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Nitrous oxide administration during washout of sevoflurane improves postanesthetic agitation in children

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Abstract The use of sevoflurane in pediatric patients, which could enable a more rapid emergence and recovery, is complicated by a high incidence of postanesthetic agitation, probably due to residual sevoflurane during washout. The present study was designed to investigate whether administration of nitrous oxide (N_2O) reduces sevoflurane concentration at awakening and suppresses postanesthetic agitation. The study enrolled 20 children classified as ASA physical status I. Anesthesia was induced with 5% sevoflurane and maintained with 2.5% end-tidal sevoflurane and N_2O in oxygen. In the control group, sevoflurane and N_2O were discontinued immediately after completion of surgery. In the N_2O group, inspired N_2O was replaced with oxygen after the bispectral index (BIS) had reached 80. The end-tidal concentrations of sevoflurane at awakening were significantly lower ($P < 0.05$) in the N_2O group than in the control group. The BIS at awakening was higher ($P < 0.01$) in the N_2O group than in the control group. The point scores of postanesthetic agitation were significantly lower ($P < 0.01$) in the N_2O group than in the control group. Using N_2O during washing out of sevoflurane may improve postanesthetic agitation at awakening in children.

Key words Sevoflurane · Bispectral index · Agitation · Pediatric anesthesia

Introduction

It is well known that sevoflurane enables a more rapid emergence and recovery because of its low blood–gas partition coefficient. The use of sevoflurane in pediatric patients, however, is complicated by a high incidence of emergence delirium, often characterized by violent threshing and inconsolable agitation [1]. Agitation may be attributed to residual sevoflurane. In fact, the expired gas still contains more or less sevoflurane during agitation, but almost no measurable sevoflurane is detected after complete emergence. To improve the quality of anesthetic recovery in pediatric patients, it is necessary to wash out sevoflurane while suppressing or prohibiting the appearance of agitation. Nitrous oxide might be a useful tool for this purpose, because it reduces MAC-awake of sevoflurane and can be quickly removed after its washoff. The present study was therefore carried out, by using the bispectral index (BIS) as a level of emergence from sevoflurane anesthesia, to examine whether administration of nitrous oxide (N_2O) during washout of sevoflurane improves postanesthetic recovery in pediatric patients.

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Material and methods

Approval for this study was obtained from the hospital's ethics committee. Informed consent was obtained from the children's parents with assent before study enrollment and patient examination. The study enrolled 20 children classified as ASA physical status I who were scheduled for minor otolaryngological surgery. The patients were randomly allocated to either the control or the N_2O group. Patients did not receive any premedication.

Anesthesia was induced with 5% end-tidal sevoflurane and nitrous oxide (N_2O) in oxygen ($FiO_2 = 0.5$) by slow induction. After tracheal intubation, anesthesia was maintained with 2.5% end-tidal sevoflurane. The inspired oxygen concentration was adjusted to N_2O in oxygen ($FiO_2 = 0.3$). Ventilation was spontaneous or, if necessary, assisted to maintain end-tidal CO_2 levels at between 35 and 45 mmHg. In the control group, sevoflurane was discontinued and the inspired N_2O was replaced with oxygen ($FiO_2 = 1.0$) after completion of surgery. In the N_2O group, sevoflurane was discontinued after completion of surgery but N_2O was continued

until the BIS reached 80 [2], when the inspired N_2O was replaced with oxygen. Postoperative pain was managed intraoperatively with local anesthesia (10 ml 0.5% lidocaine) on the surgical field.

The BIS was recorded continuously by a BIS monitor (model A1050, version 3.4; Aspect Medical Systems, Newton, MA, USA). Heart rate and noninvasive arterial blood pressure were measured every 2.5 min (Life Scope 12; Nihon Kohden, Tokyo, Japan), end-tidal CO_2, N_2O, and sevoflurane concentrations were monitored continuously (Capnomac Ultima, Datex, Finland) before and during anesthesia.

Awakening was defined as the time when the patient opened his or her eyes or when the gag reflex returned. At that time, the end-tidal sevoflurane and nitrous oxide concentrations were measured, and then the trachea was extubated. Postanesthetic agitation was assessed within a few minutes after tracheal extubation using a three-point scale assigned by a blinded nurse observer who had no other clinical responsibilities and who could evaluate patient readiness continually: 1 = asleep or calm; 2 = mildly agitated, crying but consolable, restless; and 3 = hysterical, crying inconsolably, and thrashing [3].

The data are presented as mean ± SD, and the point scores in the assessment of postanesthetic agitation are given as the median (range). All statistical analyses were performed with StatView J4.5 (Abacus Concepts, Berkeley, CA, USA), using Student's *t* test and the Mann–Whitney *U* test. $P < 0.05$ was considered statistically significant.

Results

Table 1 shows the demographic data for the control and N_2O groups. There were no differences between the groups in terms of duration of surgery and anesthesia. Anesthesia was uneventful in all patients. The otolaryngological surgical procedures performed were tonsillectomy and/or adenoidectomy. Figure 1 shows a comparison of the control and N_2O groups at awakening in terms of end-tidal concentrations of sevoflurane, N_2O, and BIS. The end-tidal concentrations of sevoflurane were significantly lower ($P < 0.05$) in the N_2O group than in the control group (sevoflurane, 0.3% ± 0.1% for the control group versus 0.2% ± 0.1% for the N_2O group; Fig. 1A). On the other hand, there were no significant differences in the end-tidal concentrations of N_2O between the control and the N_2O groups (N_2O, 5.2% ± 2.5% for the control group versus 7.0% ± 4.4% for the N_2O group; Fig. 1B). The BIS at awakening was higher ($P < 0.01$) in the N_2O group than in the control group (70 ± 9 in the control group versus 91 ± 8 in the N_2O group; Fig. 1C). The point scores in the assessment of postanesthetic agitation were significantly lower ($P < 0.01$) in the N_2O group than in the control group [median (range) 3 (1–3) for the control group versus 2 (1–3) for the N_2O group; Table 1].

Discussion

The present study showed that, at postanesthetic awakening, the end-tidal concentrations of sevoflurane were significantly lower in the N_2O group than in the control group, the BIS was significantly higher in the N_2O group than in the control group, and the point scores in the

Table 1. Clinical characteristics of patients and study data

	Control group	N_2O group
Age (years)	6 ± 2	7 ± 2
Sex (M/F)	(5/5)	(5/5)
Weight (kg)	22 ± 6	26 ± 7
Height (cm)	115 ± 14	121 ± 12
Time from the completion of surgery to awakening (min)	13 ± 4	17 ± 7
Duration of surgery (min)	33 ± 18	45 ± 19
Assessment of postanesthetic agitation median (range)	3 (1–3)	2 (1–3)**

Values are expressed as mean ± SD
** $P < 0.01$ vs. the control group

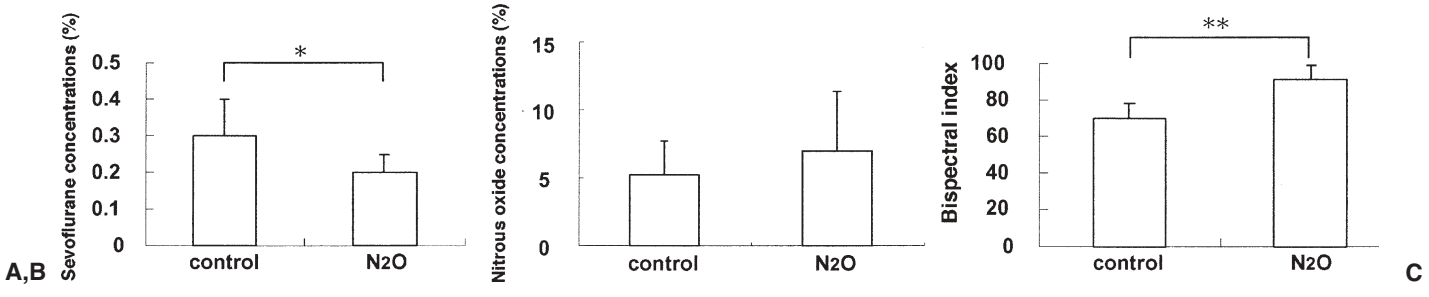

Fig. 1. Comparison of the control and N_2O groups at awakening in terms of end-tidal concentrations of sevoflurane (**A**), nitrous oxide (**B**), and bispectral index (BIS) (**C**). *$P < 0.05$, **$P < 0.01$

assessment of postanesthetic agitation were significantly lower in the N_2O group than in the control group. All these findings indicate that N_2O reduces sevoflurane concentration at awakening and improves the quality of recovery from sevoflurane anesthesia in pediatric patients. We speculate that the postanesthetic agitation is caused by residual sevoflurane at awakening. Without N_2O, patients would awake while keeping relatively higher sevoflurane concentrations, thereby causing delirium or inconsolable agitation. On the other hand, N_2O administration would prolong the hypnosis until sevoflurane concentration could be decreased below a level where the agitation would be likely to occur.

Several studies have indicated that the incidence of postoperative agitation is caused by sevoflurane by itself, not by postoperative pain [4]. Painfree children who received a regional block woke up agitated more often after the recovery from sevoflurane anesthesia compared with halothane anesthesia [1]. Beskow and Westrin [5] tried to differentiate between pain and agitation; they concluded that agitation unrelated to pain is more common after sevoflurane anesthesia in children below the age of 5 years. It has also been shown that agitation is also a problem after sevoflurane administration in children without surgery. Galinkin et al. [6] reported that the intraoperative use of opioids reduces the incidence of agitation after sevoflurane anesthesia. Opioids reduce MAC-awake and have little hypnotic action, but do not affect BIS [7]. In this respect, N_2O has essentially similar effects and may replace it. Moreover, rapid onset and recovery could be beneficial for pediatric anesthesia.

The end-tidal concentration of sevoflurane was higher by only 0.1% in the control group than in the N_2O group (0.3% $\pm$ 0.1% versus 0.2% $\pm$ 0.1%), although the lower value in the latter is in good accordance with our view. It should be noted, however, that anesthetic equilibration between the brain and the alveoli does not occur during washout. Usually the measurable end-tidal anesthetic concentrations should be lower than the cerebral concentrations, and this effect is more marked with agents such as sevoflurane that have a low blood–gas partition coefficient. In addition, the measurement of the end-tidal sevoflurane concentration is affected by a number of inevitable factors, particularly in children. For example, the respiratory deadspace is reported to be larger in children than in adults, and therefore the end-tidal concentration does not necessarily represent the concentration of sevoflurane in the blood. Furthermore, the end-tidal sevoflurane concentration was measured at awakening, which we defined as the time when the patient opened his or her eyes or when the gag reflex returned. These clinical signs would also be affected by various external stimuli such as intratracheal tube placement and other stimuli, as well as sevoflurane concentration. Such possible factors might have underestimated the effect of N_2O on reducing sevoflurane concentration at awakening.

On the other hand, the measurement of BIS clearly demonstrated a more significant effect on sevoflurane, i.e., it was higher in the N_2O group than in the control group (91 $\pm$ 8 versus 70 $\pm$ 9). This finding indicates, if BIS is affected only by sevoflurane in the brain, that the sevoflurane concentration in the brain is lower at awakening in the N_2O than in the control groups. The BIS algorithm is originally derived from adult EEG data and initial clinical utility, and validation studies have been developed in adults. Thereafter, many studies have demonstrated that BIS is a reliable measure of the level of consciousness in children [8–10]. Various anesthetics, including sevoflurane and other volatile anesthetics, have also shown to affect BIS in a concentration-dependent manner [11], except in N_2O, which had no effect on BIS [12].

Apart from the hypnosis and/or the level of consciousness, one may argue that the higher BIS value in the N_2O group could be overestimated by possible interference due to the muscle activity during the anesthetic recovery. In fact, BIS is also known to be affected by electromyographic activity [13]. At present, we cannot completely rule out such a possibility that N_2O could increase electromyographic activity. Nevertheless, we believe that N_2O successfully reduced the sevoflurane concentration in the brain at awakening.

In conclusion, prolonged administration of N_2O during recovery from sevoflurane anesthesia may improve postanesthetic agitation in pediatric patients.

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