

Assessment of an Equimolar Mixture of Oxygen and Nitrous Oxide: Effects in Pediatric Dentistry

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ABSTRACT

Background: Many studies were conducted to assess the benefit/risk of equimolar mixture of oxygen and nitrous oxide (EMONO), but evaluating the appetite associated to its use is now getting very little attention in the literature. The purpose of this study was to investigate the effects present, felt, and sought during care by the child related with the 50% nitrous oxide/oxygen (EMONO) sedation used in pediatric dentistry.

Materials and methods: All patients in consultation with the Dental Service of Nantes hospital and in need of EMONO were included in the study. In this prospective single-center study, the effects present, felt, and sought during care by the child and the assessment of EMONO appreciation were recorded. The presence of clear signs that the child was trying to extend the duration of the EMONO use was also sought.

Results: Only 62% of the patients were presented with an anxiolytic effect, and 40% relative analgesia. Both effects were associated in 33% of children. Over the 76 patients assessed, 12 attempted to extend the duration of the EMONO use (16%). After a bivariate statistical analysis, none of the variables appeared significantly associated with the extension of the EMONO use duration.

Conclusion: The significant proportion of patients who have prolonged the EMONO use seems to indicate a real attraction for nitrous oxide. This is the first study to evaluate nitrous oxide appreciation on a child.

Keywords: Equimolar mixture of oxygen and nitrous oxide, Observational study, Substance-related disorders.

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INTRODUCTION

EMONO is an equimolar mixture of oxygen and nitrous oxide which has an analgesic effect with a reduction of the perception threshold of different painful stimuli. This is the only way that nitrous oxide is available in France for dental care. At this concentration, nitrous oxide should not cause deep sedation. It causes modifications in consciousness: patients are relaxed, sedated, and less aware of their surroundings. Pulmonary absorption and elimination of nitrous oxide is very quick because of its low solubility in the blood and tissues, which explains the rapidity of the analgesic effect and the quick return to the initial status after discontinuation of inhalation.¹⁻⁵

According to the characteristics summary of the product available on the French government's public drug database, EMONO indications in dentistry are dental care in infants, children, and adolescents, as well as anxious or patients with disabilities. Nitrous oxide has weak anesthetic properties but potentiates the effects of more potent anesthetic agents. Administered in combination with oxygen, like EMONO, it improves the cooperation of patients during anxiety-related or painful medical and paramedical procedures (mild to moderate pain) and of short duration. Sedation with EMONO is very helpful in dental care, particularly with patients with behavioral disorders, mental retardation or an excessive anxiety for dental care. Patient cooperation seems to be improved under EMONO and its use is safe, when not used in association with psychotropic agents.^{6,7}

In France, EMONO is classified by the regulatory regime for drugs as known to produce dependency and is monitored by the ANSM (French National Drug Monitoring Agency). EMONO obtained its authorization to be used by medical professionals in 2001 in France in several indications, in particular dental care, in hospitals exclusively, in children, patients with anxiety or

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disability. In 2009, the authorization to use it outside a hospital setting has led to a risk management plan implementation. It has been shown nitrous oxide could cause problematic consumption: 31 cases of problematic consumption of nitrous oxide alone

or in a mixture with oxygen were reported over a period from 1978 to 2014.^{8,9} Classical vulnerability factors of addiction have been reported (family context, psychiatric vulnerability). It is possible to define several problematic consumer groups with different characteristics: the first group concerns pure nitrous oxide users, who consume it for recreational purposes; the second group is characterized by nitrous oxide used for medical purposes; and the third group is characterized by the presence of health professionals, namely dentists using the nitrous oxide/oxygen mixture.⁸ However, in none of the ANSM reports are patients notified with dependence or abuse due to EMONO use in dental care. The desired effects on patients during EMONO use are relative anxiolysis and analgesia with a preserved state of awakening.²

The Dental Service of Nantes Hospital represent the last resort at the regional level for patients with limited cooperation because of their disabilities or anxiety. The use of EMONO is often carried out several times for each patient. Indeed, very few dentists nearby uses EMONO, leading to a large influx of patients in our service. However, the authorization to use it outside a hospital setting will lead to an increasing number of dentists using EMONO.

As part of our care activity at the Dental Service of Nantes Hospital, the majority of our patients requiring the use of EMONO are children. We thought to conduct this study within this particular population to obtain usable results of any adjustment necessary to our management. For this purpose, we conducted a study observing the sought effects and felt effects and estimating their frequency. The will of contact prolongation from the patient was also observed.

MATERIALS AND METHODS

We aimed to conduct a naturalistic pilot study in our center during our usual practice.

Objectives

The main objective of the study was to describe the effects experienced by patients undergoing EMONO.

The secondary objectives were (i) to demonstrate the prevalence of patients showing appetite for EMONO during care and (ii) to characterize these patients wishing to prolong contact.

Participants

This single-center, prospective epidemiological study was conducted at the Dental Service of Nantes Hospital from November 2014 to May 2015. All patients aged 3–15 with a need of dental care under EMONO at the Dental Service of Nantes Hospital could be included. EMONO is applied with a naso-oral mask during the entire treatment session. During care, the mask is repositioned on the nose so that the practitioner can access oral cavity. Exclusion criteria were: (i) not being able to provide an answer for the evaluation, (ii) dental treatment possible without the use of EMONO, (iii) or important treatment justifying the use of general anesthetic.

Depending on the severity of the cases, children could be treated during only one session or over several sessions. For children with several sessions, data were collected during the first and final session.

All patients included were able to declare their non-opposition through a legal representative.

This study was approved by the Nantes Ethics Committee.

Assessment

The data collected included the medical history of the child, family situation (separated parents or not), parents' anxiety for the dental care of their children or not, and information about the session of dental care with the use of EMONO. This latter part of the assessment was assessed by the practitioner, taking into accounts his/her comments and the answers to questions asked to the child. Regarding the effects felt by the child, if he/she could not verbalize his/her perception, the data could not be collected. They were then rated non-collectable.

Medical History

For those with several sessions of dental care, the effective dose during the first and the final sessions were noted to see if there was an evolution.

Sociodemographic characteristics such as

- Family situation (separated parents or not) or
- Parents' anxiety for their child's dental care was recorded.

Effects of EMONO Use

The effects observed and felt during the session were recorded. Anxiolysis and relative analgesia, two of the EMONO expected effects, were particularly observed. These have either been directly observed by the practitioner or been described by the child at its questionnaire response.

All clear signs of contact extension with EMONO observed by the health professional were taken into account for the secondary endpoint. The presence or absence of these signs was noted (e.g.: hand sign to keep the mask over the nose and mouth or verbalization of the will to keep the mask). This objective criterion allowed us to take into account the child's will to prolong contact with EMONO. The investigators seemed the best able to detect the prolongation will in any form whatsoever. This allows an observation even with non-communicating patients.

A visual analogue scale (VAS) (from 0 to 10) (or sace scale according to the understanding capability of each patient) was used to assess the hedonic nature of the sensations (nasty to nice) of the child upon inhalation of EMONO. The VAS scale is usually used in dental care to assess pain, but was used in this study to evaluate the comfort of the child.

The management of the side effects (wishes to extend the duration of the EMONO use or not) were reported. In this case, the child was asked if he was willing to continue and the choice was noted.

We developed a drug-liking assessment, by asking the child if he would rather exchange the toy he traditionally received at the end of dental care, against the extension of the duration of the EMONO use. We noted the response of the child.

Statistical Analysis

A descriptive analysis of all the sought or felt effect was carried out.

For further analysis related to secondary endpoint, participants were divided into two groups on this latter criterion: "Manifest attempt or desire to prolong contact with the mask".

Exploratory univariate analyses were performed in the following way. The links between the all the sought or felt effect on the one hand, and the will of extension of EMONO use on the other hand were studied using Student tests for the quantitative variables and Fisher tests for the qualitative variables.

Thereafter multivariate analyses were performed using an iterative selection procedure to select the variables that were

significantly associated with the attempt of contact prolongation, as assessed by the likelihood ratio test. The corresponding odds ratio and associated confidence interval were estimated. Discrimination of the final logistic model, which describes its ability to discriminate between the presence and absence of a contact prolongation attempt, was assessed using the area under the receiver operating characteristic (ROC) curve and the goodness-of-fit of the model was assessed using the Hosmer–Lemeshow test.

The conditions for validity were verified for all of the tests and the model. The data were computed using the Epidata® software and all analyzes were performed using SAS software 9.3®.

RESULTS

Description of the Participants

Sociodemographic Variables

A total of 76 patients were included in this study. They were aged 3–13 years (mean 6.6 years). The sex ratio was in favor of girls (48/76, 63%). For 29% (22/76) of these patients, this was their first dental care and for 53% (40/76) their first experience of treatment under EMONO. 17 of these patients had a systemic disease and 15 patients presented a disability (Table 1).

Parental Characteristics

Information regarding parental anxiety and whether or not parents were separated was relatively well reported since 71/76 and 72/76, respectively, answered these questions. Only 49% of parents felt anxious before or during the treatment and 17% of parents who responded were separated.

EMONO Use

For the primary endpoint, 62% of patients presented an anxiolytic effect, and 40% relative analgesia. Both effects were associated in 33% of children. Table 2 describes the population and shows the most frequent effects found in patients (felt and sought) during treatment sessions. The effects were ranked in the table by a decreasing order of frequency. For each effect felt by the patient or perceived by the practitioner, the frequency at which the effect was positively felt by the patient was noted.

An estimated 16% (12/76) of children had tried to extend the duration of the EMONO use or expressed their willingness to extend it.

The average dose used in these sessions was 5.6 liters per minute.

A VAS score was filled for 53 patients. The average score was 7.87.

During the sessions, 9 adverse events occurred, them mostly being nausea or vomiting, 4 of which caused a shutdown in the will of the patient.

Table 1: Patient’s characteristics

	<i>Prolongation of the EMONO use</i>
N	76
Sex (M)	28/76 (37%)
Age (average)	6.6
First time EMONO	40/76 (53%)
VAS score average	7.87
Exchange	10/49 (20%)
Side effect	9/74 (12%)
Systemic pathology	17/73 (23%)
Handicap	15/73 (20%)
Medication	14/73 (19%)

Table 2: Description of the observed frequencies for each effect felt and their positive perception by the total sample

TOTAL = 76	Total	
	Presence (%)	Perception+ (%)
Anxiolysis	44/71 (62)	32/33 (97)
Slight decrease in the level of consciousness	44/72 (61)	27/34 (79)
Distorted sensations (sounds, paraesthesia)	33/71 (46)	18/27 (67)
Relative analgesia	29/72 (40)	22/22 (100)
Preserved state of awakening	28/72 (39)	12/13 (92)
Agitation	14/72 (19)	1/8 (12)
Abolition of judgement	11/72 (15)	3/5 (60)
Euphoric	10/71 (14)	7/8 (87)
Anguish	9/71(13)	0/7 (0)

+Positive perception

“Drug-liking”: in 20% of cases (10/49), patients were willing to trade their toy usually given to them at the end of the session.

Some trends had to be noted, particularly the high number of positive perception for anxiolysis and analgesia, as well as effects expected under EMONO. We also observed a high number of positive perceptions of the decrease in the level of consciousness and the distorted sensations, which are potentially expected by recreational drug users.

Characterization of Patients with Appetite for EMONO

A comparison of the patients according to the will or not of contact extension.

Two groups were thus formed, the first of 12 patients who tried to extend the duration of the EMONO use and the second of 64 patients who did not. The description and comparison of the two groups is shown in Table 3.

Table 3 presents the proportion of each felt or observed effect and their perceptions by the patients in each group. The effects were ranked in descending order of frequency based on the group where a contact extension was observed.

The analysis lacks power because of the small numbers involved. For the multivariate analysis, a selection of the variables of the clearest trends was made. The relevance of these variables was then checked afterwards.

The variables with $p \leq 0.3$ in the bivariate analysis were included in the multivariate model: age, previous dental care with EMONO, a preserved state of awakening, anxiolysis, euphoric state, and the presence of medical history. A step-down method was then applied. The results of the multivariate logistic regression indicate that one variable was significantly associated with an EMONO contact prolongation risk: Euphoria ($p = 0.039$). Patients who report euphoria during the administration of EMONO are more likely to want a prolonged contact with the mask (OR = 11.80). On the opposite, patients with a preserved state of awakening ($p = 0.023$) at EMONO administration were more likely to not extend the contact with EMONO (OR = 0.044). The ROC curve (0.869) and the Hosmer Lemeshow factor ($p = 0.5167$) show that the model is discriminative.

DISCUSSION

EMONO Effects

Regarding the effects felt in all patients, it is coherent to find anxiolysis as the most effective indication of EMONO. However,

Table 3: Observed frequencies for each effect felt depending on the appetite for EMONO use

<i>Effects felt</i>	<i>Prolongation</i>		<i>No prolongation</i>	
	<i>Presence (%)</i>	<i>Perception⁺ (%)</i>	<i>Presence (%)</i>	<i>Perception⁺ (%)</i>
Slight decrease in the level of consciousness	9/11 (82)	7/9 (78)	35/61 (57)	20/26 (77)
Anxiolysis	9/11 (82)	7/7 (100)	35/60 (58)	25/26 (96)
Distorted sensation (sounds paresthesia)	8/11 (73)	6/8 (75)	25/60 (42)	12/19 (63)
Relative analgesia	6/11 (54)	6/6 (100)	23/61 (38)	16/16 (100)
Euphoric	3/11 (27)	2/3 (67)	7/60 (12)	5/5 (100)
Nausea or vomiting	2/11 (18)	0/1 (0)	3/60 (5)	0/3 (0)
Preserved state of awakening	1/11 (9)	NA*	27/61 (44)	12/13 (92)
Agitation	1/11 (9)	NA*	13/61 (21)	1/8 (12)
Abolition of judgment	1/11 (9)	0/1 (0)	10/61 (16)	3/4 (75)
Side effect	0/12 (0)	NA*	9/62 (14)	

*Not applicable

⁺Positive perception

we found that only 62% of patients presented an anxiolytic effect, which seems rather low for the expected major effect of EMONO. Just after anxiolysis, relative analgesia is also one of the major known effects of nitrous oxide. In our group of patients, analgesia is only the 4th one and concerns only 29 of the 72 patients (40%). The analgesic potential of nitrous oxide in the oral sphere can also be discussed based on these treatment sessions. The anxiolytic and analgesia were associated only in 33% of children (24/71). Nevertheless, these results from the child’s responses are to be considered with caution, especially because analgesia remains a difficult criterion to assess in children. Therefore, subjectivity is likely to skew our analysis. The slight decrease in the level of consciousness is the second main effect found on EMONO sessions (61%), which makes sense because of the sedative properties of nitrous oxide. However, distorted sounds and paresthesia were found in almost half of cases (43%). Surprisingly, they were perceived globally positively (67% of patients feel comfortable).

Appetite for EMONO was assessed in our survey using the patients’ attempt to extend the duration of the EMONO use, which can indicate a consumption desire; the results must then be carefully watched. But as we previously said, it seems to be a good approximation for the will of prolongation, and allows an observation even among non-communicating patients (disabled or too young). A total of 12 cases of extended contact on the 76 patients in our study were identified, which constitutes 16% of the participants and therefore a significant proportion of patients admitted with care under EMONO.

Are Dentist Patient Concerned by the Abuse Risk?

Many studies were previously conducted in order to evaluate the benefit/risk of EMONO but data evaluating its associated appetite remain very scarce. Numerous questions may be raised in regard to its use outside a hospital setting, where the boundaries are more easily implemented and enforced, especially looking at our results. These indications are extremely broad and affect many medical specialties. Even in the particular context of dental care, the terms of use vary greatly between countries, as do the indications. The appetite for EMONO therefore deserves particular attention because of an uncertain risk associated with a widespread use.

In France, EMONO is classified by the regulatory regime for drugs known to produce dependency (part of stupeficient regulation—secure storage, theft mandatory disclosure requirement). It has been approved for marketing in France since 2001 for use at the

hospital. Its use was considered as very safe in this context by Onody et al.¹⁰ In 2009, there was an extension of the marketing authorization for out-of-hospital use. The French regulatory authority (ANSM) revised the marketing authorization conditions, namely the possibility of ambulatory use, as asked by Collado et al.¹¹ A risk management plan was requested in order to prevent safety concerns such as abuse and dependence. Risk minimization actions include reinforcement of drug safety and drug dependence surveillance with an incitation of health professionals to notify all serious cases of adverse effects, abuse and drug dependence. The Nantes Addictovigilance Center is responsible of this survey. This study allows us to further evaluate and monitor the harmlessness of the EMONO use.

As we previously said, the Dental Service of Nantes Hospital represents the last resort at the regional level for patients with limited cooperation because of their disabilities or anxiety. It allowed us to conduct this study in a population of patients normally scarce. These data are therefore particularly interesting especially seeing the difficulties encountered in their collection.

The recreational drug users’ profile, among young people, is described in literature as being mainly boys.^{12,13} In the 12 cases of extended contact, 7 of them were boys, but the insufficient number of patients in this group prevented us from noting anything else but that our results are consistent with this pattern. Botvin et al. have described the role of prevention programs to reduce risks to consumption among the young.¹⁴ The use of strict context for the use of EMONO in France seems also found its justification, explanations on EMONO being an integral part of the care session. The role of alcohol and cigarette consumption as a gateway to problematic use was noted.¹⁷ The role of a peer leading to consumption is also highlighted in the literature.¹³ However, articles describing the profile of children who are true or potential drugs consumers are rare in the literature. In our study, the upper age limit of 15 years put us in contact with young people who already had a first potentially addictive experience. The framework for the use of EMONO during care therefore seems particularly justified to not create or re-create in them a gateway to a recreational drug, nitrous oxide being particularly accessible.

These results do not highlight a particular stratum of patients admitted in consultation, with a desire to prolong contact with nitrous oxide, which makes the identification of patients considered “at risk” more difficult than expected. It is through the comments of the practitioner, patient monitoring, and analysis that “at risk”



behaviors may be identified. The “risk” is not only represented by the will to keep the mask but also the will of contact extension with a substance altering the perception of the environment. The multivariate logistic regression shows that when euphoria is observed in a patient, the risk of contact extension is substantially higher. The significant proportion of patients who have prolonged contact with the gas, or desired exchange with the toy, or indicated a high score of appreciation of the gas shows that there is a real attraction for nitrous oxide. The published data also point in this direction since many cases of abuse of pure nitrous oxide have been recognized in recent years.⁸ The fact that EMONO is appreciated by patients is particularly interesting in the context of dental care because its use is totally framed.

Of the 76 patients included in this study it is important to note that over half of them (53%) had never inhaled nitrous oxide before inclusion. The study population is made up of more than half by naive consumers, for whom the first session of care was a discovery of the product and its effects. It is interesting that among the 12 patients who attempted or showed a willingness to extend the contact with the gas, 5 consumers were “naive” and 7 had already used EMONO. An estimated 55% of patients had already experienced EMONO in those who did not attempt or show a willingness to extend the contact with the gas. It then would seem that the will of contact extension is not influenced by a previous administration.

In Which Patients there are Appetite?

In the study, social and psychological characteristics were included, seeing as they can constitute vulnerability factors in the development of abuse: family situation and parental anxiety. Indeed, a divorce usually marks the psychology of a child and exposes him to a risk of major behavioral problems.¹⁵ Moreover, it has been shown that people are more likely to consume psychotropic drugs in case of difficulties encountered in childhood.¹⁶ Therefore, it seemed interesting to investigate this criterion. Moreover, it has been shown in literature that parents could transmit their fear of dental care to their children. We thought interesting to investigate the influence of this mode of transmission of anxiety.¹⁷ Like we previously said, they may not only be vulnerable to the will to keep the mask but also to the will of contact extension with a substance with a psychotropic effect. In our study population, 17% of children were living with separated parents. However, our sample does not allow us to draw any conclusions related to the will of extended contact with the gas. We have not yet highlighted the fact that the anxiety of the people accompanying the child can affect the extension of contact for the patient. Indeed, in both groups, approximately half of the accompanist felt anxious (50% and 48%).

Univariate statistical analysis showed no significant association between the EMONO contact extension and the patient’s characteristics. However, some trends emerge from the results:

- First we found that there are more boys trying to extend the contact than girls (58% vs 33%) as we previously said. Logically the gas appreciation VAS score was higher among extenders (8.27 vs 7.76).
- In our population, only 20% (15/73) were carrying a disability (mental or motor or handset), which shows that the nitrous oxide is no longer only reserved for patients with disabilities or patients with behavioral disorders but concerns a much broader population of children in care failure, mostly because of a probable irrational fear of the dentist. It is important to

note in particular that bearing a disability does not influence the contact extension with the mask; a higher percentage of patients with disabilities were present in non-extendors (21%) than in extendors (17%).

- We also observed that none of the children who tried to extend the contact with the gas had suffered from side effects. The low presence of adverse effects moreover confirms the results of Hennequin et al. about their low occurrence and the safety of use of nitrous oxide when recommendations are respected.⁶
- The issue of “drug-liking”, which let the child chooses between a toy reward or another contact with the gas, allowed us to identify patients deliberately attracted by the gas (10/49). Indeed, some measures are directly related to the prediction of appetite for a substance; it is the evaluation of “drug-liking” that is most commonly used in testing and considered the most sensitive and reliable way to assess the potential for abuse of a substance.^{18,19} It is possible to include levels assessing the subject’s will to resume the substance, and the estimated cost of the substance on the market. These evaluations can be repeated when the effects of the substance have disappeared (the next day) to assess the memory of the overall experience. In our study, in order to implement this methodology, we asked the child if he would prefer to exchange the toy he traditionally receives at the end of care against inhalation of EMONO and noted whether there is the urge or not. The correlation between patients choosing the gas rather than the toy and the attempted extension is not demonstrated by our results; however it is interesting to note that of these 10 patients, 9 had chosen the maximum score on the EMONO appreciation scale (VAS scale marked out of 10). It might be interesting to try to determine, through a more powerful study, if a correlation between the score of appreciation and appetite for nitrous oxide can be correlated. In that case, this tool, easy to implement and use by practitioners, would be a first signal of a potentially risky behavior, and strengthen the vigilance of nursing staff in the coming sessions.

Right Framework for Dental Care

It is important to consider that in France, patients admitted for dental treatment under nitrous oxide are in a difficult clinical situation, since dental care in a classical way has generally failed. Moreover, this study included patients from the age of 3 years to 15 years old, which could have induced variation in the answer capacity. The effectiveness of the nitrous oxide previously discussed through the analgesia and anxiolytic perceptions is therefore to be analyzed in this context. Indeed, these treatment sessions under EMONO, initially provided in order to reconcile the patient with classical dental care, are very often the only alternative to general anesthesia. Since treatments have been achieved even with a difficult patient cooperation, it is considered that the care was a success. In our study, out of 76 patients, only one patient could not be processed as expected. EMONO represents a considerable advantage as long as it remains within the limits of its indication.

Further studies are needed to better understand early predictors of nitrous oxide appetite on children. At the best of our knowledge, this study is the first to evaluate nitrous oxide appetite on child. This topic had to be explored and it could be particularly interesting to monitor over time and check the validity of the predictive elements of EMONO appetite in order to link them

to the possible future use of nitrous oxide or other psychotropic substances.

CONCLUSION

The nitrous oxide has interesting properties for many medical specialties. Its use is widespread in the world, but is framed differently according to specialties and countries. If its effectiveness in the context of dental care has been widely demonstrated, the risks associated with its use must not be minimized. The significant proportion of patients who have prolonged the EMONO use seems to indicate a real attraction for nitrous oxide. The evaluation of its associated appetite in other studies seems necessary.

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