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The economic evaluation of nitrous oxide in sevoflurane anesthesia

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Background: Nitrous oxide (N_2O) is much cheaper than recently introduced volatile anesthetics such as sevoflurane and desflurane, and can reduce the consumption of these anesthetics. The use of N_2O is under current debate. The purpose of this study was to evaluate economic effect of 50% N_2O during sevoflurane anesthesia in Korea.
Methods: Seventy patients were randomly allocated to Group A or Group N. Anesthesia induction was performed using propofol, rocuronium, and 3–5% of sevoflurane with air (Group A) or 50% N_2O (Group N). Fresh gas flow (FGF) was 6 L/min during induction, and 3 L/min for maintenance. Mean arterial pressure (MAP), heart rate (HR), bispectral index (BIS), and minimum alveolar concentration (MAC) were recorded. The consumption of sevoflurane was measured at every 10 minutes for the first 1 hour. The economic effect was analyzed based on the payment criterion of Korean National Health Insurance Service.
Results: MAP, HR, BIS, and MAC showed no differences between the two groups. The sevoflurane consumptions for the first 1 hour were 39.2 ± 6.3 ml in Group A and 29.2 ± 4.9 ml in Group N ($P < 0.01$); and the N_2O consumption was 93.7 ± 1.5 L in Group N. The total costs of inhaled anesthetics were 16,190 (14.8 USD) and 13,062 (12.0 USD) Korean won for the first 1 hour in Groups A and N, respectively.
Conclusions: Use of 50% N_2O with 3 L/min FGF reduced the sevoflurane consumption by 25% and anesthetic cost by 20% for the first 1 hour. **(Anesth Pain Med 2017; 12: 23-27)**

Key Words: Economics, Nitrous oxide, Sevoflurane.

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INTRODUCTION

Nitrous oxide (N_2O) was the first inhaled anesthetic and has been safely used in clinical practice for more than 160 years. However, the use of N_2O is currently controversial. Some anesthesiologists do not advocate use of N_2O due to its adverse effects such as expansion of air-filled spaces [1], delayed postoperative recovery of bowel function [2], increased postoperative nausea and vomiting [3], increased perioperative ischemic heart problem [4], and neurotoxicity [5]. However, N_2O has minimal cardiovascular and respiratory depression effects and pharmacologic advantages underlying reduced awareness compare with volatile anesthetics [1,6]. Also, clinicians in favor of N_2O focus on economic feasibility, as well as biochemical stability [7].

The economics of anesthetic practice is an important factor in the decision-making process [8]. N_2O is much cheaper than recently introduced volatile anesthetics such as sevoflurane and desflurane, and can reduce the consumption of these anesthetics. Jakobsson et al. [9] reported that 66% N_2O caused reduction in sevoflurane consumption by 60% and anesthetic cost by 41%. However, since their study was performed on knee arthroscopic surgery for short duration (17 min) and fixed (3 L/min) fresh gas flow (FGF) during induction and maintenance, the results are not applicable in most clinical cases. Therefore, study that is more compatible with clinical practice is required. Moreover, the payment for anesthesia and costs of inhaled anesthetics differ with countries. The purpose of this study was to evaluate the sevoflurane-sparing and economic effects of 50% N_2O during sevoflurane anesthesia in Korea.

MATERIALS AND METHODS

This prospective, randomized study was approved by the Institutional Review Board of our hospital. Written informed consent was obtained from all patients. We enrolled 70 patients aged 20 to 65 years with American Society of Anesthesiologists physical status I or II, who were scheduled for open abdominal surgery under general anesthesia with an expected duration of ≥ 90 minutes. The patients were randomly allocated to one of two groups: Group A received air and O_2 with 0.5 of inspired fraction of O_2 (F_IO_2), and Group N received N_2O and O_2 with 0.5 of F_IO_2. Because 50% of N_2O is the most commonly used concentration in Korea, the authors selected the concentration [10]. Patients with preoperative hemodynamic instability, cardiovascular disease, endocrine disease, and those who received analgesics or steroids within 72 h of surgery were excluded.

After arrival at the operating room, all patients were under standard monitors, which included non-invasive blood pressure, pulse oximetry, and electrocardiogram. Bispectral index (BIS™, Covidien BIS LoC 2 Channel, Dräger Medical GmbH, Germany) was recorded. Neuromuscluar blockade was monitored by train-of-four (TOF) stimulation using TOF Watch® (Organon Ltd., Ireland). Anesthesia was induced using propofol 2.0 mg/kg, rocuronium 0.8 mg/kg, and 3–5 vol% sevoflurane with or without N_2O by group. FGF was set to 6 L/min during induction, and 3 L/min for maintenance, which is the most commonly used maintenance dose among Korean anesthesiologists [10]. Tidal volume was maintained at 8 ml/kg and respiratory rate was adjusted to maintain end-tidal carbon dioxide tension within 34 to 38 mmHg range intra-operatively. Anesthesia was maintained with 2–5 vol% sevoflurane and 1–4 vol% sevoflurane plus N_2O in Group A and Group N, respectively. Inspired sevoflurane concentration was adjusted based on blood pressure and BIS. Blood pressure and BIS were maintained within ± 20% from the baseline value at 35 to 60, respectively. If blood pressure was out of the maintenance range, the study was held and the proper treatment was conducted for the patient safety. Additional rocuronium was administered when the TOF count was > 3. The subjects who received any adjuvant agents including opioids, intravenous anesthetics, and cardiovascular drugs were excluded from analysis.

Mean arterial pressure (MAP), heart rate (HR), BIS, and minimum alveolar concentration (MAC) were recorded at pre-induction (baseline), 5 min post-intubation, 10, 30, and 60 min after skin incision. MAC was recorded as age-adjusted value. The consumption of sevoflurane was measured using specialized vaporizer (DIVA™, Zeus™, Dräger Medical GmbH, Germany) that directly injects volatile anesthetic into the anesthesia circuit. The consumption was recorded every 10 minutes. The economic effect was analyzed based on the payment criterion of the Korean National Health Insurance Service (KNHIS). The criterion is 9.5 ml for the first 15 min and 5.0 ml per 15 min thereafter. The costs are 413 won/ml for sevoflurane and 10.7 won/L for N_2O in Korea (1 USD = 1,092 Korean won; Sep. 7. 2016 exchange rate). KNHIS generally pays 10,119 won for 24.5 ml of sevoflurane consumption and 1,926 won for 180 L of N_2O consumption during the first 1 h usage.

The calculated sample size based on the KNHIS payment criterion was 29 patients per group in order to detect difference in sevoflurane consumption of 30% for the first 1 h dose with a SD of 10 ml, using an alpha level of 0.05 and a power of 0.80. To allow for attrition, the total sample size was enlarged to 70. The analysis was performed using SigmaPlot 12.5 (Systat Software Inc., USA). Data were expressed as mean ± SD. Demographic data, clinical characteristics and cost of anesthetics were analyzed by a t-test or Mann-Whitney rank sum test depending on the results of the normality and equal variance test. Hemodynamics, BIS, MAC values, and anesthetic consumption were analyzed by two-way repeated measures ANOVA and Holm-Sidak method for post-hoc test. Statistical significance was considered at $P < 0.05$.

RESULTS

Six of 70 enrolled patients did not complete the study and were excluded from the statistical results. Those who had severe hypertension (3 patients), unmeasured BIS (2 patients), and difficult airway (1 patient) were dropped from the experiment. Thirty-three patients in Group A and 31 patients in Group N completed the study. Patients and clinical characteristics were shown in Table 1. Clinical characteristics showed no between-group differences.

MAP, HR, and BIS showed no difference between the two groups during overall experimental time ($P = 0.734$ for MAP, $P = 0.699$ for HR, and $P = 0.703$ for BIS) and at pre-induction, 5 min post-intubation, and 10, 30, and 60 min after skin incision (Table 2). MAC values were not different between the two groups ($P = 0.128$, Fig. 1).

The sevoflurane consumption was significantly lower in Group N (8.6 ± 1.6 ml) than Group A (10.1 ± 2.1 ml) at the first 10 min after sevoflurane administration ($P = 0.003$). Although sevoflurane consumption differences between groups

Table 1. Patients and Clinical Characteristics

	Group A (n = 33)	Group N (n = 31)	P value
Sex (M/F)	8/25	7/24	0.890
Age (yr)	48.2 ± 10.6	45.3 ± 10.8	0.314
Height (cm)	159 ± 5.8	159 ± 6.2	0.883
Weight (kg)	60.1 ± 7.4	62.4 ± 9.4	0.355
Surgery time (min)	131.2 ± 56.8	136.2 ± 49.3	0.731
Anesthesia time (min)	150.9 ± 62.4	154.1 ± 50.7	0.839
Time from sevoflurane administration to skin incision (min)	19.0 ± 5.7	19.1 ± 6.5	0.926
Surgery type			0.589
Gynecologic	16	19	
Gastro-intestinal	10	7	
Hepatic	7	5	

Data are expressed as mean ± SD or number of patient. Group A: received air and oxygen with 0.5 of inspired fraction of oxygen. Group N: received nitrous oxide and oxygen with 0.5 inspired fraction of oxygen.

Table 2. Vital Signs and Bispectral Index

	Mean arterial pressure (mmHg)			Heart rate (beats/min)			Bispectral index		
	Group A (n = 33)	Group N (n = 31)	P value	Group A (n = 33)	Group N (n = 31)	P value	Group A (n = 33)	Group N (n = 31)	P value
Pre-induction	97.4 ± 12.5	94.8 ± 10.2	0.420	74.7 ± 13.2	78.0 ± 12.5	0.346	95.5 ± 2.1	95.2 ± 2.4	0.809
5 min after intubation	84.2 ± 13.9	80.4 ± 8.7	0.202	86.1 ± 12.2	82.6 ± 11.9	0.304	43.2 ± 3.9	43.7 ± 3.6	0.634
10 min after skin incision	89.7 ± 14.5	86.6 ± 10.8	0.327	80.1 ± 14.6	76.4 ± 14.0	0.284	44.8 ± 3.7	45.3 ± 4.4	0.718
30 min after skin incision	80.2 ± 13.4	83.7 ± 12.5	0.278	72.6 ± 12.8	71.6 ± 14.4	0.768	45.1 ± 5.0	46.2 ± 5.8	0.330
60 min after skin incision	84.9 ± 9.0	86.2 ± 12.0	0.505	70.6 ± 9.8	70.6 ± 12.7	0.942	45.0 ± 4.8	44.1 ± 4.4	0.513

Data are expressed as mean ± SD. Group A: received air and oxygen with 0.5 of inspired fraction of oxygen. Group N: received nitrous oxide and oxygen with 0.5 inspired fraction of oxygen.

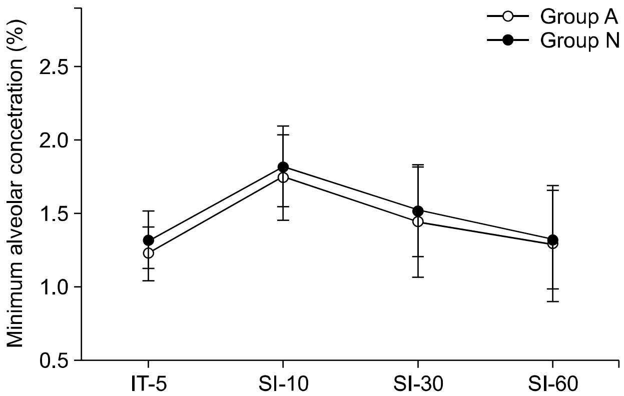

Fig. 1. Data are expressed as mean ± SD. Minimum alveolar concentration is not different between two groups during anesthetic management. Group A: received air and oxygen with 0.5 of inspired fraction of oxygen. Group N: received nitrous oxide and oxygen with 0.5 inspired fraction of oxygen. IT-5: 5 min after intubation, and SI-10, SI-30, and SI-60: 10, 30, and 60 min after skin incision, respectively.

A and N were changed, sevoflurane-sparing effect by the use of N_2O was increased after the first 10 min (Table 3). For the first 1 h, sevoflurane consumptions were 39.2 ± 6.3 ml in Group A and 29.2 ± 4.9 ml in Group N ($P < 0.01$, Fig. 2). Fifty percent N_2O with 3 L/min of FGF for anesthesia maintenance caused 25% reduction in the sevoflurane consumption. However, the KNHIS payment criterion of sevoflurane (24.5 ml/h) is lower than the sevoflurane consumptions with 3 L/min FGF for the first 1 h despite use of N_2O. The N_2O consumption for 1 h was 93.7 ± 1.5 L in Group N.

The economic analysis indicated that in Korea, the costs were 413 won/ml sevoflurane and 10.7 won/L N_2O; and the overall cost of inhaled anesthetics was 16,190 Korean won (14.8 USD) and 13,062 Korean won (12.0 USD) in Groups A and N for the first 1 hour ($P < 0.01$), respectively (1 USD = 1,092 Korean won; Sep. 7. 2016 exchange rate).

Table 3. Sevoflurane Consumptions (ml) and Sevoflurane-sparing Effect by the Use of Nitrous Oxide

	Group A (n = 33)	Group N (n = 31)	P value	Sevoflurane-sparing percent (%)
0–10 min	10.1 ± 2.1	8.6 ± 1.6	0.003	15
10–20 min	4.9 ± 1.9	3.7 ± 1.4	0.015	24
20–30 min	7.1 ± 2.4	5.2 ± 1.7	< 0.001	27
30–40 min	7.1 ± 2.8	4.6 ± 1.2	< 0.001	35
40–50 min	5.3 ± 1.8	3.8 ± 1.3	0.006	28
50–60 min	4.7 ± 1.7	3.7 ± 1.6	0.037	21

Data are expressed as mean ± SD. Group A: received air and oxygen with 0.5 of inspired fraction of oxygen. Group N: received nitrous oxide and oxygen with 0.5 inspired fraction of oxygen.

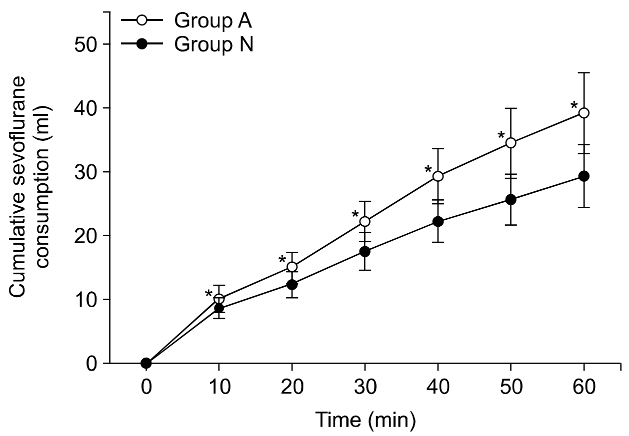

Fig. 2. Data are expressed as mean ± SD. Cumulative sevoflurane consumption is significantly different between the two groups after 10 min of sevoflurane administration. Group A: received air and oxygen with 0.5 of inspired fraction of oxygen. Group N: received nitrous oxide and oxygen with 0.5 inspired fraction of oxygen. $^{*}P < 0.05$.

DISCUSSION

In the present study, 50% N_2O with 3 L/min of FGF caused 25% reduction in the sevoflurane consumption and 20% reduction in costs for the first 1 h. In Korea, the KNHIS payment criterion for inhaled anesthetics, unlike other agents, is based on anesthetic time and not amounts of consumed anesthetics. The KNHIS payment criterion for sevoflurane is 24.5 ml (413 won/ml, 10,119 won/h) for the first 1 h. The sevoflurane consumptions for the first 1 h with 3 L/min FGF in both groups (Group A; 39.2 ± 6.3 ml, Group N; 29.2 ± 4.9 ml) were greater than the KNHIS payment criterion. Our results suggested that < 3 L/min FGF is required to meet the KNHIS criterion, although 3 L/min FGF is most commonly used among Korean anesthesiologists [10]. However, 3 L/min FGF might be surplus due to advanced development of monitoring systems and anesthetic machines. If FGF is reduced, the volatile anesthetic-sparing and economic effects by N_2O are expected to be lessened. The current economic result was analyzed under Korean medical circumstance and anesthetic cost, hence, the results may not be applicable to other countries.

A previous clinical study on the volatile anesthetic-sparing effect by N_2O [9] showed that 66% N_2O spared sevoflurane consumption by 60% during short ambulatory knee arthroscopy, which is greater than result of our study, likely due to fentanyl administration (2 μg/kg) during anesthetic induction in the previous study. The sevoflurane-sparing effect by N_2O would be magnified because the sevoflurane requirement was decreased by fentanyl; furthermore, anesthetic duration (17 vs. 150 min), control of FGF rate, surgical invasiveness (knee arthroscopy vs. open abdominal surgery), and measurement technique (weighing of vaporizer vs. direct injected amount) could have caused differences in sevoflurane-sparing effect between studies.

Interaction between N_2O and inhaled anesthetics is complex. It is generally accepted that volatile anesthetics and N_2O act in an additive manner [11]. In the present study, the MAC values were calculated by summation of MAC values of sevoflurane and N_2O. Although the MAC values were changed during operation and for individual patients, the mean values were maintained at approximately 1.5 MAC in both groups. Because 50% N_2O has about 0.5 MAC, we expected about 33% sevoflurane-sparing effect by summation of MAC values of sevoflurane and N_2O. Contrary to expectation, the results indicated a 25% sevoflurane sparing effect. This discrepancy could be due to several factors. First, the patients received sevoflurane 3–5% with high FGF rate (6 L/min) after propofol administration. Therefore, 10.1 ml and 8.6 ml sevoflurane were consumed for the first 10 min in groups A and N, respectively. The sevoflurane-sparing effect by the use of N_2O was only 15% during the first 10 min; and the effect was increased to 20–35% during anesthesia maintenance. High sevoflurane concentration with high FGF rate during anesthesia induction may attenuate the anesthetic-sparing effect by N_2O. Second, the administered sevoflurane concentration was not standardized, instead the concentration was adjusted widely by the surgical stimuli according to cardiovascular and BIS values. Sevoflurane-sparing effect was changed solely the variable concentration of administered sevoflurane; and since N_2O concentration was fixed, the sevoflurane-sparing effect of N_2O differed by surgical period. Despite lower total sevoflurane-sparing effect by N_2O than previously reported [9], the result is more applicable clinically.

N_2O can increase the incidence of PONV. In the current study, the economic analysis was limited to cost of anesthetics alone since the cost of managing immediate postoperative complications by N_2O was not evaluated. If the management cost of complications was included, the economic effect of N_2O might have differed from our current results.

Several methods are available to measure the consumption of inhalation anesthetics. First method involves the difference in weight of the vaporizer before and after anesthesia divided by the density of inhalation anesthetic [9,12]. This method cannot serially measure the consumptions during anesthesia induction, maintenance, and emergence because of one time measurement after the end of anesthesia. Second method is based calculating the amount of consumption from the pharmacokinetics of the volatile agent. This method requires constant fresh gas flow and vaporizer setting [13]; and therefore, is difficult to apply in the clinical field. Third method is the measurement of consumption from specialized vaporizer, as in our study [14]. The unique vaporizer is located out of the gas flow circuit and directly injects volatile anesthetics into the circuit. Because the consumption of volatile anesthetics can be measured by this vaporizer in real time, sevoflurane consumption reflects the surgical stimuli in the present study.

Our study had some limitations. First, it was difficult to perform the double-blinded study; therefore, the amount of sevoflurane administered could be biased despite attempts to maintain adequate anesthesia according to hemodynamics and BIS value. Second, the type of surgery was not standardized; hence, although only patients scheduled for open abdominal surgeries were enrolled, the surgical invasiveness might differ by the type of surgery.

In conclusion, 50% N_2O with 3 L/min FGF reduced sevoflurane consumption by 25% for the first 1 h. Economically, the total inhaled anesthetic cost was decreased by 20%. The KNHIS payment criterion of sevoflurane is lower than the sevoflurane consumptions with 3 L/min FGF for the first 1 h despite use of N_2O.

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