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Nitrous oxide occupational exposure in conscious sedation procedures in endoscopic ambulatories: a pilot retrospective observational study in an Italian hospital

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ABSTRACT. Introduction. Nitrous oxide (N₂O) is widely used to induce sedation also outside of operating rooms; there is a chance of workplace exposures for the operators engaged in the outpatient use of nitrous oxide. The aim of this research is to assess nitrous oxide exposure in gastroenterology outpatient settings.

Methods. We performed an observational study marked by N₂O environmental testing in a gastroenterology outpatient care; environmental research was supported by biological monitoring with urinary N₂O analysis in exposed operators. The research was conducted both without and using a collective security device (NIKI mask).

Results. The study was rolled out in 10 sessions of day shift procedures, totaling 4105 samples. The average N₂O concentration in the environment was 27.58 (SD 1.76) and 449.59 (SD 35.29), respectively with and without NIKI Mask; the distribution of gases in the environment under investigation was not homogeneous (Anova-test $P=0.001$). Biological testing revealed a substantial rise in urinary concentration of 8.97 ($p=0.001$) between the start and the end of the shift, and the use of the NIKI-mask was effective ($p=.003$).

Discussion. The exposure levels reported exceed the limits of 50 ppm (Italy operating rooms threshold value) as well as the value of 25 ppm (NIOSH threshold-value), indicating a significant issue in the outpatient use of N₂O. Technical measures are needed to contain the occupational risk from N₂O exposure outside of operating rooms; for the exposure results detected in this research, it is also evident that workers exposed to N₂O must be subject to adequate health surveillance accounting for this occupational risk.

Key words: Nitrous Oxide, Occupational Exposure, Conscious Sedation.

RIASSUNTO. ESPOSIZIONE OCCUPAZIONALE AL PROTOSSIDO DI AZOTO NELLE PROCEDURE DI SEDAZIONE NEGLI AMBULATORI DI ENDOSCOPIA: UNO STUDIO PILOTA OSSERVAZIONALE RETROSPETTIVO IN UN OSPEDALE ITALIANO.

Introduzione. Il protossido di azoto (N₂O) è usato per indurre la sedazione anche al di fuori delle sale operatorie; c'è la possibilità che gli operatori che usano il protossido di azoto in contesti esterni alle sale operatorie abbiano un'esposizione professionale. Lo scopo di questo studio è quello di valutare l'esposizione al protossido di azoto nel contesto negli ambulatori di gastroenterologia.

Metodi. Uno studio osservazionale è stato condotto testando i livelli ambientali di N₂O in ambulatori di gastroenterologia; la ricerca ambientale è stata supportata da monitoraggio biologico con analisi dell'N₂O urinario negli operatori esposti. La ricerca è stata condotta sia con che senza l'utilizzo di un dispositivo di sicurezza collettivo (maschera NIKI).

Introduction

Sedation is an essential part in any gastrointestinal endoscopic procedure since it helps gastroenterologists to relieve patient anxiety and distress while optimizing the endoscopic exam's result (1). Nitrous oxide gas, as well as benzodiazepines and opioids, can be used to induce conscious sedation (2).

Multiple research articles and reviews have thoroughly defined esophagogastroduodenoscopy (EGD) or upper endoscopy sedation monitoring. A basic diagnostic EGD is a reasonably short procedure that only requires 30 minutes of sedation. Sedation may be performed for diagnostic upper EGD with either mild sedation or controlled anesthesia, as part of monitored anesthesia care (MAC) (3,4). Nitrous oxide-sedation is also a safe and reliable alternative for patients undergoing digestive endoscopy (5,6,7).

The use of moderate to deep sedation is becoming more common, which can be difficult for both anesthesiologists and gastroenterologists (8). While deeper sedation helps gastroenterologists to conduct more complex procedures, there is a risk of multiple cardiopulmonary complications, particularly in high-risk patients (8,9,10).

Nitrous oxide has proved clinical efficacy, but at such ambient levels, it may pose a health threat to medical professionals who are chronically exposed.

This study aims to detect the critical issues with the use of this anesthetic gas in ambulatory settings (outside of surgical rooms), by sampling N₂O in this setting with and without the usage of the "NIKI 2002" Airnova mask, a double mask used to reduce gas dispersion in the room while administering anesthetic gases to patients, when compared to the use of a traditional mask (11). This study also aims to analyze the exposure conditions of health professionals engaged in these diagnostic procedures. One of the major issues in nitrous oxide conscious sedation is the definition of reference values in ambulatory rooms that are not comparable to those established for operating rooms; to this end, it should be noted that current legislation in Italy establishes environmental criteria for the use of N₂O in operating rooms but no specific references for outpatient settings.

Risultati. Lo studio è stato condotto in 10 sessioni di procedure diurne, per un totale di 4105 campioni. La concentrazione media di N₂O nell'ambiente era 27.58 (DS 1.76) e 449.59 (DS 35.29), rispettivamente con e senza la maschera NIKI; la distribuzione dei gas investigata nell'ambiente non era omogenea (test ANOVA $p=0.001$). Il campionamento biologico ha rivelato un sostanziale aumento di N₂O nella concentrazione urinaria di 8.97 ($P=0.001$) tra l'inizio e la fine del turno, e l'uso della maschera NIKI si è dimostrato efficace ($p=.003$).

Discussione. I livelli di esposizione rilevati eccedevano i limiti di 50 ppm (il valore limite stabilito in Italia per le sale operatorie) e di 25 ppm (valore limite stabilito dal NIOSH), indicando un problema rilevante nell'uso ambulatoriale di N₂O. Sono necessarie misure tecniche per contenere il rischio occupazionale di esposizione all'N₂O al di fuori delle sale operatorie; visti i risultati dell'esposizione rilevanti in questo studio, è evidente che i lavoratori esposti all'N₂O dovrebbero essere soggetti ad adeguata sorveglianza sanitaria, tenendo conto di questo rischio occupazionale.

Parole chiave: Protossido di azoto, Esposizione occupazionale, Sedazione cosciente.

In surgical rooms, the ventilation system allows anesthetic gas retrieval either locally (through patient's intubation, with a vacuum retrieval system) or through the ventilation system (with an appropriate number of air changes that allows deep gas sedation to be carried out safely). Many ambulatory environments are not equipped with gas retrieval systems and may not have a sufficient number of air changes. This implies that for superficial sedation of the patient, although estimating a low anesthetic gas emission based on the concentrations used, due to a continuous succession of procedures throughout the day, an accumulation of anesthetic gas may occur. For this reason, in order to be able to use outpatient environments that lack the same ventilation systems as surgical rooms, a possible strategy is to perform an aspiration of residual gas, even if the dispersion is not localized because the patient is not intubated, by using devices that allow to retrieve the excess gas (i.e.: the NIKI mask).

In terms of occupational toxicology, the most important factor is obviously persistent exposure to N₂O; literature cites numerous findings that correlate chronic exposure to nitrous oxide with the onset of adverse effects on workers exposed to dental procedures. The most often reported side effects are: an increase in the rate of spontaneous abortion, infertility and reproductive difficulties, congenital anomalies and fetal growth delay; an increase in the incidence of cancer in the uterine cervix and kidney, liver diseases; adverse effects on bone marrow function and immune system, generalized neurological disorders and psychomotor dysfunction (12,13,14,15,16, 17).

Occupational exposure, when exceeding TLVs, may trigger nausea, irritability, and headache (18,19), as well as liver, renal, and hematopoietic system defects (20,21), and neurobehavioral shifts (22). Furthermore, exposure to waste anesthetic gases is linked to an increased occurrence of abortion/miscarriage (23,24), decreased fertility (25), and birth defects, which are particularly linked to N₂O (26). Chronic exposure can also affect DNA (27).

The study's goal, in addition to evaluating occupational exposure of workers to N₂O, is to assist the scientific community in determining the reference environmental values

specific for endocrinology ambulatories that use nitrous oxide, with a focus on the pediatric background.

The study's key endpoint measures were associated with the determination of nitrous oxide environmental and biological concentrations during gastrointestinal endoscopic sessions. These tests are taken to monitor the degree of anesthetic gas exposure among operators and to investigate the effectiveness of the preventive system (structure/implant features, anesthesia devices, work procedures, and human factors).

Methods

The study relies on a two-step assessment: the first focus is on the interpretation of data obtained from N₂O environmental monitoring, while the second is centered on biological monitoring data from exposed operators at the beginning and at the end of their shifts.

The environmental concentrations of nitrous oxide were detected during a four months' timeframe, for a total of 10 measurements, using the photoacoustic spectrometers Innova-B&K (Brüel & Kjær, Denmark) "Multi-gas monitor model 1312" and Innova-B&K (Brüel & Kjær, Denmark) "Multi-sampler model 1309". Measurements were performed using one of these two instruments for the whole outpatient session. The measuring probes were placed in five different points in the ambulatory (Figure 1).

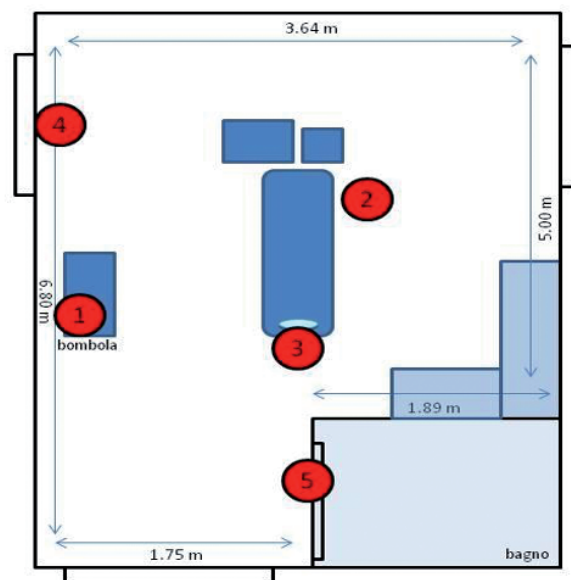


Figure 1. The measuring probes were placed in different point (1=Niki; 2=head-window; 3 head-door; 4= stabilized door; 5=access)

The environmental monitoring assessments were divided into two sessions: the first, in which patients were sedated with an O₂/N₂O mixture delivered without the use of an evacuation system, and the second, in which patients were sedated with the same O₂/N₂O mixture, but with the assistance of a mobile double mask evacuation system of type "NIKI 2002 Airnova" capable of intercepting the emitted anesthetic gases.

A descriptive study design was used to assess gas concentrations in a hospital's gastroenterology ambulatories.

For environmental sampling results, the Shapiro-Francia analysis was used to measure data dissemination. The data was then stratified using the categorical variable relating to the use of the NIKI mask. The t-Student parametric test was then used to analyze the averages in relation to the variable of NIKI mask use; the ANOVA variance test was performed in order to investigate the averages of the environmental levels of N₂O at the respective sample points, with the averages above two being corrected with the Bonferroni's test.

The study's participants were a team of health professionals who serve in the gastroenterology ambulatory for each colonoscopy session; the team included one gastroenterologist and one nurse. An operator with the qualification of prevention technician was involved in the environmental analysis and the preparation of urinary samples; biological sampling was performed on the urine for the biological analysis. The environmental data and urinary samples were analyzed in validated laboratories.

Sample collection was performed in environments free of pollution due to anesthetic gases. After collection, a urine aliquot was immediately transferred into an hermetically sealed tube; this passage was performed very quickly ($t < 1$ minute) so that the vapors loss was negligible ($< 5\%$). The urines were then acidified with sulfuric acid (200 μ l of H₂SO₄ 9N as antimicrobial agent) and stored for more than 24 h. The vials, appropriately labeled, were transported to the laboratories, through a thermostatic thermal bag and stored at 4°C up to the analysis. The samples were then analyzed in laboratory, through a Thermo Trace GC Ultra with Polaris Q Mass Spectrometer GC/MS System (IET-International Equipment Trading Ltd., Mundelein, Illinois, USA), and Thermo Direct Probe Controller (IET-International Equipment Trading Ltd., Mundelein, Illinois, USA).

A descriptive analysis of the N₂O concentrations of urine was performed. Due to the limited sample size, data distribution analysis was performed using the Shapiro-Wilk test. The t-test was thus used to compare the urinary concentration averages of N₂O for doctors and nurses at time 0 (T₀, start of shift), and the same was repeated at time 1 (T₁, end of shift). The t-test was also used to analyze N₂O averages between time T₀ and T₁ in participants who wore NIKI masks and those who did not. Statistical significance was determined by $p < .05$ values.

Results

The endoscopists and nurses engaged in the outpatient diagnostic procedure were hired for the study; the observation period lasted 10 days, and 48 patients were treated; diagnostic services were conducted during day shifts between 06:57 and 18:23.

3.1 Environmental analysis (Study 1)

The N₂O levels in the environment were first stratified in order to compare the conditions under which N₂O is used without any emission control mechanism and then with the use of the control mechanism (NIKI mask).

For a total of 10 daily observations performed in a four months' timeframe, 4105 sequential samples were collected for each of the five detection probes; having dis-

covered values well above the exposure limits (50 parts per million, ppm) in the absence of the use of containment mechanisms (NIKI mask), it was decided to discontinue the experimentation in this way and continue the sampling with the use of NIKI masks to safeguard all operators involved. Therefore, only 374 environmental determinations were obtained without using the NIKI mask, while 3731 were obtained using this mask.

The average environmental concentration of N₂O in the air was 27.58 (SD 1.76) using the NIKI mask and 449.59 (DS 35.29) without using it. The difference in averages (with and without NIKI) detected was largely significant ($P < 0.001$).

As aforementioned, the environmental probes in the room were placed in five different spots; the average concentration in each individual point (Table I) was significantly different ($P < 0.001$) from the other points, even though a low strength (F16.42) and R² were found supporting the model only of $P = 0.017$.

Table I. Average concentrations in different points

Sampling point	Number of observations	Mean value (ppm)	S.D.
1- Niki	749	40.00	85.47
	75	436.52	329.59
2- head-window	748	23.59	43.23
	75	518.77	416.95
3- head door	747	26.57	46.19
	75	424.73	308.18
4- stabilized door	746	18.33	32.06
	75	446.06	319.51
5- access	741	29.40	49.59
	73	421.11	348.20
Total	3731	27.58	54.87
	373	449.59	346.62

According to the Threshold Limit Value in the measurements in which the NIKI mask was used, the levels set by National Institute for Occupational Safety and Health (NIOSH) (25ppm) were exceeded in 982 samples, the levels set by Italian law for 'new' operating rooms (50ppm) were exceeded in 645 samples and those for 'old' operating rooms (100ppm) in 288 samples.

There were major variations in environmental concentrations of N₂O at the different sample points (Table II), implying that the lack of specific mechanisms for handling air flows and modifications causes areas of greater concentration and, as a result, greater professional exposures to anesthetic gases.

Table II. Test Comparison of N₂O concentration (in ppm) and sampling points

	1- Niki	2- head-window	3- head door	4- stabilized door
2- head-window	-16.41* $P < 0.001$			
3- head door	-13.43* $P < 0.001$	2.98 $P = 1.00$		
4- stabilized door	-21.67* $P < 0.001$	-5.26 $P = 0.62$	-8.24 $P = 0.03^*$	
5- access	-10.60* $P < 0.001$	5.82 $P = 0.39^*$	2.84* $P < 0.001$	11.08* $P < 0.001$

* significant values, $P < 0.05$

Table III. Comparison of N2O urine concentration averages

	Observations	Mean value	S.E.	S.D.	95% C.I.	p-value
Comparison of N2O urine concentration averages with the use of Niki mask						
Operators T1	16	10.14	0.94	3.78	8.13 / 12.15	P<0.001
Operators T0	16	1.17	0.58	2.32	-.06 / 2.41	
Difference	16	8.97	0.88	3.53	7.09 / 10.85	
Comparison of N2O urine concentration averages without the use of Niki mask						
Operators T1	4	77.49	33.09	66.17	-27.80 α 182.79	P=0.10
Operator T0	4	0.62	0.26	0.52	-0.21 α 1.45	
Difference	4	76.87	33.00	66.00	-28.13 α 181.88	

3.2 Biological monitoring (Study 2)

There was no discrepancy in urinary concentrations between doctors and nurses when the two classes of operators were examined. The exposure group (nurses and doctors) was then viewed as a single sample with a total of 16 determinations at T0 and 16 determinations at T1.

The urine concentration averages of N2O were analyzed, and the substantial reduction of urinary concentrations in those exposed to N2O in the two groups were compared: while using the NIKI mask the average concentration at T0 was 1.17 (SD 2.32) and at T1 it was 10.14 (SD 3.78), the variation at the start and end of the shift was significant ($P=0.001$) (Table III); without the mask the average at T0 was 1.01 (SD 0.39) and at T1 was 77.49 (SD 66.17); the protective effect of the NIKI mask was statistically significant ($P=0.003$).

Discussion

The first interesting finding from this research is that using anesthetic gases in conditions other than operating rooms exposes operators to a risk that exceeds the maximum values set by international agencies such as NIOSH (25 ppm, which is equal to 30 mg/m³ (28,29)).

Furthermore, in an Italian context, there are limits on the environmental concentration of nitrous oxide that are controlled by specific provisions; Memorandum No 5 of 14 March 1989 of the Ministry of Health sets as the reference limit value for operating rooms the threshold of 50 ppm (91 mg/m³) – which rises to 100 ppm for operating rooms that were already in existence at the time of Memorandum.

This research, in addition to discussing a topic not addressed by Italian regulations or national standards on N2O, highlights a professional field – ambulatory where medical gases are used – where operators are exposed to workplace hazards, revealing a deficiency in the health professionals' prevention and safety framework. Despite the limited sample size, the end-of-shift urinary concentration was observed to be 77.49 and 10.14 mg/l without and with a NIKI mask, respectively, against an exposure limit of 27 mg/l.

To be able to use a facility as a safe room for the use of anesthetic gases, mechanisms for reducing emissions and/or air exchange systems that can guarantee compliance with anesthetic gas exposure values must be pro-

vided. The use of the NIKI Mask tested in this study seems to be a useful intervention to aid in the reduction of environmental concentrations of N2O below the expected values in the operating rooms; however, it should be noted that, even with the aid of the mask, the average concentration is still higher than the values set for occupational exposures (NIOSH) of 25 ppm, and hence additional containment systems should be studied.

There was no noticeable variation in N2O exposure between doctors and nurses, which was most likely due to their location in the room being near the same area examined by the sampler. In this regard, it is also worth noting that in the absence of complex air collection and control systems, there are areas of higher N2O aggregation and areas with lower concentrations.

A final comment should be made on the health surveillance of the operators involved, including the fact that it is noted that these operators, as well as their counterparts working in the operating rooms, would join the health surveillance program for exposure to anesthetic gases.

The samplers were put in five different points as stated in the room; the average concentrations at the individual points were calculated (Table III) and then a comparison between the averages and the Variance test (ANOVA) was performed, revealing a significant difference ($P=0.001$) between the points despite a low intensity ($F_{16,42}$) and an R^2 supporting the model of just .017.

The study has been performed following a rigorous methodology, with the number of measurements and sample size appearing large enough to show that what has been assessed in the context of environmental monitoring in the outpatient setting needs structural actions to minimize the workplace exposures of the operators involved. The section on biological monitoring is interesting in terms of providing scientifically valid support for the assumption that outpatient exposures of healthcare professionals are at risk of N2O exposure, but the small size of the observed sample should be noted, as well as the need to expand the study to larger populations in order to provide greater consistency to the data collected in relation to the environmental monitoring.

The present study's findings highlight the need to deepen and enforce technical guidelines, requirements, and systems for the use of N2O in ambulatory settings; in the Italian setting, the need to properly identify the technical standards and exposure limit of N2O outside the operating room through norms and policies is evident.

This study emphasizes the importance of implementing additional precautions for operators who are exposed to endoscopic procedures in ambulatory facilities.

Finally, the authors would consider using nitrous oxide in conjunction with a gas scavenging device to reduce the operators' exposure.

This study also reveals that measuring the gas scavenging system is insufficient to secure operators, who would need to undergo health surveillance measures to track the medium to long-term effects.

The authors intended to add to the debate over the concept of reference standards for nitrous oxide environmental concentrations by highlighting the lack of specific regulatory limits for medical procedures involving nitrous oxide in facilities other than operating rooms.

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