ORIGINAL RESEARCH

Objectivation of the Equimolar Mixture of Oxygen and Nitrous Oxide Anxiolytic Effect in Pediatric Dentistry: A Pilot Study

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Abstract

Aim: EMONO is an equimolar mixture of oxygen and nitrous oxide. Studies investigating its anxiolytic effect mostly used behavioral scales for assessing anxiolysis in children during dental care. Observing this effect objectively in a pediatric population could be very interesting.

Materials and methods: We conducted a prospective uncontrolled monocentric pilot study to assess the equimolar mixture of oxygen and nitrous oxide (EMONO) anxiolytic effect in children during dental care by monitoring heart rate (HR) variation.

Results: A statistically significant difference could be highlighted between the HR before the dental care and after 5 minutes of EMONO inhalation, illustrating the anxiolytic effect of EMONO in an objective way. HR variation also suggests that the effect of EMONO seems to prevent a return to the initial level of stress, even during anesthesia.

Conclusion: All of the data in the literature confirm the essential role of nitrous oxide in pediatric dental care. Demonstrating the effectiveness of EMONO by objective criteria is necessary.

Trial registration: Clinical Trials Unique Protocol ID: RC17_0275.

Keywords: Dental anxiety, Equimolar mixture of oxygen and nitrous oxide, Heart rate.

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Background

EMONO is an equimolar mixture of oxygen and nitrous oxide. In France, this is the only authorized use of nitrous oxide for dental care. EMONO is registered on the French National Agency for the Safety of Medicines and Health Products list of drugs with enhanced surveillance.[1] ENOMO is indicated in the analgesia for painful acts of short duration or during medical assistance in adults and children, sedation in dental care in children and fragile subjects, as well as in obstetrics. Its therapeutic value was deemed important by the Haute Autorité de santé—the French authority in charge of the regulation of the health care system. The ENOMO use has been authorized in France since 2001, but until 2009, it was reserved for hospital use and the vehicles of the emergency medical assistance service. Since 2009, a change in authorization for nitrous oxide-based specialties has authorized their removal of the hospital reserve, which can now be issued for professional use in private medical and dental practice. Today, it takes an important place in the French dentists' therapeutic arsenal for the dental care of noncompliant children or with a disability, limiting their cooperation. It allows us to keep those patients in a state of conscious sedation, most often facilitating care realization.

The EMONO as nitrous oxide, is a colorless and odorless gas. Analgesia and anxiety are the two most sought properties. Indeed, in a conscious patient, this medication provides the reduction or elimination of pain and anxiety by acting directly on the central nervous system with a lower effect on the respiratory system.[2,3] Most of the time, the clinical effect of EMONO inhalation is more predictable than other pharmacological means available in France, such as oral conscious sedation.[4] The action mechanism of nitrous oxide contained in EMONO is not yet fully understood, but recent studies have partially elucidated this mechanism. The analgesic effect is related to the inhibitory effect of nitrous oxide on the N-methyl-D-aspartate receptors, which play an important role in the transmission of the nociceptive message and in hyperalgesia.[5] Its stimulating effect on dopaminergic neurons has also been shown by the stimulation of the secretion of dopamine and/or norepinephrine, which are involved in the transduction of some of the effects of nitrous oxide on the central nervous system. All of the recent results have led to the hypothesis that nitrous oxide induces the release of endogenous opioids in the periaqueductal gray matter. This is followed by the activation of opioid receptors, γ-aminobutyric acid

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type A ($GABA_A$) receptors, and noradrenergic pathways modulating nociceptive treatment at the spinal level.[6,7] The hypothesis of the release of opioid peptides is supported by the clinic because morphine antagonists also partially antagonize the analgesic effects of nitrous oxide.[5] The anxiolytic effect involves activation of the $GABA_A$ receptor, directly or indirectly, through the benzodiazepine binding site.[8,9] The absorption of nitrous oxide is quick and takes place through the alveoli. It is quickly excreted by the lungs. Lung absorption and elimination of nitrous oxide are very fast due to its low solubility in the blood and tissues. This explains the rapidity of the analgesic and anxiolytic effects appearance, as well as the speed of return to the initial state after cessation of inhalation.[10–14] As nitrous oxide is 34 times more soluble than nitrogen in the blood and diffusion hypoxia can occur.[4] Therefore, the nitrous oxide gas has to be used in combination with oxygen, as in the case of EMONO. It is very safe to use without any major health problems identified when it is used in the recommended concentrations.[15–18] Specific studies on EMONO have shown similar results.[19–22]

The analgesic action seems to be better known than the anxiolytic one. Indeed, clinical evaluations relating to this pharmacological substance are more frequently turned to its efficiency in analgesia.[23,24] Studies investigating the anxiolytic effect mostly used behavioral scales for assessing anxiolysis in children during dental care (21, 22, and 25–26), but to our knowledge, no study observing this effect objectively has yet been achieved in a child population in dental care. A previous study conducted at the Nantes Dental Care Center, entitled MEOPAeDent (prospective, uncontrolled, and monocentric), aimed to describe the current, felt, and desired effects of EMONO during treatment subjectively by interrogation and observation of the child.[27,28] Especially we noticed that only 62% of patients exhibited an anxiolytic effect, which appeared rather weak for one of the two major effects that we could expect from EMONO. Besides, analgesia is also one of the known main effects of nitrous oxide. In this group of patients, analgesia was felt by only 40% of patients. However, anxiolysis and analgesia were only associated with 33% of children. Those results, derived from the child's feelings and communication, should be viewed with caution, especially since analgesia and anxiolysis were difficult to assess in this context. Therefore, the subjectivity of declarative studies is a bias that should lead to interpreting our results with caution. In fact, it seemed important to consider a more objective assessment of these major effects in order to investigate the efficiency of ENOMO. Nevertheless, this study served as a basis for setting up this work and we will use it to make comparisons.

Many studies evaluating the effectiveness of nitrous oxide in medicine or in dental care are built on a noninferiority design. In fact, they compared the care realization success rate between using ENOMO or another anesthetic technique or a placebo.[25,29,30] They could also observe the patient's acceptance of this kind of sedation with minimal adverse effects.[29,31–33] Furthermore, behavioral and/or anxiety evaluation scales are often found in studies. The two most frequently found to assess the effectiveness of EMONO remain the analog visual scale, whether for these analgesic or anxiolytic properties[25,34,35] and the Venham scale modified by Veerkamp for the anxiolytic effect.[21,22,25,26] Therefore, current data from the published literature attest to an anxiolytic effect in children using EMONO. However, those assessments remain subjective and, most of the time, depending on the investigator rather than the patient. By contrast, communication with the young patient is not always easy and it could be difficult for them to give their doctor some clear answers to an oral questionnaire about their feeling after this experience. So, those measures could be under or overestimated, which could change the assessment of the effect.

We will seek through this work to study the anxiolytic effect of ENOMO, which is expected in the child when it is used during dental care. This pilot study will attempt to objectively highlight this by following changes in the HR of our young patients, which is recognized as a real stress marker in children and adults[36–38] and so considered as proxy measures of anxiety in odontology.[39,40] The EMONO impact on stress will therefore be assimilated to its effect on the fear felt by the child.

Materials and Methods

Study Oversight

We conducted a prospective uncontrolled monocentric pilot study to assess the EMONO anxiolytic effect in children during dental care, called MOPEA. After submission, this study was allowed by the French Personal Protection Committee in January 2018. The data collected during the test was subject to computer processing in accordance with the requirements of the French National Data Protection Commission. It is also recorded in clinical trials (Unique Protocol ID: RC17_0275).

Participants

The sample was selected from young patients requiring EMONO sedation for dental care. Those noncompliant or disabled children had limited cooperation indicating conscious sedation. To be included, the patient also had to be naive towards EMONO and between 3 and 15 years of age. The care provided had to involve local anesthesia—therefore, we retained patients requiring a dental avulsion or a pulpotomy.

The child's participation in the protocol was allowed after obtaining his/her informed consent and those of his/her legal representatives. For the rest, the process of dental care still remained conventional.

As it was a pilot study, we aimed to include at least 10–20 patients.

Procedures

The study started in March 2018 and continued for 1 year at the Nantes Dental Care Center.

In order to observe our primary outcome, a HR monitor was used as soon as the child was installed in order to register his HR. This allows us to assess its variations at different times of interest. It consists of a simple computer with operating software and a miniaturized sensor, in our case, to be worn on the earlobe. Thanks to this device, a continuous data recording was made. In fact, it allows us to observe changes in HR in the presence of external stimuli, whether they are causing stress or not. At the beginning of the session, the first child's anxiety evaluation by Venham scale modified by Veerkamp was also managed.

Following the installation, conscious sedation with the inhalation of EMONO could begin. Conscious sedation is typically achieved after 5 minutes of inhalation. So, at this time, a new HR measurement allowed us to objectify the anxiolytic effect of EMONO on the child. Then we started the treatment itself with local anesthesia. A final HR measurement was realized during anesthesia, allowing us to highlight if EMONO modifies the behavior of the child toward a stressful stimulus. For the rest of the session, we proceeded normally until the end of the treatment. Finally, we removed the ear sensor from the HR monitor and proceeded to the final child's anxiety

evaluation by the Venham scale modified by Veerkamp at the end of the session.

Endpoints

The main outcome of our study was to assess the EMONO anxiolytic effect in children during dental treatment. Thus, our main endpoint was the measurement of the subject's HR at three distinct moments:

- T0: Heart rate (HR) during installation—this measure has been used as a control.
- T1: Heart rate (HR) after 5 minutes of EMONO inhalation—conscious sedation, being generally obtained after 5 minutes of inhalation; this measurement allows us to objectify the anxiolytic effect of EMONO on the child.
- T2: Heart rate (HR) during anesthesia—this measurement allows us to highlight if EMONO modifies the behavior of the child facing a stressful stimulus—local anesthesia.

As a secondary outcome, the investigator also assesses the child's anxiety level at the beginning and at the end of the session using a Venham scale modified by Veerkamp. This validated scale is the most commonly used for the evaluation of patient behavior during conscious sedation care, with scores ranging from 0 to 5. "0" describes a relaxed child, "1" an uneasy patient, "2" a tense child, "3" a reluctant patient, "4" a child provoking interference, and "5" an out of contact patient. The practitioner should rate the child's anxiety based on what he observes during the session.[41]

Finally, as the third outcome, the data from the change in HR will also be compared with the results obtained using this scale.

Statistical Analysis

All the evaluation parameters were subjected to descriptive analysis. The quantitative variable evaluation parameters had been described using position parameters (mean or median) and dispersion (standard deviation, interquartile range, and range). The qualitative variable evaluation parameters were shown in the form of number and frequency tables for each modality.

A comparison using the Chi-squared test was conducted to highlight differences between HR variations at T0, T1, and T2. Thereafter univariate analyses were performed with the Wilcoxon test between T0 and T1, T1 and T2, and T0 and T2. The conditions for validity were verified for all of the tests and the model.

A comparison using the Khi2 test was also conducted to highlight differences in children's levels of stress between the beginning and the end of the session. The data was computed using Excel®.

Results

Description of the Participants

- We were able to include 15 patients.
- Eight boys and seven girls between 4 and 12 years old were included.
- Among the 15 patients, 14 required a dental avulsion and one required a pulpotomy.

Descriptive Analysis

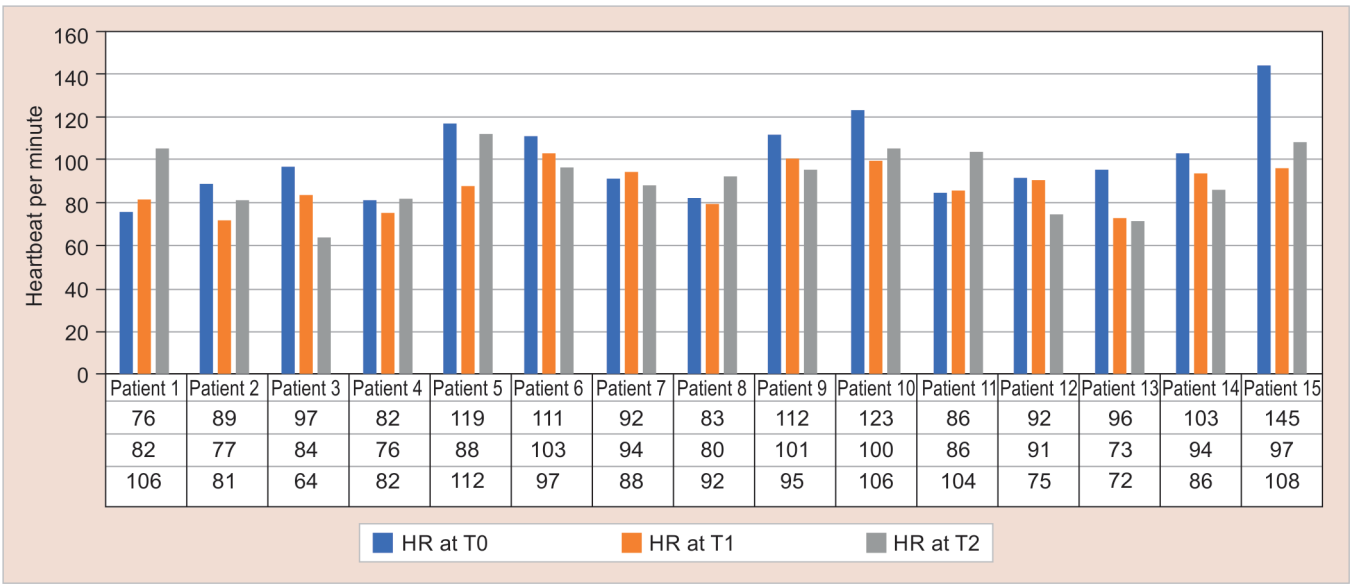
Objective Assessment

For 80% of our subjects (n = 12), we observed a decreased HR (between 10 and 30% compared to the initial measure) after the 5 minutes of EMONO inhalation (T1). Around 50% of them (n = 6) continued to slow their HR during anesthesia (T2). Otherwise, the other 50% of our sample (n = 6) showed a HR acceleration during this external stimulation. The number of heartbeats per minute remained mostly lower than it was recorded at the start of the treatment time (T0). At the end of the session, 40% of children (n = 6) had a HR lower than that of T0; however, 60% (n = 9) showed an increase or returned to the initial HR (Fig. 1).

Subjective Assessment

The observation of Venham scale modified by Veerkamp scores showed that 67% of patients (n = 10) were relaxed since the beginning of the session. For 33% of them (n = 5), their anxiety level improved at the end of the dental care.

We have presented the observation of patients using the Venham scale modified by Veerkamp and the variation in their HR in a table (Table 1).



	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15
HR at T0	76	89	97	82	119	111	92	83	112	123	86	92	96	103	145
HR at T1	82	77	84	76	88	103	94	80	101	100	86	91	73	94	97
HR at T2	106	81	64	82	112	97	88	92	95	106	104	75	72	86	108

Fig. 1: HR variation between T0, T1, T2 and the end of the session

Table 1: Table of Venham scores and HR variation between T0, T1, T2, and the end of the session

Venham-T0	*Venham—end of the session*	*HR at T0*	*HR at T1*	*HR at T2*
0	0	76	82	106
0	0	97	84	64
0	0	82	76	82
0	0	119	88	112
0	2	111	103	97
0	0	92	94	88
0	0	83	80	92
0	0	112	101	95
0	0	123	100	106
0	0	92	91	75
1	0	89	72	81
1	0	86	86	104
1	0	96	73	72
2	1	103	94	86
2	0	145	97	108

Comparative Analysis

A statistically significant difference could be highlighted between the HR at T0 and at T1, illustrating the anxiolytic effect of EMONO in an objective way and suggesting that the effect of EMONO seems to prevent a return to the initial level of stress, even during anesthesia. No statistically significant difference could also be highlighted between T0 and T2 (Fig. 2).

Concerning the Venham scale score, we observed that 33% of the patients ($n = 5$) were stressed before the beginning of induction, contrary to 67% of them ($n = 10$), who were relaxed. At the end of the session, a new evaluation showed that 13% ($n = 2$) of children remained nervous, whereas 87% ($n = 13$) were unstressed. There was no statistical difference in the children's behavior between the beginning and the end of the therapeutic time. Nevertheless, that could show an interesting trend of stress reduction using ENOMO, according to the results of the Venham scale score.

Link between Objective and Subjective Assessments

It is complicated to establish a link between Venham scale and HR variation as their end-of-evaluation time is not the same. However, it can be noted at T0 that children with a Venham scale greater than 0 do not seem to have the highest HR scores.

Discussion

Study Interests

The results of the behavioral scale show a slight improvement between the beginning and the end of the session for the patients in our study. Few patients seem stressed at the start, a most of them have a score of 0 on the Venham scale modified by Veerkamp. However, all of those patients could not be treated in a conventional manner without conscious sedation because of their anxiety. The good behavioral management associated with conscious sedation without obligation for the realization of the dental care (the patient knows he can refuse treatment after the first 5 minutes of inhalation) finally led all the patients to accept them. Therefore, it seems that the behavioral scale is not sufficient to qualify the patients who will be difficult to manage.

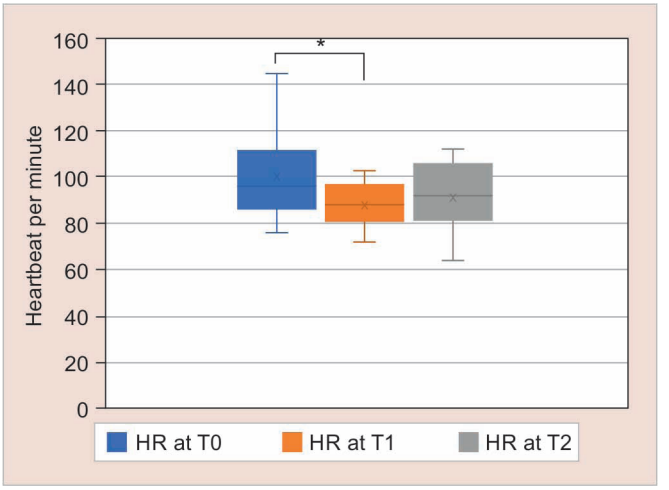


Fig. 2: Change in average HR at T0, T1, T2

Prud'homme et al. found that only 62% of patients presented an anxiolytic effect, which was lower than we could expect for one of the EMONO major effects.[28] Nevertheless, these results from the child's responses are to be considered with caution, especially because anxiolysis remains a difficult criterion to assess in children. In our study, a decrease in HR, which was the indicator that we chose to demonstrate the anxiolytic effect, was found in 80% of patients between T0 and T1. Despite the pilot nature of the study, the trend remains interesting to show that, in the future, this kind of more objective evaluation could be interesting and should be generalized in studies observing EMONO effects.

Indeed, the registered heartbeat rate variations showed a statistically significant decrease in HR after 5 minutes of inhalation. However, the stimulus responsible for stress (anesthesia) seems to be perceived differently according to the subject. A further decrease or maintenance of the HR frequency can be observed. At the end of the session, once the effects of EMONO are dissipated, there is a significant prevalence of an increase in HR, which can even return to the initial. This phenomenon could illustrate the end of the anxiolytic effect obtained thanks to EMONO.

The success rate of dental care was 100% in our small sample study on patients not cooperating with conventional care. This element, like the studies previously carried out, shows that EMONO had a special place in the therapeutic arsenal of the pediatric dental surgeon. In France, where midazolam is not authorized in the context of pediatric dentistry, it represents the only option for the dental surgeon before proposing general anesthesia to many patients. Our study, therefore, confirms ENOMO's primary interest. However, it could be considered that its use could be kept track by the measurement of HR variation during future studies in order to better characterize the anxiety effect of EMONO.

This study allowed us to consider a new way of increasing the evaluation of children's anxiety during dental care realized with ENOMO. Formerly, the realization of the technical act was the only factor observed to state the success of the therapeutic time. Then, the operator could estimate the degree of cooperation of the patient thanks to some evaluation tool, but that still remained subjective. That is why this alternative could be interesting in order to be able to follow patients' physiological functions in a more objective way.

Study Limits

Two factors made the inclusions more difficult than we expected. First of all, our desire to carry out the study on children naïve to

EMONO effects considerably reduced the number of candidates for inclusion. A large number of children seen in the specific consultation for the noncooperative patient had already experienced the EMONO effects during their lifetime, not only in dental but also in medical care. Besides, some children refused to be included in the study because of ear-sensor wearing. This considerably skews the study and removes among the noncooperating children, those who are potentially the most anxious.

The small sample size reduces the scope of the conclusions that can be drawn from our study. This work, therefore, remains a pilot study that highlights certain trends that need further investigation. The lack of a control group is also detrimental. HR monitoring could be performed in children having dental treatment without EMONO use in order to compare the pattern of HR variation at T0, T1, and T2. The comparison would, however, be made between a cooperating child population and a not cooperating one, which would limit its interest. We, therefore, did not consider it relevant for this pilot study.

Another limitation of the study is that the HR at T0 is taken during the installation in the chair, which does not really reflect the baseline level. The installation on the dentist's chair, or even the simple arrival in the treatment room, can represent stress for the child. Monitoring the HR at a distance from the session would be interesting to overcome this problem and add a measurement before T0, but it would complicate the protocol significantly.

Finally, our patient population shows significant heterogeneity in terms of age. The representations of care and pain can therefore vary significantly depending on the patient. The small size of the sample further accentuates the effects of this heterogeneity on statistical analysis.

Perspectives

In this study, we tried to carry out an objective evaluation of the anxiolytic effect of EMONO, which remains to the best of our knowledge, unpublished in France, where nitrous oxide is used in this form. The interest of this approach could be to offer in the future systematic monitoring of children during dental care under conscious sedation using EMONO in order to be able to quickly objectify its effectiveness on the subject treated, in association with other tools available to the practitioner.

Moreover, Prud'homme et al. have shown that only 33% of young patients perceive simultaneously the anxiolytic and analgesic effects, which represents very few patients despite the efficiency of ENOMO allowing dental care. It could be interesting to realize another trial assessing the analgesia while registering the HR to evaluate the decrease of stress. Because this low percentage could be attributable to the fact that children were a little bit confused after the dental care and had some difficulty associating those two variables.

Equimolar mixture of oxygen and nitrous oxide (EMONO), as we recalled during this work, occupies a particularly important place in France. Continuing this pilot work on a larger study or in addition to other studies would be interesting to validate the results drawn from a sample that unfortunately remains limited.

Conclusion

All of the data in the literature confirm the essential role of nitrous oxide in drugs inducing conscious sedation in children during dental care. The French context, in particular, its use in the form of EMONO and a strict regulatory framework reinforce this security. Previous works performed about the role of EMONO have shown its effectiveness during conscious sedation, thanks to its analgesic and anxiolytic effects, which allows an especially interesting success rate of planned care. However, it was necessary to demonstrate the effectiveness of EMONO by some objective criteria.

Ethics Approval and Consent to Participate

Our manuscript submission includes a statement on ethics approval and consent from the French National Ethic Committee.

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