Fixed 50% Nitrous Oxide Oxygen Mixture for Painful Procedures: A French Survey

Daniel Annequin, MD*; Ricardo Carbajal, MD†; Pierre Chauvin, MD, PhD‡; Olivier Gall, MD§; Barbara Tourniaire, MD¶; and Isabelle Murat, MD, PhD§

ABSTRACT. Objective. Although the equimolecular mixture of oxygen and nitrous oxide (EMONO) seems a good choice to relieve procedure-related pain in children, it has not been accepted everywhere. In France, the rapid spread of its use has elicited suspicion and doubts regarding its safety. To assess the use and the safety of this gas mixture in the pediatric settings in France, we conducted a national survey.

Methodology. Centers that had accepted a nationwide invitation to participate in the survey filled out a questionnaire after each EMONO administration during a 2-month study. Procedure and inhalation characteristics, as well as pain evaluations and side effects, were reported.

Results. One thousand nineteen EMONO inhalations from 31 centers that agreed to participate in this 2-month survey were analyzed. Median (range) age was 6.4 (0–18) years. Four percent (46) of children were 12 months old or younger, 29% (295) were 5 years old or younger, 45% (459) were 6 to 10 years old, and 26% (265) were older than 10 years of age.

The procedures performed with EMONO inhalation were: lumbar punctures (286), bone marrow aspirations (BMA; 231), laceration repairs (215), minor procedures (75), minor surgery (53), punctures (49), fractures (45), dental care (43), and pulmonary endoscopy (22). Nine percent of procedures were undertaken without the presence of a physician; the child being observed only by the attending nurse. A drug association was noted in 182 (17.9%) of procedures: midazolam (63%), acetaminophen (18%), nalbuphine (8.5%), hydroxyzine (5%), flunitrazepam (2%), chlorzepate (2%), morphine (1%), and lorazepam (5%). EMLA cream (Astra) was applied in 98.6% of procedures. Lidocaine infiltration was performed in 51% of these procedures, as well as pain evaluations and side effects, were reported.

Inhalation refusal was noted in 129 (12.7%) children; of these, 53 had an alternative method of analgesia (EMLA or lidocaine infiltration), 15 had no other analgesia, and in the remaining 61, EMONO inhalation was maintained against the child’s will.

Median (interquartile) inhalation length was 4 (3–5) minutes before starting the procedure and 6 (6–15) minutes for the total inhalation.

Median (interquartile) procedural pain evaluations were 9 (0–30) for children on a 0 to 100 visual analog scale, 1 (0–3) for both nurses and parents on a 0 to 10 numerical scale. Median (interquartile) procedural pain as evaluated by nurses for the 3 most frequent procedures were 0 (0–2) for lumbar punctures, 2 (0–4) for bone marrow aspiration, and 2 (0–4) for laceration repair. Comparison of pain assessed by nurses in children 3 years old or younger and those older than 3 years of age showed a median (range) score of 2 (0–10) versus 1 (0–10), respectively. Pain self-assessment was completed in 647 children 6 years of age or older. Median (interquartile) children pain assessments were as follows: lumbar puncture (5; 0–20), bone marrow aspiration (12.5; 0–40), laceration repair (12; 0–40), minor procedures (18; 0–32), minor surgery (10; 0–35), punctures (0; 0–18), fracture (15; 0–30), dental care (20; 0–40), and pulmonary endoscopy (15; 0–30). Ninety-three percent of the 647 children who were able to answer the question said they would accept EMONO analgesia if a new procedure were to be performed. Behavioral reactions during procedures varied with age of the child; cry was observed in 44.1%, 24.4%, 12.9%, and 11.2% of children 3 years or younger, 4 to 6 years, 7 to 10 years, and 11 years or older, respectively. Physical restraint was necessary in 34.2%, 22%, 13.5%, and 8.4% of children aged 3 years or younger, 4 to 6 years, 7 to 10 years, and 11 years or older, respectively.

Staff satisfaction regarding EMONO efficacy was as follows: very satisfied (56.7%), satisfied (31.3%), not satisfied (8.6%), and very unsatisfied (3.3%). Minor side effects were observed during 381 (37%) inhalations. These side effects were euphoria (20.1%), change in visual or auditory perception (7.0%), dreams (5.7%), nausea and vomiting (3.7%), deep sedation (2.1%), paresthesia (1.7%), dizziness (1.6%), restlessness (1.5%), nightmares and hallucinations (1.2%), and miscellaneous (1.9%). All side effects were transient and vanished within 5 minutes after removing the inhalation device. No serious side effects were noted.

Conclusions. This survey shows that EMONO is used to provide analgesia in a great variety of procedures. Although analgesia obtained during procedures is good, this gas mixture is not efficacious in all patients. Therefore, physicians should quickly detect failures to switch to another analgesic approach. The best results are obtained in children 3 years of age or older. Although minor effects are frequent during EMONO inhalation, its use...
seems very safe because no single serious side effect was noted during this study. This helpful method is still underused, and it should be readily available in each emergency and pediatric department. *Pediatrics* 2000;105(4). URL: http://www.pediatrics.org/cgi/content/full/105/4/e47; child, pain, procedure, nitrous oxide, inhalation route, safety.

**ABBREVIATIONS.** EMONO, equimolecular mixture of oxygen and nitrous oxide; VAS, visual analog scale; BMA, bone marrow aspirations.

Despite the recent improvements accomplished in pain treatment, relief of procedure-related pain in children is still a problem. For example, Jylli and Olsson found, in a study reported in 1995, that pain induced by procedures in the emergency department was unacceptably high. They noted that 44% of children cried during procedures, 16% fought against being restrained, and in 24% of the cases, the child was judged to be in a state of panic. Painful procedures are part of routine medical care of children in the pediatric or emergency departments. In these settings, aggressive procedures include venipunctures, bladder catheterizations, lumbar punctures, bone marrow aspirations, nasogastric tube placement, laceration repairs, and others. The physical restraint usually applied to perform these procedures intensifies the child’s feelings of insecurity, powerlessness, and helplessness. The recent understanding of the long-lasting effects of pain in children underlines the necessity of providing optimal pain management in all children.

Nitrous oxide, a gas with analgesic properties, has been known for more than 2 centuries. Its modern use outside the operation theater, started in 1961 when Tunstall introduced a stable mixture of nitrous oxide and oxygen in equal proportions in a single cylinder for the relief of pain during labor. Soon, the analgesic use of this gas mixture spread over other settings, such as ambulances, hospital wards, and during physiotherapy. Both the anxiolytic and the analgesic properties of the equimolecular mixture of oxygen and nitrous oxide (EMONO) have also been very useful in the dental office, where millions of inhalations have been administered in adults and children without any serious adverse effect. Nevertheless, EMONO has not been accepted in all countries of the world. It is primarily used in the United Kingdom, Australia, and South Africa. In the United States, nitrous oxide is administered by an apparatus consisting of 2 cylinders, 1 of pure nitrous oxide and the other of pure oxygen.

In France, in the late 1980s, EMONO was used only in prehospital care and in some delivery rooms. In 1990, we introduced EMONO analgesia to children and to facilitate its pediatric use, we proposed some changes in the inhalation system. These changes included the use of an anesthesia bag, a nonrebreathing respiratory valve, and a whistle, as well as the use of scented and colored masks that are chosen by the child (Fig 1). The rapid spread of this technique across the country has elicited suspicion and doubts regarding the security of such a method used by nonanaesthetists. These reactions against the use of EMONO with anesthetic devices are similar to those described by Baskett and Bennet in the United Kingdom at the end of the 1960s when EMONO was first introduced in British wards. To face these reactions, threatening the development and diffusion of EMONO analgesia, and to increase the little available data in the pediatric literature, we conducted a national survey to assess EMONO use in the pediatric settings in France.

**METHODS**

This prospective, multicenter survey was conducted by the Pediatric Pain Unit of Armand Trousseau Children Hospital. It was conducted from September 1, 1996 through November 1, 1996. An invitation to participate in the survey was sent to 15 centers that had contacted the Pediatric Pain Unit of Armand Trousseau Children Hospital for technical support, to 20 centers that were members of the pain interest group of the French Society of Pediatric Oncology, and to all of the 350 members of the French Language Society of Pediatric Anaesthesiologists. All children 18 years old or less who received an EMONO administration for a painful or invasive procedure outside the operating theater were included in the survey. Currently, no formal institutional review board is required in France for surveys performed without randomization. However, verbal informed consent was obtained from all parents and, when possible, from children participating in the survey.

EMONO prescription and its administration were under the responsibility of the attending physician. Participation in the survey did not modify the existing local protocols. The companies manufacturing EMONO did not have any participation in the design, data gathering, or analysis of the survey.

Centers that agreed to participate in the survey had to fill in a questionnaire after each EMONO inhalation. The items comprising this questionnaire were demographic data, type of procedure, drug association (local anesthesia or other drug), inhalation length (preprocedure and total), type of inhalation device used, self-assessment of procedural pain reported 10 minutes after the end of the inhalation on a 0 to 10 visual analog scale (VAS) for children 6 years of age or older, procedural pain evaluated by the nurse and parents on a 0 to 10 numerical scale, 4-level team satisfaction, and child agreement for a future EMONO administration in case of a new procedure. Behavioral reactions during the procedure were noted in an absent-present manner: cry, facial reactivity, withdrawal, restlessness, and additional restraint needed. All side effects were also recorded.

**Statistics**

The distributions of the qualitative variables were compared using the Mantel-Haenszel χ² analysis or the bilateral Fisher’s exact test for the dichotomous variables. Medians and interquartile values are given for the quantitative variables. Because the value distribution in the population was not normal and/or variances in each subgroup were different, the nonparametric test of Kruskal-Wallis was used.
RESULTS

Thirty-one centers agreed to participate in this survey and they reported 1025 EMONO inhalations during the 2-month study; 6 questionnaires were not correctly filled out, so the final analysis concerned 1019 EMONO administrations. Median (range) age was 6.4 (0–18) years. Four percent (46) of children were 12 months old or younger, 29% (295) were 5 years old or younger, 45% (459) were 6 to 10 years old, and 26% (265) were older than 10 years of age.

Procedures, Inhalation System, and Drug Associations

The procedures performed with EMONO inhalation are listed in Table 1. Nine percent of procedures were undertaken without the presence of a physician; the child being observed only by the attending nurse. A drug association was noted in 182 (17.9%) of procedures: midazolam (63%), atropine (18%), nalbuphine (8.5%), hydroxyzine (5%), flunitrazepam (2%), lorazepam (2%), morphine (1%), and lorazepam (5%). EMLA (Astra) cream was applied in 98.6% of lumbar punctures, 93.7% of bone marrow aspirations (BMA), and 54.2% of punctures including lymph nodes, hemotoma, or renal biopsies. Lidocaine infiltration was performed in 51% of minor surgery procedures, 40% of laceration repairs, and 28% of BMA.

The inhalation system included a whistle, a scented mask, and a nonrebreathing respiratory valve in 48.9%, 71.2%, and 78.3% of the patients, respectively. Initial physical restraint was needed in 18.2% of all the patients. Inhalation refusal was noted in 129 (12.7%) children; of these, 53 had an alternative method of analgesia (EMLA or lidocaine infiltration), 15 had no other analgesia, and in the remaining 61, EMONO inhalation was maintained against the child’s will.

Median (interquartile) inhalation length was 4 (3–5) minutes before starting the procedure and 6 (6–15) minutes for the total inhalation.

Pain Assessment

Procedural pain evaluations for the whole sample are shown in Table 2. Table 3 shows procedural pain as evaluated by nurses according to the type of procedure. Comparison of pain assessed by nurses in children 3 years old or younger and those older than 3 years of age showed a median (range) score of 2 (0–10) versus 1 (0–10), respectively (P < .00001). Pain self-assessment was completed in 647 children 6 years of age or older. Table 4 shows these assessments by procedures. Ninety-three percent of the 647 children who were able to answer the question said they would accept EMONO analgesia if a new procedure were to be performed. Child behaviors during EMONO administrations are shown in Fig 2.

Comparison between children who had a psychotropic drug associated to EMONO versus those who received only EMONO shows that median (interquartile) pain during procedure was 1 (0–4) and 2 (0–4), respectively, as evaluated by nurse on a 0 to 10 numerical scale, and 5 (0–30) and 10 (0–30), respectively, in self-evaluation on a 0- to 100-mm VAS. These differences were not statistically significant.

Staff satisfaction regarding EMONO efficacy was as follows: very satisfied (56.7%), satisfied (31.3%), not satisfied (8.6%), and very unsatisfied (3.3%). Correlation of staff satisfaction and pain score evaluations are shown in Table 5.

Side Effects

Minor side effects were observed during 381 (37%) inhalations; among them, euphoria was the most common reported side effect (20%; Table 6). All side effects were transient and vanished within 5 minutes after removing the inhalation device. No serious side effects were noted. Table 5 also shows the side effects observed in children who received EMONO with or without a psychotropic drug associated.

DISCUSSION

To our knowledge, this is the first multicenter prospective study on EMONO use in children for medical procedures. One previous multicenter study was conducted in the dental care office setting and included both adults and children.12 One retrospective monocenter study concerning 3000 children was reported in 1981.13 The number of young children was very high in our study; 295 (29%) patients were 5 years old or younger. No other published series has included as many young children.

TABLE 1. Procedures Performed in 1019 Children Using 50:50 Nitrous Oxide Oxygen Mixture Analgesia in 31 French Centers

<table>
<thead>
<tr>
<th>Patients</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1019</td>
<td>100</td>
</tr>
<tr>
<td>Lumbar puncture</td>
<td>286</td>
<td>28.1</td>
</tr>
<tr>
<td>Bone marrow aspiration</td>
<td>231</td>
<td>22.7</td>
</tr>
<tr>
<td>Laceration repair</td>
<td>215</td>
<td>21.1</td>
</tr>
<tr>
<td>Minor procedures*</td>
<td>75</td>
<td>7.4</td>
</tr>
<tr>
<td>Minor surgery†</td>
<td>53</td>
<td>5.2</td>
</tr>
<tr>
<td>Punctures‡</td>
<td>49</td>
<td>4.8</td>
</tr>
<tr>
<td>Fracture</td>
<td>45</td>
<td>4.4</td>
</tr>
<tr>
<td>Dental care</td>
<td>43</td>
<td>4.2</td>
</tr>
<tr>
<td>Pulmonary endoscopy</td>
<td>22</td>
<td>2.2</td>
</tr>
</tbody>
</table>

* Surgical dressing, burn dressing, gauze removal of open wounds, venous cannulation, clip removal, cast remodelling, pin removal or section, bladder catheterization, and nasal packing.
† Nail surgery, foreign body exploration and extraction, laceration exploration, and abscess drainage.
‡ Lymph nodes, renal biopsy, and hemotoma.
In this survey, lumbar puncture and bone marrow aspiration accounted for 51% of EMONO indications. This illustrates the wide acceptance of the method in the hematooncology setting, where repetitive procedures generate not only specific nociception but also conditioning anxiety that amplifies pain perception. The choice of a method that is a fast-acting, sometimes spectacular,14 immediately reversible, executable at bedside in the presence of parents, not requiring fasting regimen or specialized team or instrumental monitoring seems obvious in this setting. Other alternatives, such as midazolam associated with an opioid, intravenous ketamine,15,16 or intravenous methohexital17 are available for these procedures, specially BMA, but they are not as easy to use and safe as EMONO inhalation and they need appropriate equipment and personnel for very close respiratory and hemodynamic monitoring.18 Laceration repair accounted for 21% of the inhalations emphasizing the importance of EMONO use in the pediatric emergency department.

EMONO analgesia has been evaluated in other studies.19–23 This survey does not allow us to evaluate the analgesic efficacy of EMONO because we did not have control groups. However, we can see that median pain scores during child self-assessment for procedures like lumbar puncture, BMA, or laceration repair, which are known to be very painful, were 12.5 or lower not to 100 VAS. These median pain scores are low and, therefore, give an idea of EMONO analgesic effect. The analysis of EMONO analgesic efficacy by age of the child showed that children >3 years old experienced less pain compared with younger infants; median score on a 0 to 10 numerical scale was 1 versus 2, respectively. Poor nitrous oxide efficacy observed in young children24 seems related
Some patients had, comparisons of groups yes versus no were statistically significant only for euphoria (*P* < .01). Headache (*n* = 5), hiccup (*n* = 5), shivering (*n* = 5), and pallor (*n* = 5) were frequent but they all disappeared within 5 minutes. These results emphasize EMONO safety. The explanation is the inhalation refusal noted in 12 (7%) of the cases. This dissatisfaction can be explained by the fact that 25% of children who underwent BMA, laceration repair, and minor procedure had pain scores above 4, 4, and 3.5, respectively. A second factor was the fact that benzodiazepines were the agent in 14.6% of the cases. This association did not result in a better analgesic efficacy. This is mainly attributable to the diffusion hypoxia phenomenon does not appear attributable to the face application of the mask that induces some distress needing physical restraint and probably to the minimum alveolar concentration of anesthetic gases that is higher in this age group.

EMONO was given together with a psychotropic agent in 14.6% of the cases. This association did not result in a better analgesic efficacy. This is mainly attributable to the fact that benzodiazepines were the most frequent associated drugs. These only serve to facilitate EMONO administration but they do not have analgesic effects. However, most of these agents can potentiate nitrous oxide effects; therefore, we feel that if these situations take place, a medical presence is necessary.

Although EMONO was efficacious in most patients, staff was not satisfied with its efficacy in 12% of the cases. This dissatisfaction can be explained by the fact that 25% of children who underwent BMA, laceration repair, and minor procedure had pain scores above 4, 4, and 3.5, respectively. A second explanation is the inhalation refusal noted in 12 (7%) of children.

Regarding the security of EMONO use, no serious side effect was reported. However, minor side effects were frequent but they all disappeared within 5 minutes. These results emphasize EMONO safety. The level of sedation obtained with EMONO matches the definition of conscious sedation given by the American Academy of Pediatrics, Committee on Drugs in 1992. During EMONO inhalation, pulse oxymetry monitoring is not necessary because patients breathe 50% oxygen resulting in relative hyperoxemia, and the diffusion hypoxia phenomenon does not appear in this type of nitrous oxide use. We found that in 9% of the cases EMONO was used without a medical presence, which probably reflects the ease of its use. However, all children were observed by the attending nurse. It should be underlined that although EMONO use is safe, patients should always be clinically monitored by a dedicated staff member.

Environmental exposure to medical personnel administering nitrous oxide has received special attention. Toxicity attributable to long-term exposures to nitrous oxide outside the operation theater is still a matter of debate. One study among dentists and dental assistants heavily exposed to nitrous oxide found an increased incidence of neurologic complaints, such as torpor, ear ringing, and weakness, more frequently than in those not using nitrous oxide. In female dental assistants regularly exposed to nitrous oxide for >5 hours per week, a slight reduction in fertility and a slight predisposition to spontaneous abortions have been reported. However, in 2 other studies involving midwives exposed to nitrous oxide, neither a decrease in fertility nor an increase in spontaneous abortions were found. These adverse effects of chronic exposure to low levels of nitrous oxide might be lower in the emer-

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**TABLE 6. Side Effects Observed During 50:50 Nitrous Oxide Oxygen Mixture Inhalations in 1019 Children**

<table>
<thead>
<tr>
<th>Inhalation Length†</th>
<th>Psychotropic Drug Association‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>&lt;10 Minutes</td>
<td>&gt;10 Minutes</td>
</tr>
<tr>
<td>n = 696</td>
<td>n = 323</td>
</tr>
<tr>
<td>Whole Sample§ n = 1019</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Whole Sample§ n = 1019</th>
<th>&lt;10 Minutes n = 696</th>
<th>&gt;10 Minutes n = 323</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>62.8</td>
<td>63.8</td>
<td>60.7</td>
<td>60.9</td>
<td>75</td>
</tr>
<tr>
<td>Euphoria</td>
<td>20.1</td>
<td>20.6</td>
<td>19.0</td>
<td>12.1</td>
<td>21.4</td>
</tr>
<tr>
<td>Change in visual or auditory perception</td>
<td>7.0</td>
<td>6.5</td>
<td>8.0</td>
<td>8.7</td>
<td>6.7</td>
</tr>
<tr>
<td>Dream</td>
<td>5.7</td>
<td>5.5</td>
<td>6.1</td>
<td>.7</td>
<td>6.5</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>3.7</td>
<td>3.3</td>
<td>4.6</td>
<td>1.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Deep sedation</td>
<td>2.1</td>
<td>2.5</td>
<td>1.2</td>
<td>2.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1.7</td>
<td>1.9</td>
<td>1.2</td>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.6</td>
<td>1.3</td>
<td>2.1</td>
<td>.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Restlessness</td>
<td>1.5</td>
<td>1.4</td>
<td>1.5</td>
<td>2.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Nightmare and hallucination</td>
<td>1.2</td>
<td>1.0</td>
<td>1.5</td>
<td>.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Miscellaneous*</td>
<td>1.9</td>
<td>1.0</td>
<td>3.7</td>
<td>10.7</td>
<td>10</td>
</tr>
</tbody>
</table>

*Headache (*n* = 6), shivering (*n* = 3), cough (*n* = 2), hypotonia (*n* = 2), limb pain (*n* = 1), erection (*n* = 1), hypersalivation (*n* = 1), fixed gaze (*n* = 1), hiccup (*n* = 1), and pallor (*n* = 1).
† Comparisons of inhalation length <10 minutes versus >10 minutes were not statistically significant in all groups but miscellaneous (*P* < .01).
‡ Comparisons of groups yes versus no were statistically significant only for euphoria (*P* = .01) and dream (*P* < .01).
§ Some patients had <1 side effect; thus, total of percentages is higher than 100%.
gency department and the pediatric setting because the gas is used less frequently than in the dental setting. Scavenging devices are effective to reduce environmental exposure. To our knowledge, scavenging devices are not yet available in France (1999). It is recommended that EMONO be used in well-ventilated rooms.

CONCLUSION
Nitrous oxide/oxygen mixture analgesia has a rapid onset, is quickly reversible, does not have major side effects, and can be safely administered by trained staff members. Although analgesia obtained during procedures is good, this gas mixture is not efficacious in all patients. Therefore, physicians should quickly detect failures to switch to another analgesic approach. The best results are obtained in children 3 years of age or older. This helpful method is still underused, and we believe that it should be readily available in each emergency and pediatric department.

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