Oxygen saturation and diffusion hypoxia in children following nitrous oxide sedation
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Abstract

Oxygen saturation of arterial blood (SaO₂) was assessed in children after discontinuing N₂O/O₂ sedation for dental procedures. Two post-treatment methods were used: breathing 100% O₂ for 5 min after the procedure, and breathing room air for 5 min. Participants were 24 healthy children ages 41 to 113 months. Each child was treated twice and a crossover design was used. The mean length of procedures that were followed by O₂ was 28.8 (+ 10.9 SD) min; for those followed by room air, 28.3 (+ 12.4 SD) min. SaO₂ was monitored continuously by pulse oximetry and recorded at predetermined intervals before, during, and after N₂O/O₂ administration. When participants received post-treatment O₂, the mean SaO₂ at 1 min after N₂O cessation (99.91 ± 0.63 SD) and 5 min after cessation (99.94 ± 0.17 SD) was statistically significantly higher than the pretreatment value of 99.28 (± 0.63 SD). When participants received post-treatment room air, the mean SaO₂ 1 min after N₂O cessation (99.44 ± 0.8) was also statistically significantly higher than the pretreatment mean (99.08 ± 0.96). After 2 min, however, the mean SaO₂ decreased and was statistically indistinguishable from the pretreatment level after 5 min (99.13 ± 0.9 SD). Fluctuations in SaO₂, though statistically significant, were less than 1%. Allowing children to breathe room air immediately after cessation of N₂O/O₂ inhalation did not reduce SaO₂ below clinically acceptable levels. This study further documents the safety of N₂O/O₂ sedation, and gives the clinician additional information concerning the safe and effective administration of inhalation sedation.


Introduction

Nitrous oxide (N₂O) has long been a valuable analgesic in both adult and pediatric dental practice. In pediatric practice, N₂O/O₂ is especially effective when caring for mildly to moderately anxious children. Numerous reports have confirmed its ease of administration, wide margin of safety, analgesic and anxiolytic effects, and rapid reversibility.1–5

The adverse side effects of N₂O/O₂ analgesia, which appear to be minor, include intra-administration dreams and postadministration headache, nausea, vomiting, and possibly diffusion hypoxia.5–6 Side effects were not common in work reported by Hogue et al.7 Although Houck and Ripa8 reported vomiting with N₂O use in 8% of children studied, they concluded that some of these children had a tendency to vomit regardless of exposure to N₂O. According to Langa,9 the most undesirable side effect of N₂O/O₂ administration was nausea and vomiting, but the incidence of these conditions was less than 1%.

Diffusion hypoxia, frequently discussed as a possible untoward respiratory consequence of N₂O/O₂ use, reportedly accounts for most occurrences of headache, nausea, and lethargy after N₂O/O₂ sedation as employed in dentistry.9 Hypoxia theoretically occurs when N₂O administration is discontinued and the absorbed N₂O diffuses out of the blood and into the alveolar spaces. Because N₂ is less soluble in blood than the N₂O that replaced it, the uptake of N₂ into the blood occurs more slowly than the excretion of N₂O. This dilutes alveolar oxygen and potentially lowers the oxygen saturation of arterial blood (SaO₂).3

The greatest excretion of N₂O occurs in the first 3–5 min following cessation of administration.9 In standard clinical practice, 100% O₂ is administered during this period, ostensibly to prevent diffusion hypoxia.

Fink10 first reported the principle of diffusion hypoxia in 1955 after an in-vitro experiment and a clinical study in which SaO₂ dropped an average of 8% in eight healthy gynecologic patients who received anesthesia and recovered in room air. Anesthesia included endotracheal intubation for administration of 75% N₂O in O₂ and intravenous administration of 2.5% thiopental. Fanning and Colgen11 concurred with Fink after demonstrating a clinically significant drop in SaO₂ after administering 75% N₂O and thiopental to both animals and humans. The level of N₂O used in these studies is considerably higher than that typically used in dentistry. Quamstrom and coworkers12 stated that the results of these studies could be explained by the compromising effects of thiopental, which is known to cause respiratory depression in some patients.

Numerous studies have questioned whether diffusion hypoxia is clinically significant. Frumin and Edelist,13 who found that alveolar dilution caused by N₂O diffusion in healthy patients produced clinically insignificant changes in SaO₂, concluded that diffusion hypoxia did not occur clinically. In their study, 18 surgical patients were changed in room air. Arterial blood was withdrawn periodically and blood gas determinations were made by radiometer electrode. Of the patients with-
out respiratory obstruction, only two demonstrated SaO₂ values < 90%, but persistent significant shunting was suspected in those cases. Other studies also have concluded that diffusion hypoxia is clinically insignificant when respiratory ventilation is adequate.²⁴⁻¹⁷ In a study of 42 children who underwent minor outpatient surgery, the ratio of NzO to O₂ was as high as 70%, but no clinically significant episodes of hypoxia were observed.¹⁸ We are unaware of published studies assessing hypoxia attributed to NzO administration in children undergoing routine dental care. When NzO is used in outpatient dental care, drugs other than local anesthetics rarely are administered, and the ratio of NzO to O₂ is lower than that used in general anesthesia. Quarnstrom and coworkers¹⁹ noted that for these reasons, the use of NzO in surgery is not directly comparable to its use in outpatient dental care. Their study of adult dental patients indicated that diffusion hypoxia is extremely rare; no cases occurred among 104 adults (95% confidence interval upper limit, 2.84%).

To assess the significance of hypoxia attributed to NzO diffusion and elimination in pediatric dental patients, we compared two methods of discontinuing NzO/O₂ administration: 1) breathing 100% O₂ for 5 min after the procedure and, 2) breathing room air for 5 min.

Methods and materials

Clinical procedures

We recruited 24 children ages 41 to 113 months (mean 67.2 ± 20 SD months) from the Medical College of Georgia Hospital and School of Dentistry Clinics. All children were healthy, ASA Class I patients who required at least two visits for completion of dental treatment and who were scheduled to receive NzO/O₂ analgesia for mild to moderate anxiety. Procedures were expected to last less than 60 min. The parents were fully informed and gave written consent for their children to participate in the study, which met all requirements of the institution's Human Assurance Committee. Parents were instructed not to give the children anything by mouth for at least 2 hr prior to the procedure to reduce the risk of nausea and vomiting.

Dental treatment was rendered by five pediatric dental residents who were calibrated in administration of NzO/O₂. NzO was administered to a maximum concentration of 40% in O₂ using a Fraser MDM® NzO/O₂ machine and scavenging nasal mask (Matrix Medical, Inc., Orchard Park, NY). The flow rate was individually adjusted to maintain proper reservoir bag inflation. The gas mixture was adjusted from 100% to a minimum of 60% O₂ in 10% increments; each step lasted at least 20 sec. At the end of the procedure, the patient recovered in room air or O₂ based on prior random assignment in a crossover design. Because of the narrow criteria for entry into the study (mild to moderate anxiety), behavior was not a factor in the randomization scheme. When O₂ was to be received, the reservoir bag was flushed and the flow immediately changed to 100% O₂. When room air was to be received the flow of gases was discontinued, and the mask was removed. The reservoir bag was flushed with O₂ and the mask was retained close to the patient for emergency use.

Oxygenation of each patient was monitored throughout the procedure by using a Nellcor N-100® pulse oximeter (Nellcor, Inc., Hayward, CA) with the probe attached to the index finger. SaO₂ was recorded at 30-sec intervals five times before the nasal mask was placed. During the procedure, SaO₂ was recorded at 5-min intervals. At the end of the procedure, the SaO₂ was recorded for 5 min at 15-sec intervals. Recording was done by one of three individuals who did not know the post-treatment procedure being used. Parents were instructed to report any post-treatment symptoms that might indicate adverse effects of sedation.

Statistical analysis

We analyzed five, three, and 21 measurements from periods before, during, and after NzO/O₂ administration, respectively. Only the first three measurements taken during sedation were used because for several patients the procedures required only 10 min. For each patient, the mean measurement was calculated for the first two periods (before and during) and for each 1-min subdivision of the third period (after), for a total of seven mean values.

Summary statistics by post-treatment method were generated. One-sample t-tests were employed to evaluate the differences in SaO₂ between each post-treatment measurement (minutes 1–5) and the pretreatment value within each method (NzO or room air). The crossover design allowed the use of one-sample t-tests of the differences in the differences between pretreatment and post-treatment SaO₂ values across the two post-treatment methods. To detect experimental design problems, analysis of variance was used to test for differences by method in SaO₂ before and during treatment. Analysis of covariance was used to test for the effect of method on the response values recorded after treatment, while controlling for the values before treatment, the crossover design, and the length of the procedure.

Results

Procedures lasted from 10 to 60 min. The mean procedure length when O₂ was used postoperatively was 28.8 (± 10.9 SD) min and 28.3 (± 12.4 SD) min when room air was used. The difference by post-treatment method in mean length of procedure was not statistically significant. Fig 1 displays frequency distributions of the numbers of subjects by procedure length for each post-treatment method. A preliminary model (using analysis of covariance) evaluating the effect of procedure duration indicated no significant effect (P > 0.25). The NzO delivery protocol employed in this study ensured that administration of NzO was consistent for all procedures.

The mean and standard deviation of the SaO₂ was determined for each study segment by post-treatment
method (Fig 2). The mean difference between each post-treatment value and the pretreatment value is given in the Table for both post-treatment methods. When O₂ was used postoperatively, all differences between the pretreatment SaO₂ level and the given post-treatment levels were significantly different from zero (Table). When room air was used, the pre- and post-treatment SaO₂ levels were significantly different only for the first post-treatment minute; subsequent post-treatment levels returned to baseline. The actual post-treatment levels for the two methods were also compared. The first post-treatment values were not significantly different between the two methods; subsequent values were significantly higher for the O₂ post-treatment method. The post-treatment SaO₂ levels for the O₂ method were equivalent to levels observed during the dental procedure. The mean post-treatment SaO₂ values for the room air method did not drop below the mean pretreatment values. No parents reported adverse post-treatment signs or symptoms. All patients met the criteria outlined by the American Academy of Pediatric Dentistry for discharge following sedation.

Analysis of variance detected no group effect on SaO₂ before and during treatment (P > 0.22; P > 0.31). The results of analysis of covariance were consistent with those of the paired t-test of the differences (Table), and offered no additional insight into the data. These analyses were performed to detect design and randomization problems in our study. None was found. Because duration of procedure was not a significant factor, only the t-tests are reported.

Discussion

SaO₂ did not drop below 95% for any measurement taken during any procedure. Our results suggest that hypoxia attributed to N₂O elimination and diffusion may not be clinically significant for healthy pediatric dental patients, whether they receive room air or oxygen postoperatively. None of the untoward clinical side effects of diffusion hypoxia and N₂O/O₂ sedation after dental procedures were reported when room air was breathed. The crossover design controlled for any differences in behavior between the post-treatment group assignments, because every patient received both post-treatment methods. Assuming that no child’s behavior changed drastically, the effect of behavior and any other transient confounders were controlled by the experimental design. If, in fact, there was a learning effect, this also was controlled by the random assignment of patients to room air or O₂ as the first or second treatment session. A preliminary analysis

<table>
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<th>Minutes After Cessation of N₂O</th>
<th>Oxygen</th>
<th>P value*</th>
<th>Room Air</th>
<th>P value*</th>
<th>Difference</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.63 (0.65)</td>
<td>0.0001</td>
<td>0.37 (0.77)</td>
<td>0.0284</td>
<td>0.26 (0.91)</td>
<td>0.1797</td>
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<td>2</td>
<td>0.61 (0.70)</td>
<td>0.0003</td>
<td>0.03 (0.83)</td>
<td>0.8640</td>
<td>0.58 (0.95)</td>
<td>0.0064</td>
</tr>
<tr>
<td>3</td>
<td>0.61 (0.69)</td>
<td>0.0002</td>
<td>-0.02 (0.83)</td>
<td>0.8939</td>
<td>0.64 (1.02)</td>
<td>0.0058</td>
</tr>
<tr>
<td>4</td>
<td>0.64 (0.62)</td>
<td>0.0001</td>
<td>-0.04 (0.88)</td>
<td>0.8107</td>
<td>0.69 (1.00)</td>
<td>0.0026</td>
</tr>
<tr>
<td>5</td>
<td>0.65 (0.62)</td>
<td>0.0007</td>
<td>0.05 (0.72)</td>
<td>0.7370</td>
<td>0.60 (0.88)</td>
<td>0.0026</td>
</tr>
</tbody>
</table>

* P values from paired t-test.
detected no effect for session order. Crying was a rare event, and behavior did not affect the \( N_2O \) delivery protocol. The large standard deviations in the raw \( SaO_2 \) scores (Fig 2) indicate that no child was in danger of hypoxia.

When children breathed 100% \( O_2 \) postoperatively, post-treatment \( SaO_2 \) was higher than their preoperative level. When children breathed room air postoperatively, no difference in \( SaO_2 \) was noted between the pretreatment level and the second or later post-treatment measurement. Thus, the \( SaO_2 \), which reached a mean of nearly 100% during the procedures, rapidly returned to the pretreatment level when patients breathed room air.

The 5-min monitoring period after \( N_2O \) cessation was sufficient to include the excretion of 99% of the inspired \( N_2O \). In studies that have reported diffusion hypoxia, it occurred during the first 4 min in the majority of cases. It is possible, though unlikely, that \( SaO_2 \) could have continued to decline after 5 min of breathing room air. Reported drops in \( SaO_2 \) of 5 to 10% \( \pm 1 \) lasting several minutes should be detectable by the Nellcor pulse oximeter. Young et al. reported pulse oximeter response times of 17 to 150 sec in detecting a sudden 10% decrease in \( SaO_2 \). The mean reaction time of the Nellcor oximeter with a finger probe to this change was less than the mean reaction time for the 11 oximeters tested. We are confident that measurements every 15 sec over the 5-min post-treatment period would have detected significant diffusion hypoxia.

The duration of treatment and concentration of \( N_2O \) were typical of pediatric dental procedures. The concentration of \( N_2O \) in \( O_2 \) used in dentistry is generally low compared with that used for general anesthesia, in which higher levels of \( N_2O \) are often combined with other drugs that may have synergistic or independent effects on the physiology of respiration. Diffusion hypoxia was not found to be a problem at the \( N_2O \) levels used in this study, which were consistent with pediatric dental practice and considered optimal for most patients.

These findings are not meant to convince clinicians to discontinue the use of oxygen in the immediate post-treatment period. In fact, use of a scavenging system that removes expired gas before it enters the office environment is an indication for post-treatment \( O_2 \) administration by nasal mask. The importance of this study lies in its additional documentation of the safety of \( N_2O/O_2 \) sedation.

Conclusions

1. \( SaO_2 \) did not fall below 95% at any measurement.
2. During \( N_2O/O_2 \) administration, mean \( SaO_2 \) increased slightly but statistically significantly from baseline levels to nearly 100%.
3. Mean post-treatment \( SaO_2 \) was sustained at nearly 100% when participants breathed 100% \( O_2 \).
4. When participants breathed room air postoperatively, the mean \( SaO_2 \) at the second post-treatment minute and the mean pretreatment value did not differ, which indicates that no clinically detectable diffusion hypoxia occurred.
5. No untoward effects were reported by any participant regardless of the post-treatment method (\( O_2 \) or room air).

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19. Mueller WA, Drummond JN, Pribisco TA, Kaplan RF: Pulse oxim-
