Original Article

Adverse Effects of Nitrous Oxide on Vitamin B_{12} Levels in Health Care Personnel of Employees' State Insurance Corporation Tertiary Care Hospital

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Abstract

Background: Nitrous oxide (N2O) has a long reputation for decades as the safest general anesthetic and has a well-known function as the laughing gas. The study aimed to know the effect of nitrous oxide with chronic exposure in operation theatre (OT) personnel of the Department of Anesthesia in Sanath Nagar, Hyderabad, India.

Materials and Methods: A transversal study was conducted including 88 health workers (44 exposed and 44 non-exposed). Personal exposure to nitrous oxide for the group members was assessed indirectly by measuring the years of work experience in OT. Vitamin B_{12} levels are measured in both groups. Data were statistically tested for normality and also qualitative, quantitative assessment was performed.

Results: From the results obtained, there is no significant difference in Vitamin B_{12} levels between exposed and non-exposed groups. There is a multiple-fold increase in other health conditions like dizziness, nausea/vomiting, euphoria, and tachycardia.

Conclusion: N2O exposure in health care personnel did not show any altered vitamin B_{12} levels. Chronic exposure to nitrous oxide will lead to adverse health effects and it can be reduced by using an anesthesia gas scavenging system in OT.

Keywords: Nitrous oxide, Anesthesia, Vitamin B_{12}, Long-term exposure

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Introduction

Nitrous oxide has a long reputation for decades as the safest general anesthetic and has a well-known function as the laughing gas. Since 1844, nitrous oxide is using for general anesthesia (GA). For the first time, a dentist named Horace wells used this gas for dental operation and established its use as an anesthetic drug in 1863 in New York City. Since then it is accepted worldwide during surgeries for GA. The advantages of using nitrous oxide as GA are - less expensive, easy to supply through central hospital gas lines, and its synthesis, and storage. Nitrous oxide in blood transport as free gas, will not intermingle with hemoglobin and does not undergo any biotransformation. As an anesthetic gas, it is non-irritant to the tissues, as well- elimination of this gas from the body is simple by expiration in a reverse uptake manner, and rapidly removed for its low soluble nature (1).

Yet, these advantages were challenged, when

researchers discovered that nitrous oxide will oxidize and inactivate the Vitamin $B_{12,}$ *i.e.* methylcobalamin. The methionine synthase enzyme is a bound cofactor of methylcobalamin and is the sole responsibility for methionine recycling (2,3). It was also observed in the literature that the serum methionine levels will reduce at the time of nitrous oxide anesthesia, besides this found a wide-range of metabolic consequences (4). It also interacts with nucleic acid synthesis and causes neurological symptoms like paraesthesia of limbs, muscle weakness, altered reflexes (5-11). Some of the other disadvantages of nitrous oxide are -on a short exposure of its cases predominance of alpha-adrenergic stimulation, mildly depresses myocardial contractility. On long-term exposure to higher concentration, there is a beta-adrenergic activity, hypoxemia, and little influence on cardiac output, heart rate, stroke volume. The most common side effects include headaches, dizziness, postoperative nausea, vomiting, expansion of air-filled spaces.

Due to its adverse effects, there are many editorials on whether nitrous oxide should be routinely used for GA or not (12-17). With the advent of newer drugs and short-acting agents, many suggestions are to replace nitrous oxide. Still, the scenario in the developing countries is not changed when compared to the developed countries since the lack of availability and/or available in limited centers. Along with the patients, its adverse effect influenced the occupational exposure of health care professionals, medical personnel. Suggested rate of exposure time-weighted average of 100 ppm for an 8hr workday and an average of 400 ppm would provide adequate protection. Upon its exceeding exposure causes spontaneous abortions, miscarriages in female health personnel, and also congenital abnormalities in children (5-11). Similarly in males, a problem of sister chromatid exchange, neurological deficits, sperm indices was observed (18). Some of the recent studies on dental care professionals say that there is an increase in uterine, cervical, and kidney cancers, liver diseases, adverse effects on the immune system, bone marrow, and psychomotor impairment (19). The main objective of the study is to find out the effect of chronic exposure of N2O on Vitamin B_{12} levels in the health care personnel working in OR of employees' state insurance corporation (ESIC) medical college hospital and super specialty hospital, Sanath Nagar, Hyderabad.

Methods

Study subjects and design: This transversal study included 88 health care workers aged between 25 and 56 years, in ESIC medical college and super-specialty hospitals. The exposed group were surgeons, anesthesiologists, operation theatre nurses (surgical nurses), who routinely provide full-time assistance during operations on a day-to-day basis. They usually stay in the polluted area of the operating room for not less than 5hrs, worked for the whole occupational activity in an environment polluted with N2O and volatile anesthetics such as isoflurane, sevoflurane.

Previous studies revealed that operating theatre staff had the most exposure to N2O. The control group consisted of 44 nurses from other departments of the same hospitals, who have never been occupationally exposed to N2O or volatile anesthetics in the course of their professional careers. Excluded criteria were pregnant. All examined subjects received information on the purpose of the study and duly signed the participation consent. The protocol was approved by the local hospital ethical committee.

Each subject underwent a general medical examination. Information concerning alcohol, coffee consumption, and medication within the past three months was gathered using a questionnaire. To avoid the inclusion of additional confounding factors, subjects with overt hematological diseases (three people), serious symptoms of neurological deterioration (one person), or heart failure (one person) were excluded.

Except for minor illness personnel in both examined groups were in good health and presented with no clinical signs of Vitamin B_{12} deficiency. No apparent symptoms of acute N2O intoxication (headache, drowsiness, nausea and vomiting, paraesthesia, and reduced tendon reflexes) were registered in an exposed group.

All subjects denied receiving Vitamin B_{12} or folic acid therapy during 1 year preceding the study.

Blood collection and analytical procedures: Health

care workers in both groups were examined once in the course of the study. Blood samples were collected simultaneously in both groups at the end of the daily shift. The serum was separated by centrifugation immediately after blood collection and stored at –20°C. For determination of hematological parameters (red blood cell count (RBC), hemoglobin (Hb), hematocrit (Hct), mean cell hemoglobin (MCH), mean cell volume (MCV), and mean cell hemoglobin concentration (MCHC)), EDTA-tubes were used and blood counts were tested within 2 hr. Serum Vitamin B_{12} concentrations were categorized in a way that (normal range 156–672 pmol/liter), 22 were arbitrarily categorized as low (150–250 pmol/liter), border low (250–300 pmol/liter), medium (250–350 pmol/liter), or high (>350 pmol/liter).

Statistical analysis: all the exploratory statistical analysis was performed by using SPSS-X software. Quantitative data of arithmetic means, standard deviations, and averages were measured by central tendency, measures of dispersion. The significance of difference was tested by a two-sample t-test for exposed and non-exposed groups.

Results

Years of operation theatres (OT) exposure: All the participants had OT experience between 1 to 17 years; only one person had 40 years of exposure. As shown in figure 1 the majority of the personnel fall below 10 years and a median of 4 years and the majority were between 4 and 9 years.

Age and sex: All the samples were equally distributed and the personnel in the investigated groups were

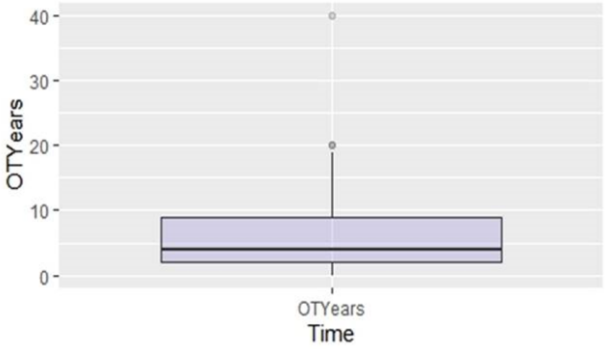

Figure 1. Total number of OT years worked by health care personnel.

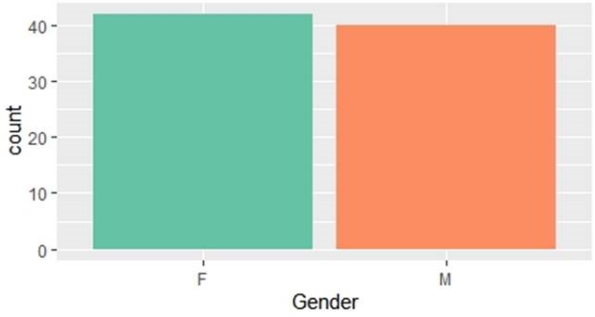

Figure 2. Gender differentiation analysis of the study personnel.

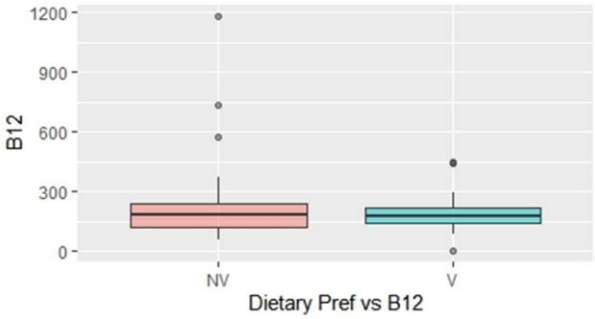

Figure 3. Comparison between vegetarians (V) and non-vegetarians (NV) and vitamin B12 concentration.

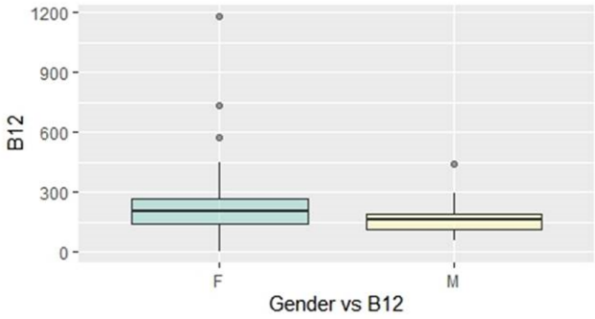

Figure 4. Vitamin B_{12} levels in both genders.

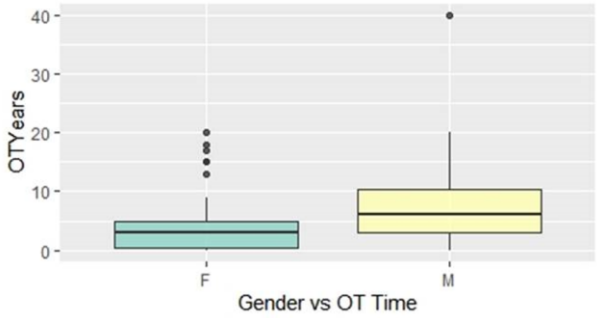

Figure 5. Vitamin B_{12} levels in both genders.

observed to be homogeneous in case of gender, and age. In terms of gender, there was no specific significant difference found (figure 2) between the respondents of the two assessed groups (p=0.785) (Table 1). When it comes to the age of the study group, we did not find any significant difference (p=0.739).

Serum Vitamin B_{12} concentrations: A comparison of serum Vitamin B_{12} levels between vegetarians and nonvegetarians did not yield any significant difference. It has resulted in figure 3 that the median levels of Vitamin B_{12} were 175pmol/liter. Vitamin B_{12} levels in males and females of the study groups were analyzed. It was observed that female personnel had comparatively higher Vitamin B_{12} levels (Figure 4).

Duration of OT exposure: When there was a comparison of OT time exposure in males and females, the results yielded that males' exposure to OT time is higher when compared to females (Figure 5). The average duration of work experience in OT of all the study groups was 10±2 years (min=1, max=20).

Health effect of N2O exposed group: Other health effects were analyzed in the exposed group. A significant difference in the health effects like dizziness, nausea/vomiting, euphoria, and tachycardia of the N2O exposed group showed in a few of the subjects (Table 2).

Comparative analysis of OT exposure vs. Vitamin B_{12}: A comparative analysis was done between the personnel exposed years and their Vitamin B_{12} levels in chronic exposure. AS shown distribution diagram (figure 6) no major significant effect was observed on the Vitamin B_{12} levels due to dietary preferences.

Discussion

In third-world countries like India, existing knowledge on adverse effects of N2O on Vitamin B_{12} in occupational exposure is still not clear. A hematological study conducted by Salo M, et al. (20) on the N2O exposed group of anesthetists and surgical nurses could not find any interaction between Vitamin B_{12} and N2O. Though the present study did not show a significant difference in Vitamin B_{12} levels in N2O exposed personnel over non-exposed health care workers, yet such observed and reported effects in the literature should be considered to avoid the N2O adverse effects on the personnel. Hematopoietic changes like macrocytic anemia are known to occur on the deficiency of Vitamin B_{12}, since then a study by W. Krajewski, et al. in 2007 was observed a significant reduction in Vitamin B_{12} in surgical nurses when compared with the control hospital staff (21).

Some researchers have suggested that Vitamin B_{12} in serum levels is not as sensitive as an indicator of cobalamin deficiency. A neurological study by Lorenzl et al, and Petchkrua et al, (22,23), showed evidence of Vitamin B_{12} deficiency in neurological abnormalities. In the study, repeated serum tests showed normal serum cobalamin levels. In the present study other parameters like dizziness, nausea/vomiting, euphoria, tachycardia were recorded in few subjects. Such kind of conclusions for medical purposes was reported in the early days of N2O usage (24,25,26). With the evidence of previous studies about Vitamin B_{12} levels determination by total homocysteine (tHcy) was planned to measure in the present study, but due to some technical issues, we could not do it.

In the present study, one interesting parameter i.e. levels of Vitamin B_{12} in females (311.12 pmol/L) was observed to be more when compared to males (283.23 pmol/L) ($p<0.001$). Deficiency prevalence was observed greater in men (26.5%) when compared

Table 1: Distribution of the study group by gender, and age.

Variable	Exposed (N1 group) (N=44)	Non-Exposed (N2 group) (N=44)
Sex	Women – 38(86.3%) Men – 6(13.6%)	Women – 33(75%) Men – 11 (25%)
Age	43.08 ± 9.36	44.10 ± 6.88

with women (18.1%). Dietary preference (vegetarian and non-vegetarian) of the study also did not influence serum Vitamin B_{12} levels, as the results did not yield any significant difference. Another interesting result was observed that the duration of the OT stay of males was higher than females in the present study; we could not conclude this could be the probability of aforementioned altered Vitamin B_{12} levels in males but a considerable reason could be established with multiple studies and increased number of subjects.

Table 2: Other health effects in the exposed subjects.

Health Parameter	Exposed	
	Yes	**No**
Dizziness	11(73.3%)	4 (26.6%)
Nausea/vomiting	13 (68.4%)	6 (31.5%)
euphoria	9 (69.2%)	4 (30.7%)
tachycardia	12 (60%)	8 (40%)

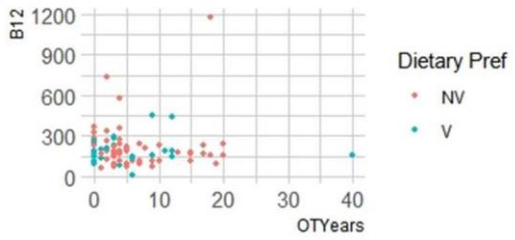

Figure 6. Operation theatre N20 exposure personnel years versus vitamin B_{12} levels.

In the present study results of other health effects like dizziness, nausea/vomiting, euphoria, tachycardia in N2O exposed group was observed to be a risk factor. The average exposure time is 10 ± 2 years in the personnel of the present study, which could be one of the risk assessments of increased other health effects in the exposed group. As shown in the Eftimova B, et al. study, chronic exposure of N2O in the 43 health workers affected with 2.85, 1.98, 3.13, 2.24 times more dizziness, nausea/vomiting, euphoria, tachycardia respectively over their counterpart exposed groups (27). The present results are co-related with the Eftimova B, et al. study in comparing chronic exposure as a risk factor for the exposed groups.

It is also understood from the literature that spontaneous abortions in female staff and azoospermia in male staff are other risk factors with N2O exposure. This kind of health disturbances due to N2O contamination for the health care professional may be effectively reduced by using combination exhaust ventilators and A/C with scavenging devices (27, 28). Though the clinical relevance of the current results remains unclear, it could be considered as one of the evidential studies for the asymptomatic Vitamin B_{12} metabolism disturbances in the exposure group. Dietary intake of Vitamin B_{12} for the susceptible group can be considered as a recommendation. Yet, clear further prospective studies are required to assess a complete clinical relevance of N2O in long-term exposed groups.

Conclusion

This study depicts that Vitamin B_{12} levels were less in the female who had N2O exposure group and dietary preferences did not have a significant effect on Vitamin B_{12} levels. There was a severe effect on the other health effects like dizziness, nausea/vomiting, euphoria, and tachycardia of some of the exposed groups. The present study reveals that the maintenance of N2O concentrations in the OT under occupational exposure limit by using an anesthesia gas scavenging system will greatly help in preventing the disturbances of Vitamin B_{12} metabolism of OT personnel.

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Conflicts of Interest

The authors declare that they have no conflict of

interest.

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