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# *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 0.4, 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 ($P = 0.7843$), 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.**

THE *Laryngeal Mask Airway™* (*LMA™*; Laryngeal Mask Company, Henley-on-Thames, United Kingdom) is widely used in pediatric anesthesia practice. *LMA™* insertion is commonly achieved after inhalational anesthesia using sevoflurane and nitrous oxide because both have low blood-gas partition coefficients and are relatively nonirritant to the airway. The minimum alveolar concentration for *LMA™* insertion ($MAC_{LMI}$) using sevoflurane in children has been reported as 1.57–2.00%,[1,2] but there are no studies determining the influence of nitrous oxide on sevoflurane $MAC_{LMI}$. In the following single-blind, randomized study, we investigate the influence of nitrous oxide on sevoflurane $MAC_{LMI}$ in children using logistic regression analysis.

## Methods

With approval from the Mito Saiseikai General Hospital ethics committee and written informed parental consent, we studied 120 unpremedicated children (age, 1–9 yr; American Society of Anesthesiologist's physical status I) scheduled for elective surgery under general anesthesia with the *LMA™*. Exclusion criteria were a predicted or known difficult airway, acute upper respiratory tract infection, asthma or gastroesophageal reflux, or a parental/patient request for premedication. Children were randomly assigned, by opening a opaque sealed envelope, to receive 1 of 15 combinations of 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 0.4, 0.6, 0.8, 1.0, or 1.2% sevoflurane (eight patients per anesthetic combination).

An electrocardiograph, pulse oximeter, gas analyzer, and noninvasive blood pressure monitor were applied before induction. The sidestream-type infrared multigas analyzer, which measured nitrous oxide to an accuracy of ± 1.5% and sevoflurane to an accuracy of ± 0.1%, was calibrated before each use, and the inspired and end-tidal concentrations of sevoflurane, nitrous oxide, carbon dioxide, and oxygen were continually measured and recorded. Before *LMA™* insertion, the end-tidal concentrations were sampled from the nose *via* a cannula using an infant circuit with an intracircuit volume of 800 ml and fresh gas flows of 6 l/min. After *LMA™* insertion, they were sampled from the distal end of the *LMA™* shaft using a cannula inserted through a self-sealing connector such that its tip was within 1 cm from the mask aperture bars. Anesthesia was induced with up to 6% sevoflurane and the designated concentration of nitrous oxide in oxygen. When the eyelash reflex disappeared, ventilation was assisted manually to maintain the end-tidal carbon dioxide partial pressure at 32–36 mmHg. The peripheral line was inserted after induction of anesthesia.

Before *LMA™* insertion was attempted, the end-tidal concentrations of sevoflurane and nitrous oxide were kept constant at the predetermined value for 15 min to

* Staff Anesthetist, ‡ Chief Anesthetist, ‖ Resident, Department of Anesthesia, Mito Saiseikai General Hospital. † Assistant Professor, Department of Anesthesia, University of Tsukuba. § Professor, Department of Anesthesia and Intensive Care, University of Queensland and James Cook University, Cairns Base Hospital.

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Address reprint requests to Prof. Brimacombe: Department of Anesthesia and Intensive Care, University of Queensland and James Cook University, Cairns Base Hospital, The Esplanade, Cairns, Australia. Address electronic mail to: jbrimaco@bigpond.net.au. 

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.[3] The cuff of the *LMA™* was inflated with air to obtain 60 cm $H_2O$ 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*

$MAC_{LMI}$ was determined using a logistic regression model where *P*, the probability of no response, is:

$$P = \frac{1}{1 + e^{\beta_0+\beta_1X_1+\beta_2X_2+\beta_{12}X_1X_2}}$$

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.[4]

**Table 1. Demographic Data**

| | 0% $N_2O$ | 33% $N_2O$ | 67% $N_2O$ |
|---|---|---|---|
| Age, yr | 4.1 ± 3.0 | 4.0 ± 2.5 | 3.8 ± 2.4 |
| Sex, M/F | 20/20 | 21/19 | 23/17 |
| Height, cm | 102 ± 21 | 101 ± 19 | 99 ± 18 |
| Weight, kg | 18 ± 9 | 17 ± 8 | 16 ± 6 |

Data are presented as mean ± SD. All nonsignificant.
$N_2O$ = nitrous oxide.

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

| Variable | Coefficient | SEM | *P* |
|---|---|---|---|
| Constant ($\beta_0$) | −11.6752 | 2.4913 | < 0.0001 |
| Nitrous oxide ($\beta_1$) | 0.0779 | 0.0406 | 0.0550 |
| Sevoflurane ($\beta_2$) | 7.3424 | 1.5963 | < 0.0001 |
| Interaction ($\beta_{12}$) | 0.00854 | 0.0312 | 0.7843 |

To determine $MAC_{LMI}$, 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 ($E_{95}$), 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

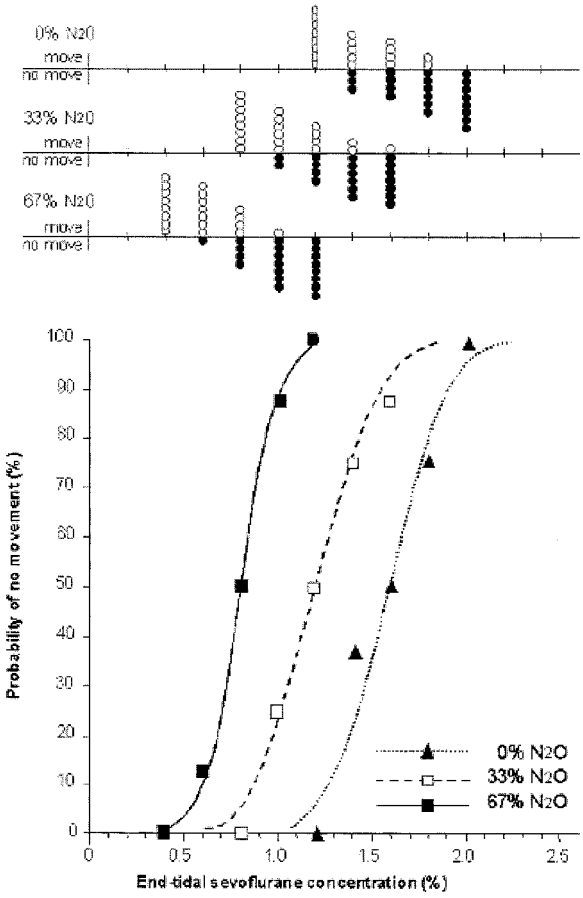


**Fig. 1. Logistic regression curves of the probability of no movement in response to the *Laryngeal Mask Airway*™ insertion in the presence of sevoflurane and 0%, 33%, and 67% nitrous oxide ($N_2O$).**

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

| | Sevoflurane Concentration, % | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0.4 | 0.6 | 0.8 | 1.0 | 1.2 | 1.4 | 1.6 | 1.8 | 2.0 |
| 0% $N_2O$ | — | — | — | — | 8/0 | 5/3 | 4/4 | 2/6 | 0/8 |
| 33% $N_2O$ | — | — | 8/0 | 6/2 | 4/4 | 2/6 | 1/7 | — | — |
| 67% $N_2O$ | 8/0 | 7/1 | 4/4 | 1/7 | 0/8 | — | — | — | — |

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

$N_2O$ = nitrous oxide.

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 $MAC_{LMI}$ 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 $MAC_{LMI}$ 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 $E_{95}$ 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 $MAC_{LMI}$ 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 $MAC_{LMI}$ were lower than those of Taguchi *et al.*[1] (2.00%) but similar to those of Aantaa *et al.*[2] (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.[1,2,4–9] 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[2,7,10,11] that are similar to those determined by the method described by Dixon.[12] 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 ($MAC_{SI}$)[5,6] and for tracheal intubation ($MAC_{TI}$).[7,8] The effect appears to vary with the type of MAC and type of volatile agent. For halothane $MAC_{SI}$,[5] isoflurane $MAC_{SI}$,[6] and sevoflurane $MAC_{TI}$,[7] the effect is linear and additive, whereas for sevoflurane $MAC_{SI}$[4] and desflurane $MAC_{SI}$,[13] 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.*[7] 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.*[4] show that sevoflurane $MAC_{SI}$ 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.

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