Original Article

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Associations of Oxidative Stress Indices in Infants Born via Natural Delivery with Entonox Exposure

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ABSTRACT

BACKGROUND AND OBJECTIVE: Entonox is an odorless, tasteless gas and the first anesthesia agent used in obstetrics. To date, no studies have evaluated the effects of Entonox on oxidative stress. This study aimed to investigate the association between infant oxidative stress indices in mothers exposed to Entonox gas during vaginal delivery.

METHODS: This cohort study was conducted on 120 pregnant women undergoing natural labor. Subjects were divided into two groups of delivery with and without exposure to analgesic Entonox (N=60). After delivery, 5 ml of arterial blood was obtained from the umbilical cords of all infants, and indicators such as malondialdehyde, thiols and total antioxidant capacity were measured and evaluated in each group.

FINDINGS: In this study, there were no significant differences in the indicators of oxidative stress between the study groups. Values obtained in groups with and without Entonox exposure were respectively as follows: total antioxidant capacity (1.33±1.21 vs. 1.59±1.3, p=0.84), thiols (0.363±0.313 vs. 0.238±0.225, p=0.07), lipid peroxidation (4.60±2.76 vs. 5.31±3.19, p=1).

CONCLUSION: According to the results of this study, exposure to Entonox had no significant effects on the indicators of infant oxidative stress. Therefore, Entonox exposure could be used as a safe analgesic approach in natural delivery.

KEY WORDS: Oxidative Stress, Natural Delivery, Painless Delivery, Infant.

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Introduction

Oxidative stress occurs when free radicals defeat the antioxidant defensive mechanism of the body. In other words, oxidative stress is defined as the disturbance of balance between free radicals and antioxidant defenses. Although oxygen is inherent to survival, high concentrations of oxygen could produce dangerous substances such as free radicals. Free radicals are electronically unstable atoms or molecules, which are able to remove electrons from other molecules in order to achieve stability (1). According to the literature, oxidative stress in the fetus activates gene sequences responsible for inflammation, coagulation, fibrinolysis and regulation of the cell cycle (2). Reactive oxygen species play a key role in fertilization and fetal development if the antioxidant defense mechanism of the body is in optimal condition

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(3). Under circumstances, free radicals overcome this defense mechanism, causing damage to different tissues and organs of the infant, including lungs, brain and retina. These damages could occasionally be life-threatening and have adverse effects on the quality of life of infants. Several studies have confirmed the pivotal role of oxidative stress in the incidence of various neonatal diseases, such as bronchopulmonary dysplasia, retinopathy of prematurity and enterocolitis (4,5). Newborns are particularly susceptible to the negative effects of free radicals. First, oxygen pressure at birth is five times higher than the level of intrauterine oxygen (20 vs. 100 torr). Second, antioxidant defense in newborns is relatively disproportionate to the high level of environmental oxygen. In addition, premature infants are normally prone to various disorders, such as inflammation, infection and free iron excess, and these conditions could increase the production of free radicals. Therefore, inhibiting the production of free radicals significantly affects neonatal health (6,7). A few studies have evaluated oxidative stress during labor (8,9). According to the findings, inflammatory mediators, such as arachidonic acid metabolites (prostaglandin E2) and interleukin -6, which are involved in the onset of labor, increase the production of free radicals (10). Intense pain, severe contractions and high oxygenation are other factors that could trigger the production of free radicals during labor (11). Entonox is composed of 50% oxygen and 50% N2O. This gas is odorless and tasteless and is the first substance used in obstetric anesthesia. Entonox is quickly absorbed through the lungs and enters the bloodstream; however, it cannot be combined with hemoglobin. Rapid entrance and exit of Entonox from the blood occurs due to its low solubility in the blood. After entering the bloodstream, nitrogen is removed, and gas volume increases in body cavities, such as the middle ear, sinuses, pleural cavity and intestines. Entonox is quickly excreted through the mother's lungs and seems to have no adverse effects on the fetus (12). This study aimed to evaluate the relationship between oxidative stress indices of infants whose mothers were exposed to Entonox during natural delivery.

Methods

This cohort study was conducted on 120 pregnant women admitted to the labor room after obtaining written informed consent. Based on the formula proposed by case-control studies, 80% power, α=0.05, expected odds ratio of 3, and 40% level of antioxidants in the control group, sample size was calculated at 60 patients in each group. Sampling was performed after providing the approval of Taleghani Hospital authorities in Arak, Iran.

According to the health protocol of this medical center, pregnant women are allowed to use Entonox selectively for painless delivery. To evaluate oxidative stress indices in natural delivery with Entonox exposure, subjects were selected from the women who opted for Entonox exposure and met the inclusion criteria.Subjects were divided into two groups of 60, including natural delivery without Entonox, and natural delivery with exposure to Entonox. Mothers in the Entonox group received exposure during the active phase of delivery in order to reduce labor pain. Inclusion criteria were the absence of acute and chronic pregnancy complications, single-gestation pregnancy and gestational age of 38-40 weeks. During the postpartum, 5 ml of cord blood was obtained from all the neonates. Samples presented with any complications or neonatal Apgar score of <7 were excluded from the study.

In addition, two women in the Entonox exposure group, as well as one subject in the natural delivery group without analgesia, were excluded due to cesarean section. Blood samples were transferred to the laboratory, and the following tests were performed: Hu to evaluate protein oxidation (9), thiobarbituric acid (TBA) to assess lipid peroxidation (maximum absorption of pink MDA-TBA complex was recorded using a spectrophotometer at 532 nm) (9). To evaluate total serum antioxidant capacity, used the ferric reducing ability of plasma (FRAP), and three FRAP groups were added containing 2, 4, 6-tripyridyl triazine (TPZ) (maximum absorption of the blue complex of $TPTZ+Fe^{2}$ was recorded using a spectrophotometer at 593 nm) (9). Data analysis was performed using descriptive statistics (number and percentage) and independent t-test in SPSS, and $p<0.05$ was considered significant.

Results

In this study, mean age of the subjects in the Entonox-delivery group was 24.08±4.08 years, and it was 22.83±0.52 years in the delivery group without Entonox exposure. In the Entonox-delivery group, mean of gestational age was 39.06±0.80 weeks and it was 39.02±0.63 weeks in the delivery group without

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exposure. In addition, mean of delivery duration in the first phase of labor was 4.17±1.14 hours in the Entonox-delivery group and 4.52±1.26 hours in the delivery group without exposure.

In the study group without Entonox exposure, mean birth weight of neonates was 3127.6±32.7 g, while it was 3142±281.65 g in the Entonox exposure group. Duration of the second phase of labor in the group with Entonox exposure was 45.935±20.65 minutes, while it was 47.67±28.39 minutes in the group without exposure. No significant differences were observed in the aforementioned variables between the study groups (table1).

Table 1. Mean and Standard Deviation (SD) of Oxidative Stress Indices in Infants of Study Groups with and without Entonox Exposure

Index \ Group	Delivery		
	Without Entonox Mean±SD	With Entonox Mean±SD	p-value
Total Antioxidant Capacity (nμ/mm)	1.33±1.21	1.59±1.35	0.84
Thiol Groups (mμ/mm)	0.363±0.313	0.238±0.225	0.07
Lipid Peroxidation (nμ/mm)	4.60±2.76	5.31±3.19	1

Discussion

According to the results of the present study, no significant differences were observed in the indicators of oxidative stress in infants born via natural delivery with and without exposure to Entonox. According to the literature, type of delivery significantly affects the level of antioxidant substances in the fetus and newborn. One study conducted in this regard indicated that concentration of tocopherols and superoxide dismutase was lower in the cord blood of infants born via caesarean section compared to those born via natural delivery without Entonox exposure (11). Results of another research performed on mice showed that induction of anesthesia by N2O gas increased lipid peroxidation in the liver of the studied animals (13).Considering the fact that exposure to Entonox had no significant effects on the lipid peroxidation of neonates, it seems that fetal antioxidant components, especially bilirubin and red blood cells, are able to encounter free radicals efficiently (14). The findings of the current study indicated that total antioxidant capacity of the neonates in the delivery group with Entonox exposure was higher compared to the neonates in the delivery group without exposure. In other words, antioxidant defense increased in infants of the delivery group exposed to Entonox; however, this increase was not statistically significant.

After crossing the placenta, maternal oxidative stress markers reach the fetus, and due to the great antioxidant capacity induced by high bilirubin levels, the fetus is able to exhibit resistance against the stress (14). In a study by Vakilian et al., it was demonstrated that the fetus could overcome maternal oxidative stress through potent antioxidant mechanisms, and there was no significant association between the total antioxidant capacity of the mother and infant (15).

Therefore, it is probable that fetal antioxidant mechanisms are markedly different with maternal antioxidant mechanisms. According to the results of the present study, concentration of thiols was higher in neonates born via natural delivery without Entonox exposure; however, the difference was not significant. In one research, it was reported that as a thiol group, glutathione was higher in neonates born via natural delivery compared to those born via cesarean section (16). Results of another study indicated that storage of non-enzymatic antioxidants was higher in infants who were born via vaginal delivery (17).

In this research, we could not identify any studies about the changes caused by Entonox exposure in the maternal and fetal antioxidant system. Nevertheless, previous studies regarding various delivery modes have shown that total serum antioxidant capacity is lower in neonates born via caesarian section (8, 18).On the other hand, several studies were found on the comparison of the indicators of maternal oxidative stress in both natural and caesarian deliveries. According to one of these researches, level of oxidative stress is lower in neonates born via caesarean section compared to those born via vaginal delivery. This could be due to long labor and time in the birth canal (19).

In their study, Mehmetoúlu et al. noticed that lipid peroxidation was lower in neonates born via natural delivery compared to those born via caesarean section (14). Conversely, Mine et al. reported the level of oxidative stress to be higher in infants born via vaginal delivery compared to those born via caesarean section.Inconsistencies between the findings of different studies could be due to the production of compensatory antioxidants, which are able to neutralize free radicals (20). According to the findings of the present study, N2O exposure could not change the indicators of oxidative stress in neonates. As such,

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there was no increase in the amount of substances produced by the decomposition of lipid peroxides (e.g., malondialdehyde). Furthermore, no significant reduction was observed in the level of antioxidant substances, such as thiols and total antioxidant capacity, due to oxidation. In conclusion, it seems that Entonox could be used as a safe analgesic approach in natural childbirth. One of the limitations of our study was that degree of Entonox exposure was not equal among the subjects. Therefore, it is recommended that future studies be conducted about the indicators of oxidative stress in mothers undergoing labor with exposure to Entonox

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