it was demonstrated that the highest percentage (66%) of satisfaction with delivery was related to the Entonox group. On the other hand, 42% of the subjects in the control group were dissatisfied with their childbirth, which revealed a significant difference between the two groups (29). Higher satisfaction in the Entonox group could be due to the analgesic effects of Entonox on pain during delivery. In the present study, it seems that no significant difference was observed between the intervention and control groups in terms of the rate of satisfaction with pain relief method, which is directly correlated with labor pain reduction by this method. The most frequent side effect observed in our study was dizziness, and all side effects were transient and eliminated after the cessation of inhalation.

One of the major drawbacks of this study was differences in the pain threshold of patients (i.e., differences in the expression of pain and its impact on the outcome of the evaluation). In addition, responses to pain intensity and answers of all research units, which have been assumed as correct answer and could not be controlled by the researcher, could play a role in this regard. In addition, all stages of the study, including sampling, initial assessments, training the proper method of Entonox inhaling, correct method of placing the Entonox mask, delivery and episiotomy, were performed in the presence and by the researcher that added to the accuracy of the study. However, the only exception was the measuring of pain intensity by VAS and client satisfaction with pain relief method during episiotomy, which was conducted by a midwife as the co-researcher.

Conclusion

According to the results of the present study, lidocaine injection, which is currently used as a pain relief method during episiotomy, is painful. In addition, accidental intravascular injection of this compound could be associated with serious complications. Meanwhile, Entonox gas is a non-invasive mechanism with transient side effects. This substance is easy to use with fast and analgesic effects and could be used to relieve pain during episiotomy. Therefore, it is suggested that Entonox be used as an alternative to lidocaine to relive pain during episiotomy.

Acknowledgements

This study is extracted from a master's thesis in midwifery with the code of (RHTRC-9408), funded by the research deputy of Ahvaz University of Medical Sciences. Hereby, we extend our gratitude to the maternity staff of Shushtar AlHadi Hospital and all the participants for their cooperation in this study.

Conflicts of Interest

There are no conflicts of interest.

References

1. Robinson JN, Lockwood CJ, Barss VA. Approach to

episiotomy. UpToDate. Available at: URL: www.Up to Date; 2013.
2. Berlit S, Tuschy B, Brade J, Mayer J, Kehl S, Sutterlin M. Effectiveness of nitrous oxide for postpartum perineal repair: a randomized controlled trial. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2013; 170(2):329–332.
3. Aradmehr M, Azhari S, Shakeri MT. Study of factors associated with postoperative pain following episiotomy in primiparous women at Mashhad Omalbanin hospital in 2012. Journal of Midwifery and Reproductive Health. 2015; 3(1):305-314.
4. Shojae KK, Dawati A, Zayeri F. Frequency and side effect of episiotomy in primiparous women: a three- month longitudinal survey. Qom University of Medical Sciences Journal. 2009; 3(2):47-50 (Persian).
5. Lam KW, Wong HS, Pun TC. The practice of episiotomy in public hospitals in Hong Kong. Hong Kong Medical Journal. 2006; 12(2):94-98.
6. Abushaikha L, Oweis A. Labour pain experience and intensity: a Jordanian perspective. International Journal of Nursing Practice. 2005; 11(1):33-38.
7. Franchi M, Cromi A, Scarper S, Gaudino F, SiestoG, Ghezz F. Comparison between lidocaine-prilocaine creams (EMLA) and mepivacaine infiltration for pain relief during perineal repair after childbirth: a randomized trial. American Journal of Obstetrics and Gynecology. 2009; 201(2):186-e1.
8. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong YC, et al. Williams Obstetrics. 24th ed. New York, NY: McGraw-Hill; 2014. P. 605-607.
9. Mohammad JR, Barati M, Torabzadeh BVA, Torabzadeh BAA. The effect of Entonox gas inhalation on the duration of active phase of labor and outcome of delivery. Jundishapur Scientific Medical Journal. 2013; 12(1):13-19.
10. Rezayi H, Khodabande S, Mohammadalizadeh S. Entonox gas effect on labor-related variables referring to Imam Ali (AS) in Zarand. Iranian Journal of Nursing and Midwifery Research. 2006; 6(1):15-22.
11. Maslekar S, Gardiner A, Hughes M, Culbert B, Duthie GS. Randomized clinical trial of entonox® versus midazolam–fentanyl sedation for colonoscopy. British Journal of Surgery. 2009; 96(4):361–368.
12. Meskine N, Vullierme MP, Zappa M, Assignies G, Sibert A, Vilgrain V. Evaluation of analgesic effect of equimolar mixture of oxygen and nitrous oxide inhalation during percutaneous biopsy of focal liver lesions. Academic Radiology. 2011; 18(7):816–821.
13. Gleeson AP, Graham CA, Meyer AM. Intra-articular lignocaine versus Entonox for reduction of acute anterior shoulder dislocation. Injury. 1999; 30(6):403–405.
14. Rosen MA. Nitrous oxide for relief of labor pain: a systematic review. American Journal of Obstetrics and Gynecology. 2002; 186(5):110-126.
15. Harding TA, Gibson JA. The use of inhaled nitrous oxide for flexible sigmoidoscopy: a placebo-controlled trial. Endoscopy. 2000; 32(6):457-460.
16. Cleary AG, Ramanan AV, Baildam E, Birch A, Sills JA, Davidson JE. Nitrous oxide analgesia during intra-articular injection for juvenile idiopathic arthritis. Archives of Disease in Childhood. 2002; 86(6):416-418.
17. Cook HL, Newsom RS, Mensah E, Saeed M, James D, Ffytche TJ. Entonox as an analgesic agent during panretinal photocoagulation. British Journal of Ophthalmology. 2002; 86(10):1107-1108.
18. Parlow JL, Milne B, Tod DA, Stewart GI, Griffiths JM, Dudgeon DJ. Self-administered nitrous oxide for the management of incident pain in terminally ill patients a blinded case series. Palliative Medicine. 2005; 19(1):3-8.
19. Gerhardt RT, King KM, Wiegert RS. Inhaled nitrous oxide versus placebo as an analgesic and anxiolytic adjunct to peripheral intravenous cannulation. The American Journal of Emergency Medicine. 2001; 19(6):492-494.
20. Masood J, Shah N, Lane T, Andrews H, Simpson P, Barua JM. Nitrous oxide (Entonox) inhalation and tolerance of transrectal ultrasound guided prostate biopsy a double-blind randomized controlled study. The Journal of urology. 2002; 168(1):116-120.
21. Mahshidfar B, Asgari-Darian A, Ghafouri HB, Ersoy G, Yasinzadeh MR. Reduction of anterior shoulder dislocation in emergency department; Is entonox® effective? Bioimpacts. 2011; 1(4):237–240.
22. Becker DE, Rosenberg M. Nitrous oxide and the inhalation anesthetics. Anesthesia Progress. 2008; 55(4):124–131.
23. Rosen MA. Relief of labor pain. Journal of University of California. 2003; 186(5):110.
24. Emmanouil DE, Quock RM. Advances in understanding the actions of nitrous oxide. Anesthesia Progress. 2007; 54(1):9-18.
25. Sullivan Í, Benger J. Nitrous oxide in emergency medicine. Emergency Medicine Journal. 2003; 20(3):214–217.
26. Yazdi Moghadam H, Rahnemai Rahsepar F, Haider A. Studying the effect of Entonox gas on the APGAR of the neonates. Journal of Rafsanjan University Medical Sciences. 2011; 10(3):165-174 (Persian).
27. Emmanouil DE, Quock RM. Advances in understanding the actions of nitrous oxide. Anesthesia Progress. 2007; 54(1):9-18.
28. Calleary JG, Masood J, Van-Mallaerts R, Barua JM. Nitrous oxide inhalation to improve patient acceptance and reduce procedure related pain of flexible cystoscopy for men younger than 55 years. The Journal of Urology. 2007; 178(1):184-188.
29. Salehian T, Safdari F, Jahantighi S. The effect of

entonox on labor pain and outcome of delivery in primiparous in Iranshahr, Iran (2009). Journal of Gorgan Nursing Research. 2010; 7(1):1-9 (Persian).
30. Iravani M. Effect of inhaled Entonox on the severity and duration of delivery. The Iranian of Journal of Obstetrics, Gynecology and Infertility. 2009; 3(21):7 (Persian).
31. Talebi H, Nourozi A, Jamilian M, Baharfar N, Eghtesadi-Araghi P. Entonox for labor pain: a randomized placebo controlled trial. Pak J Biol Sci 2009; 12(17):1217-1221.
32. Bodion CA, Freedman G, Hossain S, Eisenkraft JB, Beilin Y. The visual analog scale for pain: clinical significance in postoperative patients. Anesthesiology. 2001; 95(3):135-136.
33. Fitting JH, Grochow LB, Folstein MF, Ettinger DS, Colvin M. The course of nausea and vomiting after high dose cyclophosphamide. Cancer Treatment Reports. 1992; 6(7):1487-1493.
34. Navarro NC, Aquino AA, Vásquez JC, García MR. Comparison of sevoflurane/nitrous oxide and thiopental/fentanyl in anesthesia for minor gynecologic surgery. Ginecologia y Obstetricia de Mexico. 2003; 71:284-290.
35. Young A, Ismail M, Papatsoris AG, Barua JM, Calleary JG, Masood J. Entonox inhalation to reduce pain in common diagnostic and therapeutic outpatient urological procedures: a review of the evidence. Annals of the Royal College of Surgeons of England. 2012; 94(1):8–11.
36. Manikandan R, Srirangam SJ, Brown SC, O'reilly PH, Collins GN. Nitrous oxide vs. periprostatic nerve block with 1% lidocaine during transrectal ultrasound guided biopsy of the prostate: a prospective, randomized, controlled trial. The Journal of Urology. 2003; 170(1):1181–1883.
37. MazdakH, AbazariP, GhassamiF, NajafipourS. The analgesic effect of inhalational Entonox for extracorporeal shock wave lithotripsy. Urological Research. 2007; 35(6):331–334.
38. Bruce E, Franck L, Howard RF. The efficacy of morphine and entonox analgesia during chest drain removal in children. Pediatric Anesthesia. 2006; 16(3):302-308.
39. Kan AS, Caves N, Wong SY, Ng EH, Ho PC. A double-blind, randomized controlled trial on the use of a 50:50 mixture of nitrous oxide/oxygen in pain relief during suction evacuation for the first trimester pregnancy termination. Human Reproduction. 2006; 21(10):2606-2611.
40. Sewell E. Entonox for the relief of pain or anxiety during IUS/IUD fitting. Journal of Family Planning and Reproductive Health Care. 2014; 40(2):150.
41. Klomp T, van Poppel M, Jones L, Lazet J, Di Nisio M, Lagro-Janssen AL. Inhaled analgesia for pain management in labour. The Cochrane Database of Systematic Reviews2012; 12:9.
42. Rosen MA. Nitrous oxide for relief of labor pain: a systematic review. American Journal of Obstetrics and Gynecology. 2002; 186(5):110-126.