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Evaluation of Oxidative Stress Induced by Occupational Inhalation Exposure to N_2O, an Anesthetic Gas

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ABSTRACT

Introduction: Nitrous oxide (N_2O) is the most common anesthetic gas used in operating rooms. The major objective of this investigation is to measure N_2O values in two modes: first, when the ventilation system is on, and second, when it is off; and to determine the biomarkers of oxidative stress associated with this exposure among operating room personnel.

Materials and Methods: A cross-sectional study was conducted on 60 operating room personnel as the N_2O exposed group, and on 60 nurses as the referent group. N_2O concentrations were determined according to NIOSH method 6600. Total antioxidant capacity (TAC) levels, malondialdehyde (MDA), and superoxide dismutase (SOD) activities were also measured.

Results: The concentrations of N_2O in the presence and absence of ventilation systems were significantly higher than the recommended exposure limit (REL) of 25 ppm recommended by NIOSH. The levels of TAC and SOD were significantly lower in participants exposed to N_2O in comparison with the referent group. Adjusted for age, work experience, and sex, exposure to N_2O was found to be an occupational risk factor for low levels of TAC and SOD, so that exposure to N_2O reduced TAC and SOD levels by 0.16 mM and 0.75 U/ml, respectively.

Conclusion: The present study shows that the operating room personnel are exposed to levels of N_2O several times more than the REL of this gas and this heavy exposure is associated with a significant increase in oxidative stress.

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Introduction

Nitrous oxide (N_2O) is a non-flammable and colorless gas which induces rapid anesthesia without skin or trachea irritation. However , there have been concerns about toxic effects of N_2O among operating room personnel who are regularly exposed to different values of N_2O for several years since the mid-1950s [1].

Chronic exposure to anesthetic gases affect the developing of fetus, [2] and results in infertility [3] in

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operating room personnel. Using employment records, Teschke et al. conducted a study through a telephone survey on Canadian nurses with a history of exposure to anesthetic gases during 1990-2000. They identified 1,079 cases of congenital malformations and 80 stillbirths among 15,317 live births recorded from 9,433 mothers. In mothers exposed to N_2O, congenital malformations were 1.42 times more than others [4].

N_2O also affects liver, [5] kidney, [6] nerves system, [7]and DNA [8, 9].

Some studies have also reported the generation of oxidative stress (OS) by inhalational anesthetics. Oxidative stress is caused by an imbalance between the generation of reactive oxygen species (ROS) such as hydroxyl radical ($HO^{\bullet}$), superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and antioxidant defense [10, 11, 12]. Many studies have shown that ROS is related to reproductive, neurological, cardiovascular, and cancer diseases [13].

ROS can damage proteins and nucleic acids [13-16]; it also affects the lipids of the cell membrane (lipid peroxidation) and leads to the formation of malondialdehyde (MDA), which is the most significant measure of lipid peroxidation [12].

Some studies have shown that anesthetics gases increase MDA levels in the operating room personnel [6, 14]. Significant lower levels of superoxide dismutase (SOD) and higher MDA were reported in the personnel exposed to anesthetics in comparison with the non-exposed group [17].

The N_2O indirectly induces genotoxicity through ROS mediators [18].There is also some evidence that N_2O toxicity is related to vitamin B12 deficiency [1]. Vitamin B12 helps DNA metabolism and methionine synthesis [19]. N_2O irreversibly oxidizes the cobalt atom in vitamin B12 (cobalamin) and inhibits methionine enzyme synthesis. Oxidized vitamin B12 by N_2O causes the creation of $O_2^{\bullet-}$ and $HO^{\bullet}$ radicals that impairs the conversion of homocysteine to methionine. A high level of homocysteine decreases the expression of antioxidant-related genes, [18] production of ROS, mitochondrial dysfunction, and DNA damage. These subtle changes are associated with observed adverse health effects such as genotoxicity, neurotoxicity, and teratogenicity [1].

Enzymatic ROS scavenging like glutathione peroxidase (GPx), SOD, catalase, and non-enzymatic ROS scavenging such as vitamin E and vitamin C protect cells against mutations and reduce radical attack on DNA [13, 14, 16, 20].

To prevent the adverse effects of N_2O, National Institute of Occupational Safety and Health (NIOSH) and American Conference of Governmental Industrial Hygienists (ACGIH) recommended a maximum permissible concentration of 25 ppm and 50 ppm nitrous oxide , respectively [21, 22].

In Iran, most of general anesthesia is performed using N_2O [23]. In this regard, the main objective of this study is to measure N_2O concentrations based on two modes: first, when the ventilation system is on, and second, when it is off and to measure the biomarkers of oxidative stress associated with this exposure among operating room personnel

Materials and methods

Study area and sampling

This study was conducted on 60 operating room personnel in Shiraz, Iran, and oxidative stress biomarkers were determined in these subjects. The inclusion criteria were at least 3 years of exposure to anesthetic gases and 36 to 44 hours of work per week during the past 3 months, except for weekends. All the operating room personnel worked 8 hours a day, except for surgeons who spent 6 hours a day in the operating room.

60 nurses without history of exposure to N_2O, who were compared to the exposed group in terms of age, sex, and work experience, were randomly selected from other departments of the same hospital as the referent group.

Ethics permit and questionnaire

Prior to conducting the research, ethical clearance was obtained from Ethics Committee of the Shiraz University of Medical Sciences. Demographic information and the data regarding work experience, alcohol consumption, smoking status, use of drugs including antibiotics, exposure to other chemicals causing oxidative stress, medical history, and detailed work history including job position and

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working hours per day were collected through a questionnaire.

Participants who suffered from lung and liver diseases, chronic cardiovascular diseases, autoimmune, inflammatory, digestive, neurological diseases, diabetes, cancer, high blood pressure, had a BMI of more than 30 kg/m^2, people with a history of surgery, those with acute infections who needed to take drugs such as antibiotics during the last three months, those who used antioxidants such as vitamins E and C and the subjects with working hours of less than 6 hours a day were excluded from the study.

Exposure assessment

Exposure to N_2O was measured by NIOSH 6600 method [24]. The concentration of N_2O gas was measured in 8 operating rooms and 1 recovery room under conditions where the ventilation systems were either on or off. Collectively 900 measurements in 8 operating rooms and 1 recovery room in morning shifts during a period of 2 months were conducted. To determine N_2O gas, an IR spectrophotometer (Bacharach model 3010, New Kensington, PA, USA) was used, which was field readout device. The sampling collection points were:

- From a distance of 15 cm from the breathing zone of the operating room personnel
- From a distance of 15 cm from the breathing zone of the recovery personnel
- From a distance of 5 cm from the tracheal tube or anesthesia mask of the patients
- From a distance of 5 cm from the anesthesia machine
- From a distance of 5 cm from the exhaust air grille
- From a distance of 15 cm from the breathing zone of the referent group

Evaluation of antioxidant status

Blood samples were collected from studied groups and transferred to tubes, and after clotting, they were centrifuged at 1200 rpm for 10 minutes so that the sera were separated. Serum specimens were kept in a refrigerator at -80°C until analysis.

MDA, SOD, and TAC were measured using kit (Zellbio Lab, Ulm, Deutschland, Germany) according to the manufacturer's protocol on a Stat FAX 2100 ELISA plate reader (Awareness Inc, USA).

Statistical analysis

Data was managed employing SPSS software, and chi-square test was used to assess the distribution of categorical variables. Independent t-test and one-way ANOVA were used to compare the quantitative indicators between the two and the more than two groups, respectively. A multivariate linear regression model was used to evaluate the association between oxidative stress status and N_2o exposure after adjustment for the effect of confounders (age, work experience, and sex).

Results

Table 1 shows some of the main characteristics of the studied groups. There were no significant differences regarding age, work experience, BMI, sex, and marital status between the groups ($p > 0.05$).

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Table 1: Demographic information of the subjects

Variables	Referent group Mean ± SD	Exposed group Mean ± SD			P-value
		Technician	Nurses	Surgeons	
Age (year)	35.13 ± 6.36	37.81 ± 6.97	34.15 ± 6.76	40.40 ± 8.19	0.06*
Work experience (year)	10.27 ± 6.03	12.67 ± 5.39	9.98 ± 5.51	11.50 ± 5.93	0.42*
BMI (kg/m^2)	20.99 ± 3.14	20.56 ± 3.54	20.73 ± 2.45	21.10 ± 2.90	0.94*
Sex		Number (percent)			
Male	35 (58.30)	5 (31.20)	18 (52.90)	7 (70)	0.36**
Female	25 (41.70)	11 (68.80)	16 (47.10)	3 (30)	
Marital status		Number (percent)			
Single	13 (21.70)	2 (12.50)	7 (20.60)	1 (10)	0.73**
Married	47 (78.30)	14 (87.50)	27 (79.40)	9 (90)	

*One-way ANOVA
**Chi-square test

Table 2 shows the mean N_2O concentrations at 6 measured points at ppm range. The mean concentrations of N_2O in the off mode of ventilation were 582.33 ± 87.38, 263.06 ± 15.22, 1135.27 ± 48.31, 1905.57 ± 130.48, and 2219.98 ± 233.45, and not detectable for measurement points 1 to 6, respectively. The corresponding values in the on mode of ventilation system were 241.49 ± 63.67, 118.50 ± 13.17, 707.43 ± 42.93, 1523.63 ± 125.67, and 1412.64 ± 102.39, and not detectable, respectively. These differences were statistically significant ($p < 0.05$).

Table 2: Mean concentrations of nitrous oxide (ppm) according to the ventilation system at different points

Measurement points		Number	Ventilation system off Mean ± SD	Number	Ventilation system on Mean ± SD	P-value*
1	From a distance of 15 cm from the breathing zone of the operating room personnel	200	582.33 ± 87.38	200	241.49 ± 63.67	< 0.001
2	From a distance of 15 cm from the breathing zone of the recovery personnel	50	263.06 ± 15.22	50	118.50 ± 13.17	< 0.001
3	From a distance of 5 cm from the anesthesia mask	50	1135.27 ± 48.31	50	707.43 ± 42.93	0.01
4	From a distance of 5 cm from the exhaust air grille	50	1905.57 ± 130.48	50	1523.63 ± 125.67	0.01
5	From a distance of 5 cm from the anesthesia machine	50	2219.98 ± 233.45	50	1412.64 ± 102.39	0.02
6	From a distance of 15 cm from the breathing zone of the referent group	50	ND	50	ND	-

* Independent sample t-test
ND: Not detectable

Oxidative stress biomarkers in the studied groups based on demographic data are summarized in Table 3. MDA and TAC levels and SOD activities did not change significantly with age and work experience. However, When SOD and TAC were separated by sex, males had lower SOD and TAC levels than females in the exposed and referent groups, respectively. (SOD: 9.72 ± 3.73 U/ml vs. 12.72 ± 5.87 U/ml in the males and females exposed group, respectively) (TAC: 1.86 ± 0.50 mM vs. 2.32 ± 0.67 mM in the males and females of the referent group, respectively).

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Table 3: Oxidative stress biomarkers of the studied groups based on demographic data

Variables	Referent group				Exposed group			
	n	MDA (µM)	SOD (U/ml)	TAC (mM)	n	MDA (µM)	SOD (U/ml)	TAC (mM)
		Mean ± SD				Mean ± SD		
Age (year)								
< 35	28	2.19 ± 0.70	13.31 ± 3.72	2.10 ± 0.64	34	2.47 ± 0.68	11.14 ± 4.64	1.79 ± 0.64
≥ 35	32	2.32 ± 0.76	13.40 ± 4.49	2.16 ± 0.65	26	2.46 ± 0.65	11.33 ±5 .76	1.71 ± 0.54
		P = 0.50	P = 0.94	P = 0.76		P = 0.96	P = 0.89	P = 0.63
Work experience (year)								
≤ 10	34	2.28 ± 0.76	13.71 ± 4.43	2.12 ± 0.64	34	2.37 ± 0.67	12.15 ± 4.92	1.89 ± 0.63
> 10	26	2.24 ± 0.70	12.89 ± 3.70	2.15 ± 0.65	26	2.56 ± 0.66	10.23 ± 5.20	1.62 ± 0.52
		P = 0.87	P = 0.45	P = 0.88		P = 0.25	P = 0.15	P = 0.08
Sex								
Male	25	2.05 ± 0.81	13.26 ± 3.95	1.86 ± 0.50	34	2.46 ± 0.66	9.72 ± 3.73	1.75 ± 0.52
Female	35	2.41 ± 0.63	13.43 ± 4.28	2.32 ± 0.67	26	2.48 ± 0.67	12.72 ± 5.87	1.76 ± 0.67
		P = 0.07	P = 0.87	P = 0.004		P = 0.98	P = 0.02	P = 0.92

The average levels of TAC, SOD, and MDA based on job titles are given in Table 4. As shown, the lowest levels of TAC and SOD were observed among the operating room nurses and technicians, respectively (1.70 ± 0.59 mM for TAC and 9.50 ± 3.46 U/ml for SOD).

Table 4: Oxidative stress biomarkers in the studied groups based on job titles

Groups	TAC (mM) Mean ± SD	SOD (U/ml) Mean ± SD	MDA (µM) Mean ± SD
Referent group	2.13 ± 0.64	13.36 ± 4.12	2.19 ± 0.68
Technicians	1.81 ± 0.60	9.50 ± 3.46***	2.32 ± 0.67
Operating room nurses	1.70 ± 0.59**	11.46 ± 5.30	2.58 ± 0.65
Surgeons	1.88 ± 0.63	13.18 ± 6.18	2.30 ± 0.67
P-value*	0.001	0.01	0.03

* One-way ANOVA
**A statistically significant difference was observed between operating room nurses and the referent group (p = 0.02).
***A statistically significant difference was observed between technicians and the referent group (p = 0.03).

Variables such as age, work experience, and sex were considered as confounders, and their effects on the oxidative stress were controlled using linear regression analysis. The model was made based on the main exposure variable, N_2O exposure, as well as all the confounding variables.

Table 5 presents the results obtained from the linear regression analysis. As shown in Table 5, there was a negative association between N_2O exposure and TAC and SOD levels. Exposure to N_2O resulted in a 0.16 mM and 0.75 U/ml decrease in TAC level and SOD activity, respectively (Table 5).

Table 5: Association between oxidative stress status and nitrous oxide exposure in the studied groups

Variables	B	95% confidence interval	P-value
TAC	-0.16	-0.27 to -0.06	0.002
SOD	-0.75	-1.53 to 0.03	0.05
MDA	0.80	-0.03 to 0.20	0.16

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Discussion

N_2O gas is one of the most common pollutants in operating rooms. N_2O concentrations, in both on and off modes of ventilation system were several-fold higher than the REL value of 25 ppm suggested by NIOSH [21] and the threshold limit value (TLV) of 50 ppm suggested by ACGIH [22].

Similarly, Souza et al. and Braz et al. reported mean N_2O concentration of 170 ppm and 155 ppm in operating room personnel, respectively [25, 26].

Wiesner et al. in a study on hospitals with and without a ventilation system reported N_2O concentrations of 170 ppm and 12 ppm, respectively [27].

In the present study, N_2O concentrations were substantially higher in comparison with similar studies. The reasons could be improper ventilation and scavenging systems, gas leakage from the anesthesia machine and patient's mask, , and large number and duration of daily surgeries [28].

In this study, the scavenging system to remove waste anesthetic gases and exhausts were improperly designed. Moreover, air circulations were less than the standard of 15 and 6 air changes per hour in operating and recovery rooms, respectively.

In this study, higher levels of TAC and SOD were observed in females compared with males. Similar findings had been reported by others [29, 30].

The followings are some of the reasons for the higher levels of TAC and SOD in women:

1- Female's mitochondria levels generate almost half the amount of hydrogen peroxide as compared to males.

2- Mitochondrial glutathione levels are almost twice in females than males.

3- Females overexpress SOD and glutathione peroxidase and mitochondrial enzymes [29], and this is due to estrogens that bind to estrogen receptors and activate the mitogen-activated protein (MAP) kinase and nuclear factor kappa (NF-κB) signaling pathways [31].

4- Males also produce more ROS due to NADPH oxidase activity, which is a major oxidative stress producer in cells [29, 30].

5- Males have more homocysteine than females due to their sex hormone (progesterone). Homocysteine is an indicator of folate and B-12 deficiency, [30] which also increases as a result of exposure to N_2O, and high levels of homocysteine lead to a decrease in the expression of antioxidant-related genes, production of ROS, mitochondrial dysfunction, and DNA damage [18].

In the present study, operating room personnel had a lower mean regarding TAC and SOD levels in comparison with the referent group. This finding was in line with the finding of Turkan et al. [32].

In 2005, Malekirad et al. reported a significant lower thiol groups and higher lipid peroxidation in 66 exposed operating room personnel with 9 years of work experience [14].

Izdes et al. showed that exposure to anesthetic gases significantly reduced TAC and glutathione in comparison to the control group [20]. Similar findings were reported in 2014 by Cerit et al. [33]

Cegin et al. in a study on 32 operating room staff and 32 control groups in 2016, showed a significant increase in lipid peroxidation and serum myeloperoxidase activity as well as a decrease in catalase activity and sulfhydryl levels in the exposed group compared to the non-exposed group [34].

Similarly, according to Paes's study in 2014 on 15 medical residents in Brazilian hospitals [10] and Baysal's research on 30 operating room personnel in Turkey, antioxidant capacities in operating room personnel were significantly lower than the control group [35].

In the study by Jafari et al. in Iran in 2018, an increase in MDA was observed following exposure to high levels of inhalational anesthetics [6].

As oxidative stress induced by inhalational anesthetics is one of the mechanisms of DNA damage, the protective impacts of antioxidants had been confirmed in some studies on operating room personnel [20, 36-38]. For example, Sardas et al. reported that the use of vitamins E and C by operating room personnel could reduce DNA damage in operating room staff in comparison with the control group [37]. Similarly, a worldwide cohort study from 1989 to 2009, in which 16 countries and 5,424 people were studied, reported that the micronucleus frequency in subjects who consumed

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fruits and vegetables once a day was 32% lower than those who reported no consumption [36]. Similar results were reported in 2010 by Izdes et al. regarding operating room staff [20].

Ranjbar et al. reported that the daily consumption of 0.10 g of cinnamon in 100 cc of water for 10 days caused a significant decrease in the level of lipid peroxidation (3.25±1.32 versus 5.03±2.01 nmol/ml) [39].

Similarly, Sami et al. reported that daily consumption of two cups of tea (including 1.873 grams of chamomile in 300 cc of water) for 21 days significantly increased salivary TAC levels (6.62 ± 0.77 µmol/ml versus 4.81 ± 0.39 µmol/ml) [40].

Due to the inherent limitations of cross-sectional studies such as this one, it is impossible to assess a causal association. Thus, it may be argued that a significant reduction in antioxidant defense in operating room staff is not related to exposure to N_2O. Though from the point of view of epidemiology, this is correct, the authors believe that there are multiple proofs to prove that the observed effects may well be attributed to exposure to N_2O. These include:

1- There were no significant differences between demographic data of the studied groups.

2- The exposed group had no history of autoimmune disorders, inflammatory diseases, or lung or liver disorders that could affect oxidative stress.

3- The exposed group had no history of exposure to other physical and chemical factors causing oxidative stress biomarkers.

4- All the exposed groups were non-smokers.

5- Antioxidant biomarkers were significantly lower, while the oxidative stress biomarkers were significantly higher in the exposed group than in the referent group.

6- After adjusting for the confounders, the association between low levels of SOD and TAC and exposure to N_2O remained significant, indicating that the observed changes were associated with exposure to N_2O.

"A limitation of this study was that the effect of shiftwork was not studied. Therefore, more studies regarding the role of shiftwork are needed".

Conclusion

The present study shows a decrease in antioxidant status in operating room staff compared to the control group. Since there were no significant differences in the main variables of age, BMI, sex, smoking status, and work experiences between the studied groups, the observed effects can be associated to exposure to high levels of N_2O. Therefore, engineering and administrative control measures are suggested to reduce workers exposure to N_2O.

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Conflict of interest

The authors declared no conflict of interest.

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Ethical considerations

The study was conducted in accordance with the Helsinki Declaration of 1964 as revised in 2013.

Code of ethic

The protocol of the study was approved by Shiraz University of Medical Sciences ethics committee (IR.SUMS.REC.1395.S729).

Authors' contributions

Neghab M developed and designed the study, Kargar-Shouroki F collected and analyzed data, Yousefinejad S, Alipour H, Mozdarani H, Fardid R, Anoosheh VS wrote the first draft of the manuscript, and Rostami M revised the manuscript. All the authors read and approved the final manuscript.

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