

Pretreatment with nitrous oxide enhances induction of anesthesia with sevoflurane: A randomized controlled trial

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Abstract

Background and Aims: Inhalation anesthesia with sevoflurane may be enhanced by several drugs or techniques. The aim of the present study was to investigate the effect of nitrous oxide (N₂O) pretreatment on the speed of anesthesia induction with sevoflurane.

Material and Methods: Eighty patients scheduled for hysteroscopy under general anesthesia were randomly assigned to inhale for 10 min before induction 50% N₂O in oxygen or air via a facemask. Anesthesia was induced with 7-8% sevoflurane in oxygen via a facemask. Bispectral index (BIS), end-tidal carbon dioxide (EtCO₂) tidal volume, respiratory rate, oxygen saturation (SpO₂), and heart rate were recorded every minute during the 10 min pretreatment periods and every 30 s during the first 300 s of induction with sevoflurane. During induction of anesthesia inspired and end-tidal sevoflurane concentrations were also recorded.

Results: During the 10 min of inspired 50% N₂O or air BIS, EtCO₂, tidal volume, respiratory rate and heart rate values did not differ between the two groups except for the SpO₂, which was higher in the N₂O group ($P < 0.001$). During induction of anesthesia the N₂O group exhibited lower BIS values ($P = 0.001$), being significant at 60-150 s ($P < 0.001$, $P < 0.001$, $P = 0.002$, $P = 0.014$) as well as at 270 s ($P = 0.004$). EtCO₂ and tidal volume were consistently lower in the N₂O group ($P = 0.001$, $P = 0.041$ respectively) and respiratory rate was higher ($P = 0.007$).

Conclusion: Our results show that pretreatment of the patients with 50% N₂O for 10 min enhances the speed of induction with sevoflurane as assessed by the BIS monitoring.

Key words: Bispectral index, inhalation induction, nitrous oxide, sevoflurane

Introduction

Sevoflurane has a low blood/gas partition coefficient and does not irritate the airways. These properties render sevoflurane suitable for inhalation induction of anesthesia. Inhalation induction should provide rapid loss of consciousness to ensure patient's comfort and satisfaction and to avoid adverse effects such as excitations, breath holding, coughing and/or laryngospasm. Several adjuvants and techniques have been proposed to ensure a rapid induction of anesthesia with sevoflurane, such as intravenous (IV) midazolam,^[1]

clonidine,^[2] fentanyl,^[3] breathing different gas flows,^[4] or ventilation with larger tidal volumes.^[5]

The effect of nitrous oxide (N₂O) when added to the inhalation of sevoflurane in oxygen has been controversial.^[2,6-8] N₂O added to oxygen was reported to make shorter the induction time with sevoflurane, an effect similar to that produced by clonidine.^[2] These results are not consistent with the results obtained from other studies, which conclude that the addition of N₂O to the sevoflurane/oxygen mixture is not advantageous regarding the speed of induction of anesthesia.^[6-8] In contrast, results from previous studies point out that the addition of N₂O to the sevoflurane/oxygen mixture may be associated with more, though minor, excitatory phenomena.^[7]

Our hypothesis was that the speed of inhalation induction with sevoflurane may benefit from the pretreatment with N₂O, and subsequent volume contraction^[9] before sevoflurane administration. The aim of the present study was to investigate the effect of pretreatment with 50% N₂O in oxygen on the speed of inhalation induction of anesthesia with sevoflurane in women undergoing minor gynecological procedures.

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Material and Methods

The study was approved by the Institutional Review Board (N-79/04-04-06). Eighty patients American Society of Anesthesiology physical status I or II scheduled for hysteroscopy under general anesthesia, who accepted an inhalation induction with no premedication, gave their written informed consent to participate in the study protocol. The study was conducted between October 2006 and March 2009. Patients with body weight exceeding the ideal body weight by 25%, with central nervous system disease, respiratory disease, hyper- or hypothyroidism, intake of sedatives, hypnotics, and antidepressants were excluded from the study before randomization. Difficult airway was not an exclusion criterion.

Patients were randomly allocated to the air ($\text{FiO}_2 = 0.21$) or N_2O ($\text{N}_2\text{O}/\text{O}_2$:50/50, $\text{FiO}_2 = 0.5$) group. Randomization was done by means of odd and even numbers retrieved from a computer-generated table (<http://www.randomizer.org>) corresponding to the N_2O and to the air group respectively. The pretreatment gas was administered via N_2O -oxygen flow meters or an air flow meter connected to the wall pipelines, all covered by drapes so the investigators were blinded to the gas administered. Group allocation to intervention was done by an independent anesthesiologist not participating in the study who arranged the gases before induction (air or $\text{N}_2\text{O}/\text{O}_2$), covered the flow meters with drapes and recorded the group each patient was assigned.

Induction of anesthesia

In the operating room a peripheral vein was catheterized and a Ringer's solution infusion was started. Monitoring consisted of pulse oximetry, electrocardiogram, heart rate, noninvasive arterial pressure, end-tidal carbon dioxide (EtCO_2), inspired and end-tidal sevoflurane concentrations, tidal volume and respiratory rate (S/5™ Anesthesia Monitor, Datex-Ohmeda Division, Datex-Ohmeda, Helsinki, Finland) and bispectral index (BIS xp A-2000™ Monitor, System Rev 3.21, ASPECT Medical Systems, Leiden, The Netherlands).

According to the group allocation, in the preinduction period patients were fully awake, breathing spontaneously either 50% N_2O in oxygen ($\text{FiO}_2 = 0.5$) or air ($\text{FiO}_2 = 0.21$) for 10 min via a Mapleson C breathing system and a tightly fitting face mask. The face mask was held by the attending anesthesiologist. In the meantime, the anesthetic circuit was primed with 8% sevoflurane: An oxygen flow 6 L/min was allowed to pass through the circle anesthetic system with the sevoflurane vaporizer dial being set at 8% for 5 min. An endotracheal tube was attached to the end of the anesthetic system with the distal end tightly surrounded by a plastic bag.^[9] After the completion of the 10 min administration of

the N_2O /oxygen or air, the face mask was connected to the sevoflurane primed anesthetic circuit and all patients were allowed to breathe spontaneously sevoflurane in oxygen with the sevoflurane vaporizer set at 8% and an oxygen flow rate 6 L/min. After a 5 min period of sevoflurane inhalation, the study protocol and data collection were completed. A short acting opioid was given IV and a supraglottic airway device was inserted for the ventilation of patients during surgery.

Measurements

During the 10 min preinduction period, BIS, respiratory rate, tidal volume, EtCO_2 , heart rate and oxygen saturation (SpO_2) were recorded every minute. The same parameters were recorded every 30 s during the first 5 min induction period with the patient breathing sevoflurane in oxygen. During the induction period inspired and end-tidal sevoflurane concentrations were also recorded every 30 s. Arterial blood pressure was recorded only before starting the pretreatment with the gas and after completion of measurements to avoid stimulus during cuff inflation affecting BIS measurements.

We hypothesized that the speed of inhalation induction with sevoflurane will be enhanced by N_2O pretreatment, and possible subsequent volume contraction occurring before sevoflurane administration. BIS was the primary outcome measure, the rest variables being secondary outcome measures. At each time point, three consecutive BIS values were read and the median one was selected.

Data analysis

Initial sample size estimation showed that approximately 40 patients are needed in each group to detect a clinically relevant reduction of BIS after induction of anesthesia by 30% with a power of 0.80 and level of significance of 5%.

To assess differences in patients' characteristics between the two groups, two independent samples *t*-tests for normally distributed responses and Mann-Whitney tests for nonnormally distributed responses were carried out. Overall group differences in all variables were assessed by using repeated measures ANOVA. A paired samples *t*-test or a Mann-Whitney test was used to assess differences at each time point wherever appropriate. All analyses were performed using the Statistical Package for Social Sciences (SPSS) software, version 11.0 (SPSS Inc., Chicago, IL, USA).

Results

The N_2O and the air groups did not differ in age, body weight, and height. Similarly, they did not differ in systolic and diastolic arterial pressure before or after the end of measurements [Table 1].

Of the 80 patients recruited for the study, 43 patients were assigned to the N₂O and 37 to the air group. Four patients in the N₂O group and one patient in the air group did not accept the facemask from the very beginning and no data were collected from these patients. One patient in the N₂O group presented excitatory movements and removed the mask after N₂O inhalation for 7 min and no further data were collected. In another patient in the air group BIS values were not at any time point obtained due to technical reasons, but all the other variables were recorded and analyzed [Figure 1].

During sevoflurane inhalation in the N₂O group the study was interrupted in one patient at 120 s due to persisting cough and salivation, in one patient at 180 s due to tachypnea, tachycardia and upper airway obstruction, in one patient at

210 s due to tachypnea and tachycardia, in one patient at 240 s due to upper airway obstruction, and in one patient at 270 s due to prolonged apnea. The overall incidence of complications in each group is shown in Table 2.

Table 1: Patient characteristics, SAP and DAP blood pressures before and after the measurements

Patient characteristics and hemodynamics	N ₂ O group	Air group
Age (years)	35 (6.9)	35 (8.5)
Body weight (kg)	62 (10.3)	62 (10)
Height (cm)	164 (6)	166 (7)
SAP before (mmHg)	124 (14)	127 (15)
SAP after (mmHg)	106 (15)	106 (16)
DAP before (mmHg)	77 (11)	76 (8)
DAP after (mmHg)	64 (12)	62 (11)

Values are mean (SD), SAP = Systolic arterial pressure, DAP = Diastolic arterial pressure, SD = Standard deviation, N₂O = Nitrous oxide

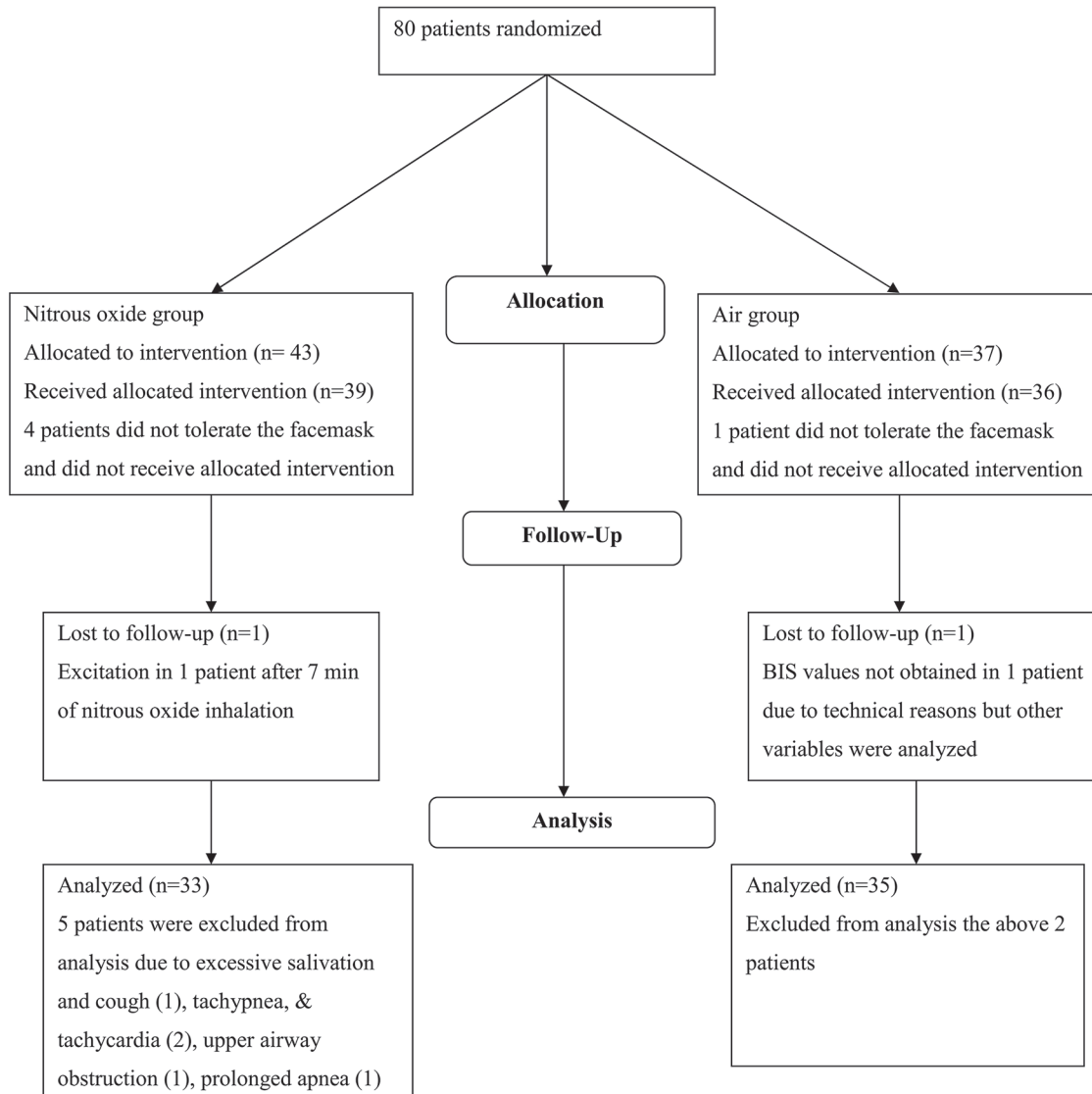


Figure 1: The flow diagram of the study

During the 10 min period of breathing 50% N₂O in oxygen or air, the BIS, EtCO₂, tidal volume, respiratory rate and heart rate did not differ between the group given N₂O and that given air, nor was there a trend to a difference. SpO₂ was slightly but significantly greater in patients given N₂O, consistent with the higher inspired oxygen concentration of oxygen breathed.

During sevoflurane induction BIS values were lower in the N₂O group [Table 3 and Figure 2]. At the time points 60, 90, 120 and 150 s, the BIS values in the N₂O versus air group were: 77 ± 19.0 versus 92 ± 8.6 ($P < 0.001$), 44 ± 19.8 versus 73 ± 21.4 ($P < 0.001$), 36 ± 12.4 versus 55 ± 24.7 ($P = 0.002$) and 32 ± 11.0 versus 45 ± 20.8 ($P = 0.014$), respectively. EtCO₂ and tidal volume values were lower and respiratory rate higher in the N₂O group when compared to the air group. SpO₂, heart rate, inspired and end-tidal sevoflurane concentration did not differ significantly between the two groups during the first 300 s of sevoflurane inhalation [Table 3].

Discussion

The results of the present study suggest that pretreatment with N₂O in 50% oxygen for 10 min before inhalation induction with sevoflurane enhances induction as assessed by decreased

Table 2: The incidence of complications during pretreatment with N₂O or air followed by sevoflurane induction in the N₂O and air groups

Complication	N ₂ O group	Air group
Excitations	9/39	4/36
Obstruction	7/39	1/36
Breath holding	5/39*	16/36*
Coughing	3/39	1/36
Tachypnea	3/39	0/36
Tachycardia	3/39	3/36

* $P < 0.001$, N₂O = Nitrous oxide

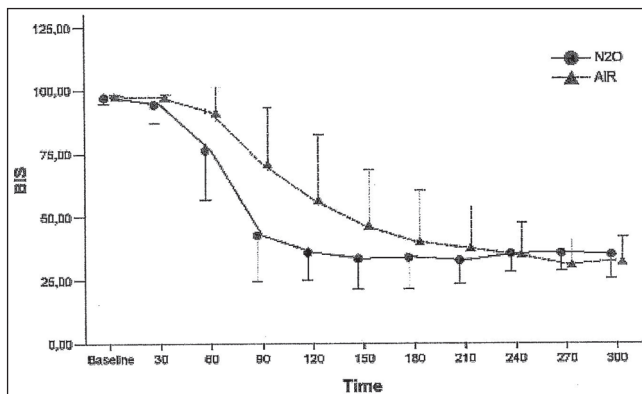


Figure 2: Bispectral index values (mean ± standard deviation) during inhalation with sevoflurane in the nitrous oxide and air groups

BIS values. These results are not consistent with other studies when N₂O was administered concomitantly with sevoflurane for inhalation induction. Nevertheless, these studies were based on clinical criteria, which are subjective and therefore more difficult to be quantified.

O'Shea *et al.* found that the addition of 50% N₂O to the sevoflurane/oxygen mixture had no effect on the speed of induction and was associated with more excitatory effects. The investigators defined induction time as the time needed for the raised arm to fall to the horizontal level.^[7]

Also, according to Siau and Liu, 66% N₂O added to oxygen did not decrease the induction time with 8% sevoflurane when compared to the induction time of 8% sevoflurane in oxygen alone. Adverse events during induction were similar in the two groups. The induction time was defined as the time to cessation of finger tapping. These investigators administered higher concentrations of N₂O than those administered in the present study but did not prime the circle breathing circuit with sevoflurane.^[8]

In a previous study, we have shown that pretreatment with 100% oxygen enhances the inhalation induction with ≥7% sevoflurane as assessed by BIS monitoring.^[10]

Replacing nitrogen in the lungs with a more soluble gas like oxygen, results in lung collapse, decreased functional residual capacity and increased alveolar concentration of the inhaled anesthetic, that is, sevoflurane.^[11,12] In contrast to oxygen, in the present study the N₂O was discontinued during induction. It is worthy to note that during induction, the end-tidal (F_E) sevoflurane concentration (though no statistically significant) was higher during the first 120 s. The higher F_E is consistent with increased ventilation in the N₂O group, as indicated by the higher respiratory rates and the lower CO₂ values. Increased ventilation favors the uptake of the volatile anesthetic.

In the present study, oxygen is also expected to enhance the sevoflurane uptake and to diminish the difference between the N₂O and air groups as it is more soluble than nitrogen and part of the lungs will collapse to some extent (absorption atelectasis).^[12] Similarly, N₂O-being 32 times more soluble than nitrogen - is rapidly up taken by the blood, resulting in lung contraction and increased alveolar concentration of sevoflurane. However, eventually alveolar collapsing will be associated with pulmonary shunt which will delay sevoflurane uptake.^[13] The time points at which BIS values differ significantly in the present study are between 60 and 150 s.

The inspired and expired sevoflurane concentrations did not differ between the N₂O and the air groups during the

Table 3: BIS, EtCO₂, V_T, RR, SpO₂, HR and F_I and F_E sevoflurane concentrations in the N₂O- and air-breathing groups during induction of anesthesia with sevoflurane

Time-points	0	30 s	60 s	90 s	120 s	150 s	180 s	210 s	240 s	270 s	300 s
BIS (0-100)											
N ₂ O	97±2.7	94±8.4	77±19.0	44±19.8	36±12.4	32±11.0	32±10.0	33±8.5	35±7.4	36±6.6	36±9.4
Air	98±0.5	97±1.2	92±8.6	73±21.4	55±24.7	45±20.8	39±19.8	37±16.6	35±13.1	31±10.4	32±9.6
<i>F</i>	11.35, <i>df</i> =1, <i>P</i> =0.001										
<i>P</i>	0.427	0.35	<0.001	<0.001	0.002	0.014	0.299	0.330	0.643	0.004	0.180
EtCO₂ (mmHg)											
N ₂ O		33±4.4	33±2.9	32±3.2	29±3.9	29±2.9	28±3.8	27±4.2	25±4.1	25±4.6	24±3.9
Air		36±4.1	36±3.5	35±3.7	34±3.8	32±6.4	32±5.7	30±5.8	29±5.8	28±5.1	29±5.5
<i>F</i>	14.06, <i>df</i> =1, <i>P</i> =0.001										
<i>P</i>		0.449	0.037	0.043	<0.001	0.007	0.001	0.067	0.073	0.141	0.014
V_T (ml)											
N ₂ O		324±96	369±105	332±120	298±60	276±81	276±51	231±54	211±55	211±64	176±41
Air		409±114	428±152	351±107	368±115	314±82	261±83	249±92	245±105	233±85	251±116
<i>F</i>	4.49, <i>df</i> =1, <i>P</i> =0.041										
<i>P</i>		0.041	0.332	0.338	0.180	0.036	0.743	0.458	0.365	0.206	0.034
RR (breaths/min)											
N ₂ O		14±3.6	15±4.2	17±4.8	19±4.9	22±4.8	24±6.6	25±7.2	26±7.1	27±7.1	27±6.6
Air		15±3.4	14±3.4	15±3.4	16±3.3	18±4.5	20±5.4	21±5.8	22±6.1	22±5.9	22±6.3
<i>F</i>	8.08, <i>df</i> =1, <i>P</i> =0.007										
<i>P</i>		0.46	0.038	0.001	0.008	<0.001	<0.001	0.001	0.003	0.010	0.013
SpO₂ (%)											
N ₂ O	99±0.7	99±0.6	99±0.7	99±0.7	99±0.7	99±0.7	99±0.8	99±0.7	99±0.7	99±0.7	98±1.7
Air	98±1.0	98±1.0	99±0.7	99±0.6	99±0.6	99±0.6	99±0.7	99±0.7	99±0.6	99±0.6	99±0.6
<i>F</i>	2.517, <i>df</i> =1, <i>P</i> =0.117										
HR (bts/min)											
N ₂ O	80±14	81±14	82±14	81±17	82±19	84±24	85±25	83±25	82±26	81±24	80±24
Air	80±10	81±9.0	79±10	74±10	73±11	74±11	76±13	76±14	76±18	77±18	75±15
<i>F</i>	2.30, <i>df</i> =1, <i>P</i> =0.134										
Sevo F_I (%)											
N ₂ O		6.9±0.5	7.0±0.5	7.1±0.4	7.0±0.5	7.1±0.4	7.1±0.4	7.0±0.4	7.1±0.4	7.1±0.4	7.1±0.3
Air		6.9±0.6	7.1±0.5	6.8±0.9	7.2±0.7	7.2±0.6	7.2±0.6	7.2±0.5	7.2±0.6	7.2±0.5	7.1±0.5
<i>F</i>	2.27, <i>df</i> =1, <i>P</i> =0.137										
Sevo F_E (%)											
N ₂ O		3.0±0.9	3.7±0.5	4.3±0.6	4.8±0.7	4.9±0.5	5.1±0.6	5.2±0.7	5.5±0.7	5.6±0.6	5.7±0.5
Air		2.7±0.8	3.3±0.9	3.9±1.0	4.5±0.7	4.8±0.8	5.0±0.8	5.2±0.7	5.4±0.8	5.5±0.8	5.4±0.7
<i>F</i>	1.99, <i>df</i> =1, <i>P</i> =0.165										

Values are mean ± SD, SD = Standard deviation, BIS = Bispectral Index Score, EtCO₂ = End-tidal carbon dioxide, V_T = Tidal volume, RR = Respiratory rate, SpO₂ = Oxygen saturation, HR = Heart rate, F_I = Inspired, F_E = End-tidal, N₂O = Nitrous oxide

300 s period of induction, though the end-tidal /inspired concentration (F_E/F_I) ratio for sevoflurane was consistently higher by 2-7% in the N₂O group. Sevoflurane due to its low blood gas partition coefficient might not benefit from the second gas effect phenomenon. However Taheri and Eger have nicely demonstrated the second gas effect for desflurane, an agent even less blood soluble.^[14] Hendrickx *et al.* demonstrated a higher ratio of alveolar /inspired (F_A/F_I) sevoflurane concentration when N₂O was added to the inspired mixture.^[15] Peyton *et al.* reported a two to three times more powerful second gas effect of N₂O on arterial versus the end-expired sevoflurane pressures and attributed this effect to ventilation perfusion inhomogeneity by general anesthesia.^[16]

In both studies, sevoflurane measurements were performed after IV induction of anesthesia and during mechanical ventilation.^[15,16] Our data were collected with the patients breathing spontaneously and receiving solely sevoflurane without other anesthetics or adjuvants.

Pretreatment with N₂O may not ensure an overall faster inhalation induction, but highlights the failure of previous studies to demonstrate enhancement of sevoflurane induction by concomitant N₂O administration. Nonetheless, shorter periods of exposure may also enhance the sevoflurane induction. Previous studies failed to show a more rapid induction of anesthesia with sevoflurane for various reasons. As sevoflurane

is an agent with low solubility, it may not benefit the very first minutes of induction by the concomitant administration of N_2O . The additive synergism of the N_2O and sevoflurane might also enhance the inhalation induction. However, such a synergism should also enhance the induction times in other studies. So we remain with our hypothesis that this difference between the N_2O and air groups may be attributed to the pretreatment rather than the co-administration of N_2O during sevoflurane induction of anesthesia.^[13] A very early increased concentration effect due to volume reduction and before the “shunt” effect, as N_2O is taken up by the pulmonary capillaries or increased ventilation, as shown by the lower $EtCO_2$, in the N_2O group may have influenced the speed of the sevoflurane uptake.

In clinical practice, fast inhalational induction may be beneficial for both patients and hospitals; it may shorten the second stage of anesthesia, thus reducing the risk of agitation/adverse respiratory events, and increase patient’s satisfaction, while depending on the time saved - it may also decrease the overall operating room time and facilitate fast turnover.^[17,18]

Our measurements are limited by the sensitivity of the device we used to measure sevoflurane and N_2O , thus the infrared analyzer, as the gold standard to measure concentrations of inhaled anesthetics is the gas chromatography or the mass spectrometry. Other limitations of the study are the number of dropouts, which may have an impact on the study power and the relatively long period of N_2O pretreatment which weakens the clinical implementation of our results and shorter pretreatment periods like 2 or 3 min may be clinically applicable.

Conclusion

Under the present study design, breathing of 50% N_2O in oxygen before induction with sevoflurane enhances the speed of induction in the very early period as assessed by the BIS monitor.

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