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Usefulness of Nitrous Oxide in Sevoflurane Anesthesia: Hemodynamic Changes at Induction and Postoperative Complications

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Abstract

Background: Nitrous oxide is decreasingly used due to theoretically considered complications. However, we have not had clinically obvious complications for many decades. The present study was done to investigate usefulness of nitrous oxide in sevoflurane anesthesia in terms of hemodynamic changes at induction and postoperative complications.

Methods: One hundred and twenty patients for body surface surgery were enrolled. Anesthesia was induced with sevoflurane 5% for 5 min. or 8% for 3 min. with or without 50% nitrous oxide and maintained with sevoflurane with or without 50% nitrous oxide (5%GOS, 8%GOS, 5%OS, and 8%OS groups, each 30 patients). Blood pressure, heart rate, loss of eyelash reflex and verbal response, sevoflurane consumption, time to emergence, and postoperative complications including nausea and vomiting were compared among the groups.

Results: Time to loss of eyelash reflex and verbal response were significantly shorter in 5% GOS and 8% GOS than those in 5% OS and 8% OS, respectively. Sevoflurane consumption was significantly larger with 5% OS than 5% GOS. Time to extubation was not different. Changes in blood pressure were significantly higher in 8% OS than that in 8% GOS. Increase in heart rate by intubation was significantly larger in 5% OS and 8% OS than those in 5% GOS and 8% GOS, respectively. The frequency of nausea and vomit were not different among the groups. No clinically obvious complication was observed for postoperative one-month period.

Conclusion: In sevoflurane anesthesia, nitrous oxide decreased hemodynamic changes at induction and intubation, and did not induce any clinically obvious complications.

Keywords: Nitrous oxide; Sevoflurane; Hemodynamics; Complication

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Introduction

Recently, nitrous oxide is decreasingly used in general anesthesia because nitrous oxide inhibits vitamin B12 [1], induces nausea, vomit [2] and neuronal damage [3,4], and increases air pollution [5]. However, in our daily clinical practice, we have not experienced these problems for many decades. In contrast, nitrous oxide has strong analgesic effects [6], which decrease hemodynamic changes at induction of anesthesia. Many studies investigated usefulness of nitrous

oxide at induction of anesthesia, but almost all of them used rapid inhalation induction [7,8], not common inhalation induction. We have already reported that nitrous oxide was useful to decrease induction time and hemodynamic changes at laryngeal mask insertion by common inhalation induction [9]. In that study, we used nitrous oxide only at induction. However, the side effects shown might occur by long-term exposure to nitrous oxide. The purpose of the present study was to investigate the effects of nitrous oxide on hemodynamics at induction and tracheal intubation, and postoperative nausea, vomit and other complications in sevoflurane anesthesia.

Materials and Methods

After the approval of the ethics committee of the hospital and informed consent from patients, 120 patients for body surface surgery under general anesthesia were enrolled in the study. Those who had hypertension, cardiac, respiratory, liver, renal, gastric, or brain disease, or who had taken psychiatric drugs were excluded. Patients were divided into four groups at random by an envelope method.

Anesthesia was induced with sevoflurane gradually increased to 5 % in one minute and kept for 4 minutes with nitrous oxide 3 L/min in oxygen 3 L/min (5% GOS, 30 patients) or with oxygen 6 L/min (5% OS, 30 patients), or sevoflurane gradually increased to 8% in one minute and kept for 2 minutes with nitrous oxide 3 L/min in oxygen 3 L/min (8% GOS, 30 patients) or with oxygen 6 L/min (8% OS, 30 patients). Tracheal intubation was facilitated with vecuronium 0.15 mg/kg. Anesthesia was maintained with sevoflurane 1 – 2.5 % with nitrous oxide 3 L/min in oxygen 3 L/min in 5% GOS and 8% GOS groups and with air 4 L/min in oxygen 2 L/min in 5% OS and 8% OS groups to maintain bispectral index between 40 and 60.

Blood pressure, heart rate, end-tidal sevoflurane concentration, time to loss of eyelash reflex and verbal response at induction, sevoflurane consumption by direct measurement (filling volume – residual volume in the vaporizer), time to extubation (from stop of sevoflurane and nitrous oxide to extubation), nausea and vomit for postoperative 12 hours by medical records and any obvious complications for one month checked at outpatient ward were compared among the groups.

Data were shown as mean ± standard deviation, number of patients, or median and range. The power analysis was performed to get the power of 0.95 with effect size 0.25 for changes in blood pressure and heart rate by the G power 2.1.2^{TM} (University of Trier, Trier, Germany). Power analysis showed 52 patients were necessary to compare GOS and OS groups; therefore, we enrolled 60 patients each in 5% and 8% group. Statistical analysis was performed with repeated measures or factorial analysis of variance followed by Student-Newman-Keuls test as a post hoc analysis for age, body weight, height, duration of surgery, blood pressure, heart rate, end-tidal sevoflurane concentration, sevoflurane consumption, time to loss of eyelash reflex and verbal response, and time to extubation. Gender, surgery, and number of patients with nausea and vomit were analyzed with chi-square test. Number of times of vomit was compared with the Kruskal Wallis test followed by the Mann-Whitney U test. A p value less than 0.05 was considered to be statistically significant.

Results

Demographic data were not different among the groups (Table 1).

Time to loss of eyelash reflex and verbal response were significantly shorter in 5% GOS and 8% GOS than those in 5% OS and 8% OS, respectively (Table 2). Sevoflurane consumption was larger with 5%OS and 8% OS than 5% GOS and 8% GOS, respectively, but was statistically significant only between 5%OS and 5% GOS (Table 2). Time to extubation was not different among the groups (Table 2). Blood pressure 1 minute after intubation (Figure 1), and increase by intubation (Table 3) was significantly larger in 8% OS group than that in 8% GOS group. Heart rate after intubation (Figure 2), and increase in heart rate by intubation (Table 3) was significantly larger in 5% OS and 8% OS groups than those in 5% GOS and 8% GOS groups, respectively. End-tidal sevoflurane concentration was significantly higher in 5% GOS group than

that in 5% OS group before intubation (Figure 3). One minute after intubation 8% OS group had significantly higher end-tidal sevoflurane concentration than 8% GOS group (Figure 3). The frequency of nausea and vomit were not different among the groups (Table 4). No clinically obvious complication was observed for postoperative one-month period.

Table 1: Demographic data

	5%GOS	5%OS	8%GOS	8%OS
Age (years)	48 ± 7	49 ± 8	47 ± 7	49 ± 7
Male/Female	18/12	16/14	16/14	12/18
Body weight (kg)	57 ± 7	56 ± 5	58 ± 5	57 ± 4
Height (cm)	163 ± 6	164 ± 4	165 ± 7	164 ± 5
Duration of surgery (min)	178 ± 51	181 ± 54	168 ± 50	170 ± 58
Surgery				
Plastic surgery	20	18	16	16
Mastectomy	10	16	14	14

Mean ± standard deviation or number of patients; G, nitrous oxide; O, oxygen; S, sevoflurane

Table 2: Induction time and sevoflurane consumption

	5%GOS	5%OS	8%GOS	8%OS
Time to loss of eyelash reflex (sec)	100 ± 25	124 ± 17*	81 ± 11*	95 ± 13$^{+,\#}$
Time to loss of verbal response (sec)	97 ± 22	108 ± 20	76 ± 7*	86 ± 8$^{+,\#}$
Sevoflurane cumsumption (mL)	62 ± 23	82 ± 24*	65 ± 21	79 ± 24
Time to extubation (min)	6 ± 3	5 ± 3	7 ± 4	6 ± 4

Mean ± standard deviation; G, nitrous oxide; O, oxygen; S, sevoflurane

*: P < 0.05 vs. 5%GOS; $^{+}$: P < 0.05 vs. 8%GOS; $^{\#}$: P < 0.05 vs. 5%OS

Table 3: Changes in blood pressure and heart rate

	5%GOS	5%OS	8%GOS	8%OS
Systolic blood pressure (mmHg)				
Pre-intubation – control	-18.8 ± 14.4	-22.2 ± 13.4	-26.7 ± 10.3	-33.7 ± 9.0$^{\#}$
Post-intubation– pre-intubation	18.6 ± 16.7	26.7 ± 9.0	24.7 ± 13.6	44.0 ± 12.0$^{+,\#}$
Heart rate (beats/min)				
Pre-intubation – control	6.5 ± 4.4	2.8 ± 8.7	8.4 ± 6.6	13.5 ± 11.0$^{\#}$
Post-intubation– pre-intubation	-6.1 ± 6.7	16.7 ± 5.2*	0.5 ± 6.2*	13.6 ± 11.7^{+}

Mean ± standard deviation; G, nitrous oxide; O, oxygen; S, sevoflurane

*: P < 0.05 vs. 5%GOS; $^{+}$: P < 0.05 vs. 8%GOS; $^{\#}$: P < 0.05 vs. 5%OS

Table 4: Nausea and vomit

	5%GOS	5%OS	8%GOS	8%OS
Nausea (number of patients)	8	6	9	7
Vomit				
Number of patients	4	4	4	3
Number of times (median (range))	2 (1-3)	1.5 (1-2)	1.5 (1-2)	2 (1-3)

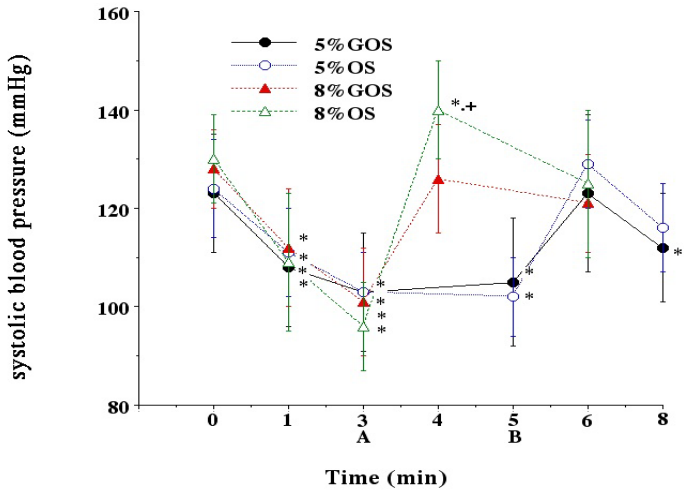

Figure 1: Blood pressure

Systolic blood pressure is shown as mean ± standard deviation; *: P < 0.05 vs. time 0 (control); $^{+}$: P < 0.05 vs. 8% GOS; A, intubation in the 8% groups; B, intubation in the 5% groups

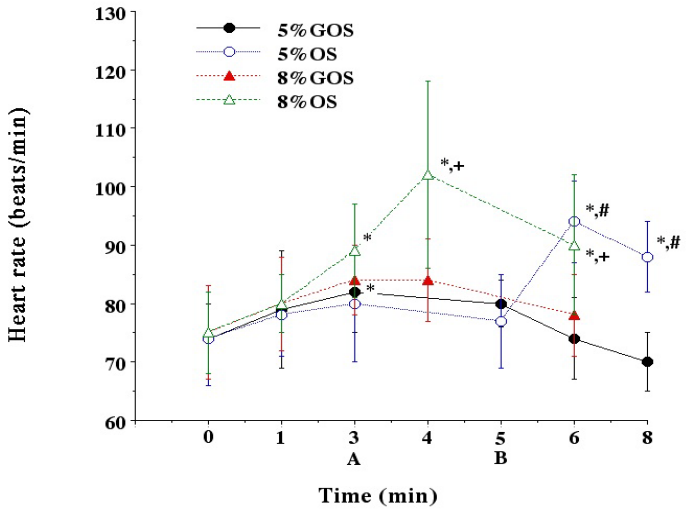

Figure 2: Heart rate

Heart rate is shown as mean ± standard deviation; *: P < 0.05 vs. time 0 (control); $^{+}$: P < 0.05 vs. 8%GOS; $^{\#}$: P < 0.05 vs. 5%GOS; A, intubation in the 8% groups; B, intubation in the 5% groups

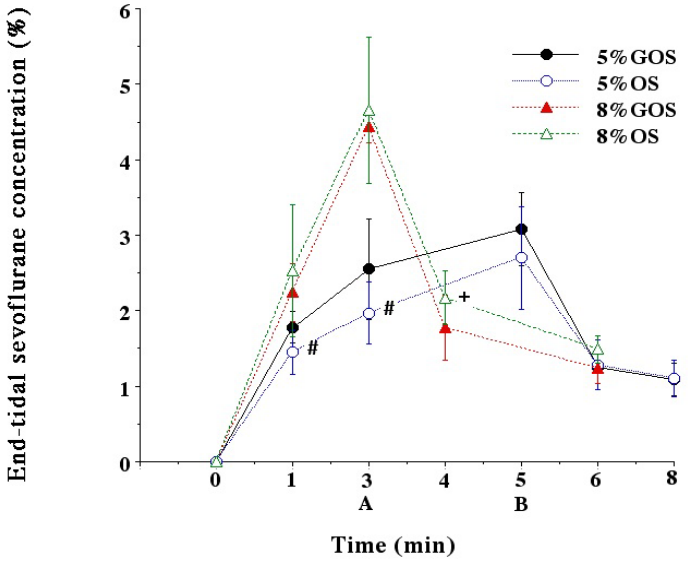

Figure 3: End-tidal sevoflurane concentration

End-tidal sevoflurane concentration is shown as mean ± standard deviation; $^{+}$: P < 0.05 vs. 8%GOS; $^{\#}$: P < 0.05 vs. 5%GOS; A, intubation in the 8% groups; B, intubation in the 5% groups.

Discussion

This clinical study showed that nitrous oxide fastened induction of anesthesia and prevented hemodynamic changes by induction and tracheal intubation in sevoflurane anesthesia without increasing time to extubation and postoperative complications including nausea and vomit. Vitamin B12 was inactivated by nitrous oxide [1]. Myles et al. [10] showed that nitrous oxide increased plasma homocysteine and damaged endothelial function, but they did not observe complications induced by these changes. In addition, in their study, oxygen

concentration was different between nitrous oxide group and control. Nitrous oxide increased neuronal nitric oxide synthase, which suggests pro-apoptotic action of nitrous oxide, a risk of neuronal cell death [4]. Two cases of spinal cord degeneration due to vitamin B12 deficiency by nitrous oxide were reported [3]. However, they did not show the details of anesthesia, therefore, we could not confirm those were side effects of nitrous oxide because the duration of exposure to nitrous oxide might be too short. Nitrous oxide induced myelopathy [11] was also reported. However, the case received 40% nitrous oxide for only one hour and revealed symptom with low serum cobalamin levels two weeks later. Therefore, it is quite difficult to conclude that symptom was induced by nitrous oxide.

Regarding air pollution, nitrous oxide contributes about 5% of the "greenhouse effect", but medical use of nitrous oxide has only 0.35% to 2% of the total release of nitrous oxide [5], which means nitrous oxide contributes only 0.0175 to 0.1 % of the "greenhouse effect". All the above reported side effects has not been observed as clinical problems in quite huge number of patients for more than 100 years, although these might theoretically occur. Our study showed no clinically obvious complications in one month follow up of patients, but we included only a small number of patients and duration of anesthesia was short, therefore, we cannot conclude that these side effects do not occur in nitrous oxide exposure from the present results. Further large clinical observation is necessary.

Nitrous oxide is commonly considered to increase postoperative nausea and vomiting, however, which may be significant only in those already at high risk for nausea and vomiting [12]. It is also reported that nitrous oxide in concentrations at 50% or less rarely induces nausea [13]. Our results also showed that nitrous oxide did not increase postoperative nausea and vomiting.

In contrast to these rare complications, there are many advantages in nitrous oxide anesthesia. In rapid inhalation induction with sevoflurane, of which there are many studies, good intubation condition was obtained more quickly with 66% nitrous oxide than with 100% oxygen in young adults [14], and 67% nitrous oxide decreased body movement [15]. The addition of nitrous oxide to sevoflurane in rapid inhalation induction fastened induction without increase of complication [8]. Nitrous oxide decreased induction time and hemodynamic changes in anesthesia induction with sevoflurane 8% for laryngeal mask insertion without increasing postoperative nausea and vomit [9]. Nitrous oxide decreased hypotension by propofol [16] probably due to the augmentation of sympathetic nervous activity [17]. Our results were consistent with these studies to get stable hemodynamics with faster induction of anesthesia using nitrous oxide.

Nitrous oxide has strong analgesic effects partially mediated by endogenous opioid system [18]. Nitrous oxide 30% is reported to be equal to 10 to 15 mg morphine [6]. Adrenergic α receptors are also involved in analgesic effects of nitrous oxide [19, 20]. In addition, nitrous oxide has anxiolytic effect mediated by brain benzodiazepine mechanisms [21]. In sevoflurane anesthesia, nitrous oxide had similar sevoflurane saving effects as remifantanil without significant difference in hemodynamic and neuroendocrine changes [22]. In short anesthesia, nitrous oxide decreased consumption of sevoflurane by about 60% and fastened emergence from anesthesia [23]. Our results showed that nitrous oxide significantly decreased sevoflurane consumption in 5% induction.

In conclusion, in sevoflurane anesthesia, nitrous oxide was useful to fasten induction and decrease hemodynamic changes by induction and tracheal intubation, and did not induce any clinically obvious postoperative complications.

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