Influence of Nitrous Oxide on Minimum Alveolar Concentration of Sevoflurane for Laryngeal Mask Insertion in Children

Shinichi Kihara, M.D.,* Yuichi Yaguchi, M.D.,* Shinichi Inomata, M.D.,† Seiji Watanabe, M.D., Ph.D.,‡ Joseph R. Brimacombe, M.B., Ch.B., F.R.C.A., M.D.,§ Noriko Taguchi, M.D.,* Tetsuya Komatsuzaki, M.D.||

Background: Inhalational induction with sevoflurane and nitrous oxide is frequently used for Laryngeal Mask Airway™ (LMA™; Laryngeal Mask Company, Henley-on-Thames, United Kingdom) insertion in children. The authors determined the influence of nitrous oxide on the minimum alveolar concentration (MAC) of sevoflurane for LMA™ insertion.

Methods: One hundred twenty unpremedicated children (age, 1–9 yr; American Society of Anesthesiologists physical status I) were randomly assigned to receive 1 of 15 end-tidal concentrations of nitrous oxide and sevoflurane for inhalational induction via a facemask: 0% nitrous oxide with 1.2, 1.4, 1.6, 1.8, or 2.0% sevoflurane; 33% nitrous oxide with 0.8, 1.0, 1.2, 1.4, or 1.6% sevoflurane; or 67% nitrous oxide with 0.6, 0.8, 1.0, or 1.2% sevoflurane. The LMA™ was inserted after steady state end-tidal anesthetic concentrations had been maintained for 15 min. The response to insertion was recorded by three independent blinded observers. The interaction between nitrous oxide and sevoflurane was determined using logistic regression analysis.

Results: The MAC of sevoflurane for LMA™ insertion (95% confidence limit) was 1.57% (1.42–1.72%), and the concentration of sevoflurane required to prevent movement in 95% of children was 1.99% (1.81–2.57%). The addition of 33% and 67% nitrous oxide linearly decreased the MAC of sevoflurane for LMA™ insertion by 22% and 49%, respectively (P < 0.001). The interaction coefficient between nitrous oxide and sevoflurane did not differ from zero (P = 0.7893), indicating that the relation was additive.

Conclusions: Nitrous oxide and sevoflurane suppress the responses to LMA™ insertion in a linear and additive fashion in children.
allow equilibration between the alveolar and central nervous system concentrations. A single experienced LMA™ user (S. K., > 1,000 LMA™ uses) inserted and fixed the LMA™ (size 1.5, 5–10 kg; size 2, > 10–20 kg; size 2.5, > 20–30 kg; size 3, > 30–50 kg) using the standard technique. The cuff of the LMA™ was inflated with air to obtain 60 cm H₂O of intracuff pressure.

The response of the patient was observed for 1 min after the LMA™ insertion and classified as “no movement” or “movement.” No movement was defined as the absence of purposeful movement of the extremities, coughing, bucking, and breath holding/laryngospasm. Movement was defined as difficulties of mouth opening before the insertion. All responses were assessed by three independent observers (an anesthesiologist, a surgeon, and a nurse) who were unaware of the end-tidal anesthetic concentrations being used. When at least two of the observers documented any responses, the case was described as “movement.” The patients who moved were treated by deepening anesthesia with sevoflurane and/or intravenous propofol. The insertion time (from removal of the facemask to capnographic confirmation) was also recorded. Any adverse events were recorded.

Statistical Analysis
MACₐ₃₉ was determined using a logistic regression model where \( P \), the probability of no response, is:

\[
P = \frac{1}{1 + e^{\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2}}
\]

where \( P \) is the probability of no movement, \( X_1 \) is the end-tidal nitrous oxide concentration, \( X_2 \) is the end-tidal sevoflurane concentration, \( \beta_0 \) is the regression intercept constant, \( \beta_1 \) is the coefficient for nitrous oxide, \( \beta_2 \) is the coefficient for sevoflurane, and \( \beta_{12} \) is the coefficient for the product of the end-tidal nitrous oxide and sevoflurane concentrations (the interaction coefficient).

The main effects components, \( \beta_1 \) and \( \beta_2 \), determined whether nitrous oxide and sevoflurane independently affected the response to LMA™ insertion. The interaction coefficient, \( \beta_{12} \), determined whether nitrous oxide and sevoflurane interacted to affect the response to LMA™ insertion. The likelihood ratio test was used to determine which of the independent variables significantly affected the model. Age was not included in our logistic model because sevoflurane MAC remains constant in children aged 6 months to 12 yr.

### Table 1. Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>0% N₂O</th>
<th>33% N₂O</th>
<th>67% N₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>4.1 ± 3.0</td>
<td>4.0 ± 2.5</td>
<td>3.8 ± 2.4</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>20/20</td>
<td>21/19</td>
<td>23/17</td>
</tr>
<tr>
<td>Height, cm</td>
<td>102 ± 21</td>
<td>101 ± 19</td>
<td>99 ± 18</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>18 ± 9</td>
<td>17 ± 8</td>
<td>16 ± 6</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. All nonsignificant.
N₂O = nitrous oxide.

### Table 2. Coefficient Estimates for the Logistic Regression Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>SEM</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant (( \beta_0 ))</td>
<td>-11.6752</td>
<td>2.4913</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Nitrous oxide (( \beta_1 ))</td>
<td>0.0779</td>
<td>0.0406</td>
<td>0.0550</td>
</tr>
<tr>
<td>Sevoflurane (( \beta_2 ))</td>
<td>7.3424</td>
<td>1.5963</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Interaction (( \beta_{12} ))</td>
<td>0.00854</td>
<td>0.0312</td>
<td>0.7843</td>
</tr>
</tbody>
</table>

To determine MACₐ₃₉, the probability of no response in 50% of patients was evaluated at \( P = 0.5 \), and the above equation was solved for \( X_2 \). Likewise, to determine the concentration of sevoflurane required to prevent movement in 95% of children (E₉₅), the probability of no movement was evaluated at \( P = 0.95 \), and the equation was solved for \( X_2 \). The chi-square test and one-way analysis of variance after Bonferroni-Dunn test were used to compare the sex, age, weight, and height of the patients. \( P < 0.05 \) was considered statistically significant.

### Results

There were no demographic differences among groups (table 1). There were no differences among the
three independent observers. Coefficient estimates for the logistic regression model are given in table 2. Based on the likelihood ratio test, the interaction coefficient for nitrous oxide and sevoflurane, $\beta_{12}$, did not differ significantly from zero ($P = 0.7843$) and was removed from the model. The logistic regression curves of the probability of no movement in response to intubation in the presence of sevoflurane and 0, 33, and 67% nitrous oxide are shown in figure 1. The number of move and no-move patients in each pair of nitrous oxide and sevoflurane concentrations are given in table 3. The MACLMI of sevoflurane without nitrous oxide was 1.57% (95% confidence limit: 1.42–1.72%). The addition of 33% and 67% nitrous oxide decreased the MACLMI from 1.57% (1.42–1.72) to 1.23% (1.07–1.39) and 0.80% (0.68–0.92), respectively ($P < 0.001$). The addition of 33% and 67% nitrous oxide decreased the E95 from 1.99 (1.81–2.57) to 1.70% (1.07–1.39) and 1.07% (0.94–1.50), respectively ($P < 0.001$). Insertion was easy in all patients. Insertion time did not differ among groups (8 ± 3 s). Immediately after the LMA™ insertion, breath holding/laryngospasm that was unrelated to the nitrous oxide concentration or the sevoflurane concentration within the nitrous oxide groups occurred in 10 children. These patients were easily treated with intravenous propofol administration. There were no other adverse events.

Discussion

We found that nitrous oxide at end-tidal concentrations of 33 and 67% were associated with a linear, dose-related reduction in sevoflurane MACLMI from 1.57% to 1.23% and 0.80%, corresponding to reductions of 22% and 49%, respectively, and that the interaction between nitrous oxide and sevoflurane was additive. Our results for sevoflurane MACLMI were lower than those of Taguchi et al. (2.00%) but similar to those of Aantaa et al. (1.57%). This may be because of differences in insertion skill among the LMA™ users participating in these trials.

Several aspects of study design can influence the validity of estimates of anesthetic potency. First, the stimulus applied by the LMA™ should be similar and clinically reproducible. In our study, all insertions were easy and performed by a single experienced user. Higher anesthetic concentrations may be required for difficult insertions or for inexperienced users. Second, the technique used to sample respiratory gases should provide a reliable estimate of the end-tidal anesthetic concentration as the latter, at equilibrium, is taken to represent the concentration of anesthetic in the blood and brain. We took great care to minimize dead space for sampling the gases and, in all patients, a square capnograph was obtained. The equilibration time used in the current study have been validated in many previous studies. Third, appropriate mathematical methods should be applied to the dose–response data. We used logistic regression analysis, which has been shown in previous studies to yield MAC values that are similar to those determined by the method described by Dixon. In contrast to Dixon’s approach, our study design permitted prospective randomization of all patients and yielded information about the interaction between independent variables.

The effects of nitrous oxide on volatile agent potency has been reported for skin incision (MACSI) and for tracheal intubation (MACTI). The effect appears to vary with the type of MAC and type of volatile agent. For halothane MACSI, isoflurane MACSI, and sevoflurane MACSI, the effect is linear and additive, whereas for sevoflurane MACSI and desflurane MACSI, the effect is nonlinear and additive with 60% nitrous oxide reducing MAC by approximately 25% rather than 55%. Interestingly, our findings and those of Swan et al. show that nitrous oxide reduces the MAC of sevoflurane for instrumentation of the airway in a linear and additive fashion, but the findings of Lerman et al. show that sevoflurane MACSI is reduced in a nonlinear and additive fashion. Perhaps the influence of nitrous oxide on MAC also depends on the type of stimulus in addition to the type of MAC and volatile agent.

We conclude that nitrous oxide and sevoflurane suppress the responses to LMA™ insertion in a linear and additive fashion in children.

References


Table 3. Number of Move and No-move Patients in Each Pair of Nitrous Oxide and Sevoflurane Concentrations

<table>
<thead>
<tr>
<th>Sevoflurane Concentration, %</th>
<th>0.4</th>
<th>0.6</th>
<th>0.8</th>
<th>1.0</th>
<th>1.2</th>
<th>1.4</th>
<th>1.6</th>
<th>1.8</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>0% N2O</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>8/0</td>
<td>5/3</td>
<td>4/4</td>
<td>2/6</td>
<td>0/8</td>
</tr>
<tr>
<td>33% N2O</td>
<td>—</td>
<td>—</td>
<td>8/0</td>
<td>6/2</td>
<td>4/4</td>
<td>2/6</td>
<td>1/7</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>67% N2O</td>
<td>8/0</td>
<td>7/1</td>
<td>4/4</td>
<td>1/7</td>
<td>0/8</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Data are presented as No. (move/no move).

N2O = nitrous oxide.