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1-1-8 one-step sevoflurane wash-in scheme for low-flow anesthesia: simple, rapid, and predictable induction



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Abstract

Background: Sevoflurane is suitable for low-flow anesthesia (LFA). LFA needs a wash-in phase. The reported sevoflurane wash-in schemes lack simplicity, target coverage, and applicability. We proposed a one-step 1-1-8 wash-in scheme for sevoflurane LFA to be used with both N₂O and Air. The objective of our study was to identify time for achieving each level of alveolar concentration of sevoflurane (F_AS) from 1 to 3.5% in both contexts.

Methods: We recruited 199 adults requiring general anesthesia with endotracheal intubation and controlled ventilation—102 in group N₂O and 97 in group Air. After induction and intubation, a wash-in was started using a fresh gas flow of O₂:N₂O or O₂:Air at 1:1 L·min⁻¹ plus sevoflurane 8%. The ventilation was controlled to maintain end-tidal CO₂ of 30–35 mmHg.

Results: The rising patterns of F_AS and inspired concentration of sevoflurane (F_IS) are similar, running parallel between the groups. The F_AS/F_IS ratio increased from 0.46 to 0.72 within 260 s in group N₂O and from 0.42 to 0.69 within 286 s in group Air. The respective time to achieve an F_AS of 1, 1.5, 2, 2.5, 3, and 3.5% was 1, 1.5, 2, 3, 3.5, and 4.5 min in group N₂O and 1, 1.5, 2, 3, 4, and 5 min in group Air. The heart rate and blood pressure of both groups significantly increased initially then gradually decreased as F_AS increased.

Conclusions: The 1-1-8 wash-in scheme for sevoflurane LFA has many advantages, including simplicity, coverage, swiftness, safety, economy, and that it can be used with both N₂O and Air. A respective F_AS of 1, 1.5, 2, 2.5, 3, and 3.5% when used with N₂O and Air can be expected at 1, 1.5, 2, 3, 3.5, and 4.5 min and 1, 1.5, 2, 3, 4, and 5 min.

Trial registration: This study was retrospectively registered with ClinicalTrials.gov (NCT03510013) on June 8, 2018.

Keywords: Wash-in, Low flow anesthesia, Nitrous oxide, Air, Sevoflurane

Background

Low-flow anesthesia (LFA; fresh gas flow (FGF) ≤ 1 L·min⁻¹) is gaining in popularity because it has a relatively lower cost, causes less environmental burden, and medically because it increases the humidity and temperature of inspired gas, leading to improved mucociliary function of the patient [1]. Since use of low FGF leads to a long time constant, a wash-in phase using a high FGF and high vaporizer concentration of volatile anesthetic (F_V) is warranted in order to rapidly achieve the required concentration of inhalation anesthetic in

the breathing system. Sevoflurane—when used with strong base-free CO₂ absorbent—is suitable for use in LFA because it has low blood-gas solubility. The minimum alveolar concentration (MAC) of sevoflurane varies with patient age—from 1.4% at age 80 to 2.3% at age 1 year [2]. The optimal alveolar concentration of sevoflurane (F_AS) to prevent motor movement and autonomic response during anesthesia is MAC-Bar which approximates 1.5 MAC. Thus, the target of F_AS during anesthesia in daily practice varies between 1 to 3.5%, depending on the adjuvant drugs used. A good wash-in scheme should be able to precisely and promptly achieve every target of F_AS. There are a few reports regarding wash-in schemes of sevoflurane LFA but those studies

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achieved only one or two targets of F_{A_S} [3–5]. In highly developed healthcare areas—where an anesthetic gas monitor is placed in every operating theatre—a wash-in scheme would be unnecessary. By contrast, in less developed areas where anesthetic gas monitors are rare or nonexistent, a precise and reliable wash-in scheme is mandatory for sevoflurane LFA. Since the carrier gases used in anesthesia comprise both O_2 plus N_2O and O_2 plus Air, we propose a simple one-step 1-1-8 wash-in scheme for sevoflurane LFA using FGF of $2\text{ L}\cdot\text{min}^{-1}$ by combining O_2 with N_2O or Air at $1:1\text{ L}\cdot\text{min}^{-1}$ and a F_V of sevoflurane (F_{V_S}) 8%, which can be used to estimate the time to achieve each F_{A_S} in daily practice. The hypothesis is that this scheme can precisely and promptly achieve every F_{A_S} from 1 to 3.5% within 5 min.

The primary outcome of the current study was the time to achieve a F_{A_S} of 1, 1.5, 2, 2.5, 3, and 3.5% in both contexts. The secondary outcomes were to identify the changes in heart rate and blood pressure during wash-in.

Methods

The current study was approved by the Khon Kaen University Ethics Committee in Human Research (HE601228) and was registered with ClinicalTrials.gov (NCT03510013). The study was conducted in accordance with Declaration of Helsinki and the ICH GCP. All participants gave written informed consent before being recruited into the study.

This was a prospective, descriptive study. We aimed to recruit two groups of patients: group N_2O and group Air. We calculated the sample size from a pilot study on 20 patients, which identified a standard deviation of 40 s at an F_{A_S} of 3.5%. With the total width of the expected confidence interval of 16 s, and a significance criterion of 0.05, the total number of patients required was 96. The inclusion criteria were adult patients, between 18 and 64, with an American Society of Anesthesiologists (ASA) physical status of 1–2, undergoing elective surgery under general anesthesia at Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand. The exclusion criteria were patients with a $BMI > 30\text{ kg}\cdot\text{m}^{-2}$; a contraindication for N_2O or succinylcholine; having pulmonary or cardiac disease; or, being pregnant.

All patients received standard intra-operative anesthetic monitoring and care. The monitoring included electrocardiogram, pulse oximetry, non-invasive blood pressure measurement, capnography, and MAC value. The anesthetic machine—with an integrated anesthetic gas analyzer used in this study was the Dräger Primus (Dräger AG, Lübeck, Germany). We used a standard circle circuit with Litholyne as the CO_2 absorbent. Heart rate and blood pressure were recorded as baseline parameters before induction of anesthesia. After pre-oxygenation for 3 min, each patient was

premedicated with fentanyl $1\text{--}2\text{ }\mu\text{g}\cdot\text{kg}^{-1}$, then propofol $2\text{ mg}\cdot\text{kg}^{-1}$ was given as the induction agent. Endotracheal intubation was facilitated with succinylcholine $1.5\text{ mg}\cdot\text{kg}^{-1}$. After a correct endotracheal tube position was confirmed, cisatracurium $0.15\text{ mg}\cdot\text{kg}^{-1}$ was given.

Group N_2O

The ventilation was controlled using $O_2:N_2O$ at $1:1\text{ L}\cdot\text{min}^{-1}$ and F_{V_S} of 8%. The ventilator was set at volume-control with an inspiratory:expiratory (I:E) ratio of 1:2, a positive end-expiratory pressure (PEEP) of 0, and a tidal volume of $8\text{ mL}\cdot\text{kg}^{-1}$ with a respiratory rate of 12 min^{-1} —which was adjusted periodically to achieve an end-tidal CO_2 of 30–35 mmHg. The times to achieve a respective F_{A_S} of 1, 1.5, 2, 2.5, 3, and 3.5% were recorded as the primary outcome. The inspired concentration of sevoflurane (F_{I_S}), heart rate, and blood pressure at each F_{A_S} were recorded as the secondary outcomes. When the F_{A_S} reached 3.5%, the FGF was reduced to $1\text{ L}\cdot\text{min}^{-1}$ and the F_{V_S} readjusted at the discretion of the attending anesthesiologist. Surgery started after completion of recording the study parameters.

Group air

The same procedure was used except using O_2 :Air at $1:1\text{ L}\cdot\text{min}^{-1}$ and F_{V_S} of 8%.

Statistical analysis

Continuous data were presented as means \pm standard deviation (SD) while categorical data were presented as numbers (%). The primary outcomes were presented as means \pm SD with a 95% confidence interval (CI). The secondary outcomes (viz., heart rate and blood pressure at different time points) were compared using repeated measures analysis of variance. A $P < 0.05$ was considered statistically significant. All data were analyzed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 199 patients were recruited between September and December 2018—102 in group N_2O and 97 in group Air. The patient and clinical characteristics are presented in Table 1. The trajectories of time to achieve each F_{A_S} for all patients of group N_2O and group Air are presented in Figs. 1 and 2. The gradual rising pattern of F_{A_S} and F_{I_S} are similar and parallel in both groups (Fig. 3). The ratio of F_{A_S}/F_{I_S} of both groups rises rapidly from 0.46 to 0.72 within 260 s for group N_2O and 0.42 to 0.69 within 286 s in group Air (Fig. 4). The respective time to achieve a F_{A_S} of 1, 1.5, 2, 2.5, 3, and 3.5% (in sec) with 95% CI and the approximate upper limit of the 95% CI (in min) of group N_2O and group Air are presented in Tables 2 and 3. A F_{A_S} of 3.5% can be achieved within 4.5 min in group N_2O and 5 min in group Air. The heart rate and blood pressure

Table 1 Patient and clinical characteristics

Parameter	Nitrous oxide (n = 102)	Air (n = 97)
Age (years)	42.5 ± 12.7	46.0 ± 12.1
Weight (kg)	58.6 ± 10.0	58.4 ± 9.9
Height (cm)	159.8 ± 6.4	160.3 ± 7.7
Sex		
Male	22 (21.6)	24 (24.7)
Female	80 (78.4)	73 (75.3)
ASA classification		
1	71 (69.6)	57 (58.8)
2	31 (30.4)	40 (41.2)
Systolic blood pressure (mmHg)	135.6 ± 20.2	128.7 ± 17.5
Diastolic blood pressure (mmHg)	80.9 ± 10.2	77.0 ± 11.7
Heart rate (beat/min)	80.2 ± 14.5	76.2 ± 11.3

Data are presented as means ± SD or numbers (%)
 ASA American Society of Anesthesiologists

significantly increased initially (albeit slightly) then gradually decreased as the $F_{A,S}$ increased in both groups ($p < 0.001$ for all parameters) (Fig. 5).

Discussion

Sevoflurane is a popular and widely used volatile anesthetic because it does not irritate the airway, hence it can be used as an induction agent, especially in children. Moreover, its low blood and fat solubility leads to rapid onset, easy depth

of anesthesia adjustment, and early recovery [6]. Due to its high cost, however, LFA is used to reduce the amount needed [7]. The more important reasons to implement sevoflurane LFA are benefits to environment and mucociliary function of the patient [1]. Previously, the recommended lowest FGF to be used with sevoflurane was $1 \text{ L}\cdot\text{min}^{-1}$ for exposures up to 1 h and $2 \text{ L}\cdot\text{min}^{-1}$ for exposures > 1 h because of compound A concern [8]. With the introduction of strong base-free CO_2 absorbents (e.g., Amsorb Plus and Litholyme), the issue with compound A from sevoflurane has been resolved and sevoflurane can be safely used in LFA [9]. LFA, however, needs a wash-in phase to rapidly build up $F_{A,S}$ to the required target concentration. The wash-in can be achieved by (a) increasing FGF to reduce the time constant [10]; (b) increasing $F_{V,S}$ to induce a concentration effect [11]; or (c) integrating both methods.

A few studies have addressed the wash-in technique for sevoflurane LFA. Lindqvist et al. reported a 2-step wash-in technique to achieve a $F_{A,S}$ of 1.2%; starting with FGF $1 \text{ L}\cdot\text{min}^{-1}$ and $F_{V,S}$ 8% for 1 min, then reducing FGF to 1, 0.7, 0.5, and $0.3 \text{ L}\cdot\text{min}^{-1}$. They found that the respective time to achieve the target $F_{A,S}$ was 1.8, 1.5, 2.5, and 3.6 min [3]. Horwitz et al. reported that by using a FGF of 1.0 or $0.5 \text{ L}\cdot\text{min}^{-1}$ with a $F_{V,S}$ 6% during the wash-in, the respective time to reach 1 MAC was 6.2 ± 1.3 and 15.2 ± 2.4 min and up to 1.5 MAC at 7.5 ± 2.5 and 19 ± 4.4 min [4]. The limitation of these two schemes is that they cover only 1 or 2 $F_{A,S}$ targets, and hence cannot be applied for other required $F_{A,S}$ targets.

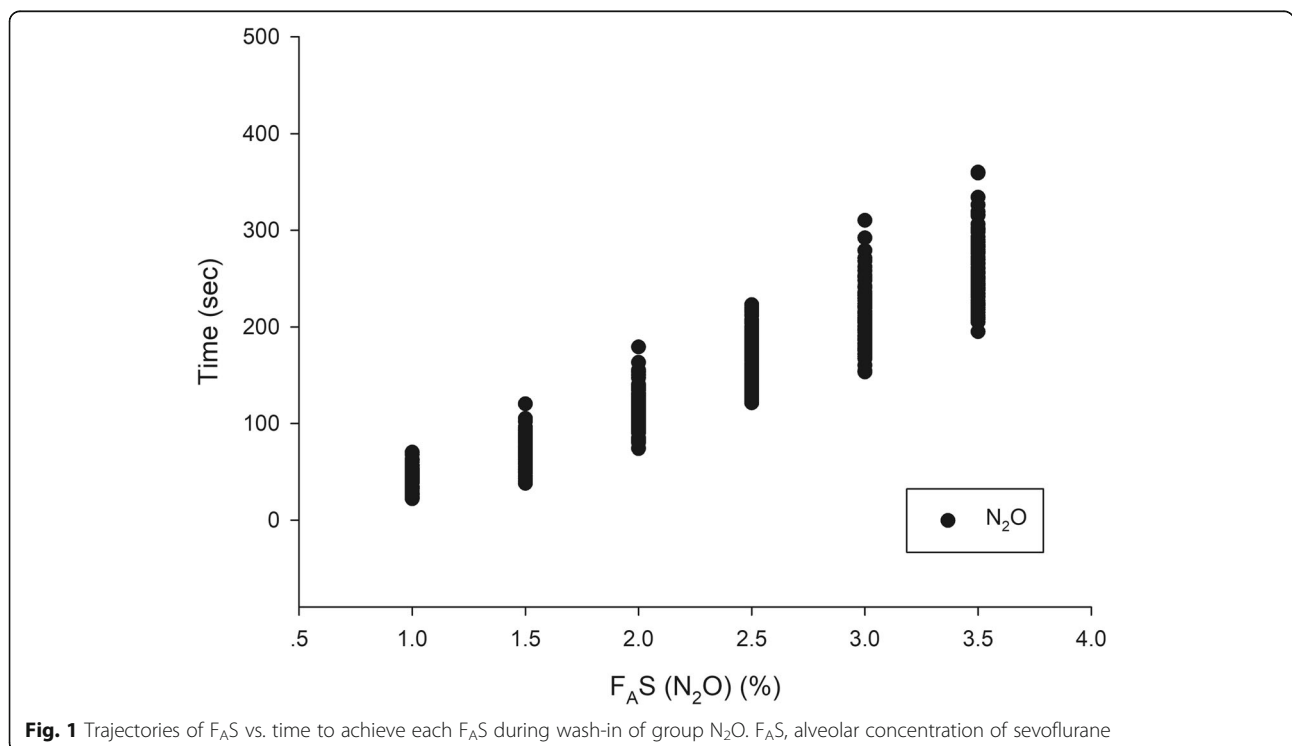
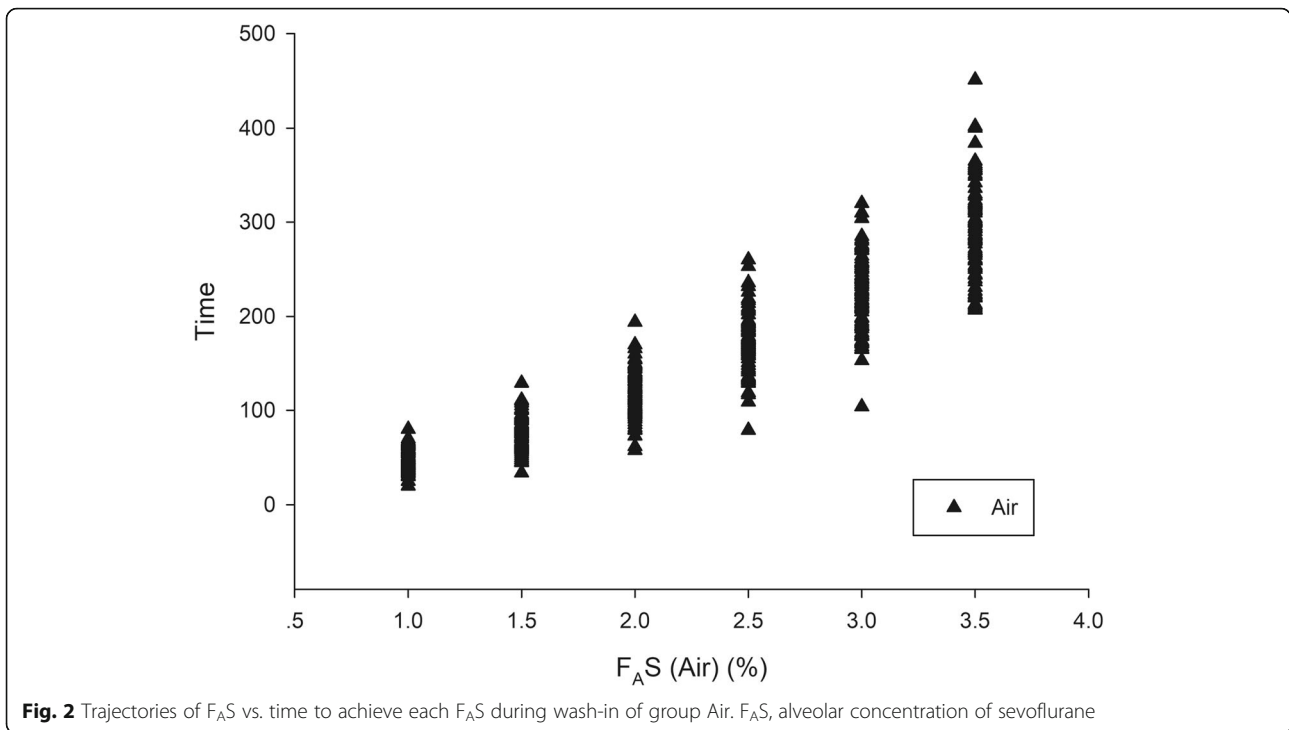
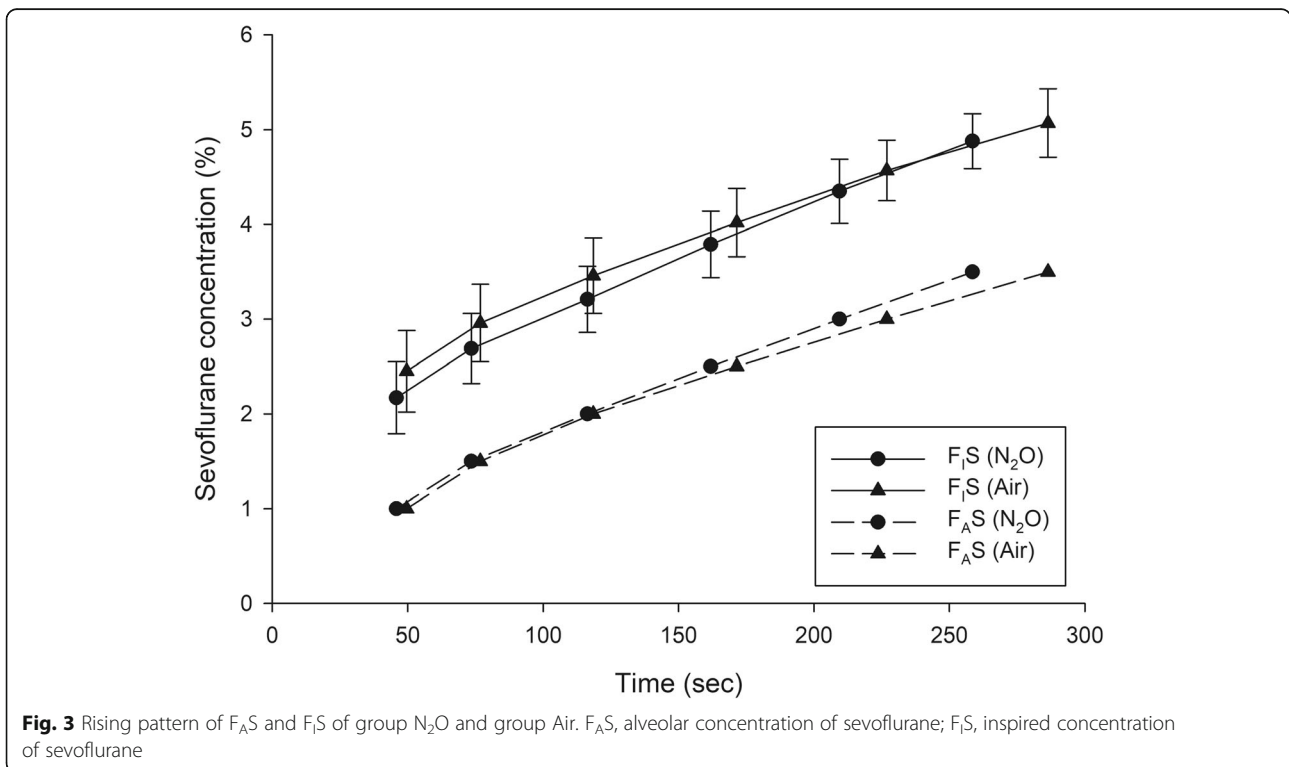


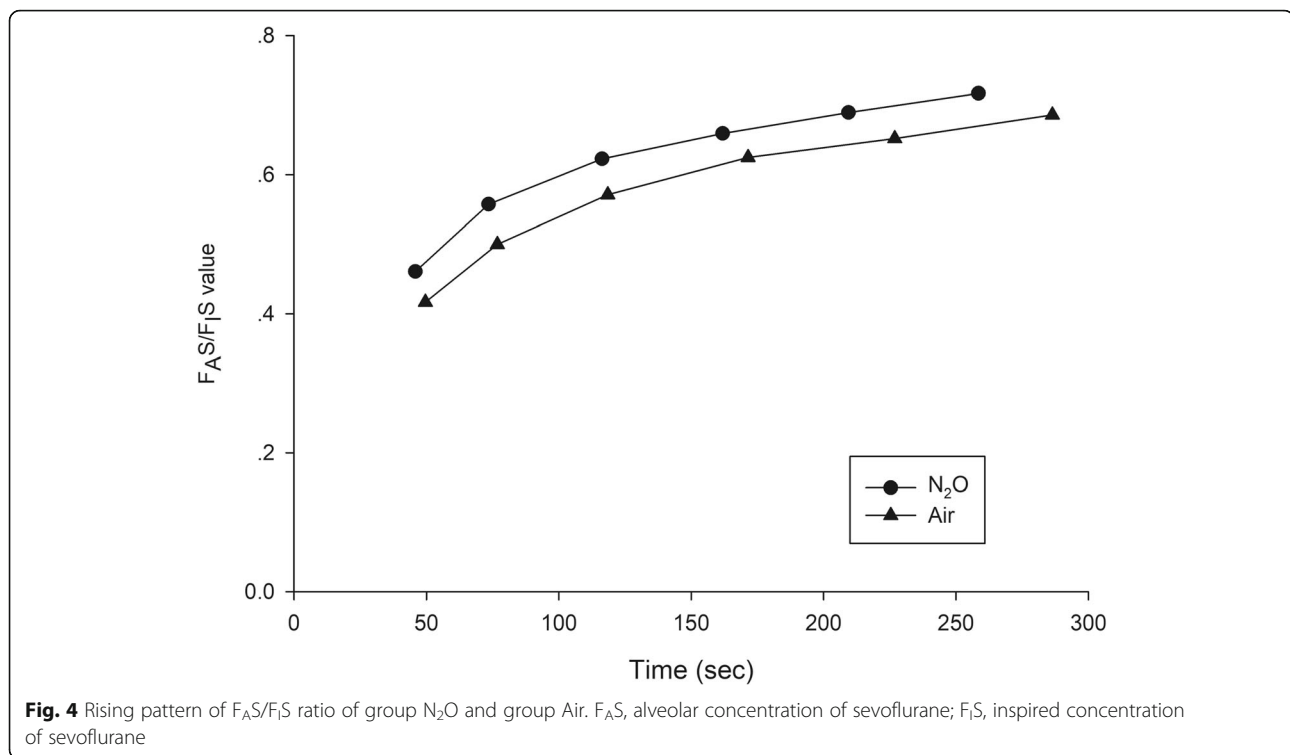
Fig. 1 Trajectories of $F_{A,S}$ vs. time to achieve each $F_{A,S}$ during wash-in of group N_2O . $F_{A,S}$, alveolar concentration of sevoflurane



Jakobsson et al. reported a wash-in in a test-lung model with a respective FGF of 0.3 and $4\text{ L}\cdot\text{min}^{-1}$ and a $F_{V}S$ of 8%. They found that the $F_{A}S$ reached 1 MAC (2.1%) at 547 ± 83 and 38 ± 6 s, respectively [5]. Leijonhufvud et al. reported a wash-in in a test-lung using a respective FGF

of 1, 2, 4, 4.8, 6, and $8\text{ L}\cdot\text{min}^{-1}$ and a $F_{V}S$ 6% in a Flow-I and a Aisys anesthetic machine. They found that the respective mean time to achieve 1 MAC was 431.3, 185.6, 66, 53.6, 53.6, and 52.6 s for the Flow-I and 262.7, 144.3, 57.7, 52.3, 57.7, and 58.3 s for the Aisys [12]. Finally, Shin





et al. performed a wash-in study using a Primus anesthetic machine connected to a test-lung, using a FGF of 0.5, 1, and 3 $L \cdot \text{min}^{-1}$ and setting the F_{V_S} to 6%. The respective mean time to reach a F_{A_S} of 4% for each FGF was 1165, 534, and 155 s [13]. The latter 3 studies were, however, all performed in test-lungs such that the uptake of sevoflurane by body tissues was not considered, so the results cannot be generalized to clinical practice.

The current study proposed a 1-1-8 wash-in scheme for sevoflurane LFA using N_2O or Air—which can rapidly and predictably achieve each F_{A_S} (i.e., 1 to 3.5% as is used in daily practice within 4.5 and 5 min, respectively). The time to achieve every F_{A_S} was identical for both groups except at F_{A_S} of 3 and 3.5% where the time in group Air was a nominally longer than group N_2O because of the second gas effect of N_2O [11]. When this wash-in scheme uses O_2 : N_2O 1:1 $L \cdot \text{min}^{-1}$ as the carrier gases, 50% N_2O provides

0.5 MAC in addition to the MAC of sevoflurane [14], hence this protocol can further reduce the use of sevoflurane. When N_2O is contraindicated or Air is preferred, a higher F_{A_S} is required, and yet this wash-in scheme consistently, precisely, and promptly achieves the required target.

Comparing with a similar 1-1-12 wash-in scheme for desflurane LFA which uses desflurane 12% (2 MAC) [15, 16], the current 1-1-8 sevoflurane wash-in scheme uses a higher MAC (8% or 4 MAC) of sevoflurane. The reasons are that (a) sevoflurane has greater blood and fat solubility than desflurane, leading to higher body tissue uptake, which results in a longer time to achieve an equivalent MAC; and, (b) sevoflurane has a 3 times lower MAC value, hence 4 MAC of sevoflurane was used to augment a concentration effect [11].

The trajectories of the times to achieve each F_{A_S} in both groups (Figs. 1 and 2) suggests that the tested wash-in

Table 2 Actual time in seconds with 95% CI and approximate upper CI limit time in minutes to achieve each F_{A_S} in group N_2O ($n = 102$)

F_{A_S} (%)	F_{I_S} (%)	Time (sec)	95%CI (sec)	Approximated upper CI limit time (min)
1	2.2	45.8 ± 9.8	43.9–47.8	1
1.5	2.7	73.5 ± 14.5	70.7–76.4	1.5
2	3.2	116.3 ± 20.4	112.3–120.3	2
2.5	3.8	161.9 ± 23.3	157.3–166.4	3
3	4.4	208.4 ± 30.6	202.4–214.4	3.5
3.5	4.9	258.5 ± 35.0	251.7–265.4	4.5

Data are presented as means ± SD or ranges

F_{I_S} inspired concentration of sevoflurane, F_{A_S} alveolar concentration of sevoflurane, CI confidence interval

Table 3 Actual time in seconds with 95% CI and approximate upper CI limit time in minutes to achieve each $F_{A,S}$ in group Air ($n = 97$)

$F_{A,S}$ (%)	$F_{I,S}$ (%)	Time (sec)	95%CI (sec)	Approximated upper CI limit time (min)
1	2.4	49.6 ± 10.9	47.4–51.8	1
1.5	3.0	76.8 ± 16.5	73.5–80.2	1.5
2	3.5	118.5 ± 24.0	113.6–123.3	2
2.5	4.0	171.5 ± 30.5	165.4–177.7	3
3	4.6	226.9 ± 38.4	219.1–234.6	4
3.5	5.1	286.4 ± 48.1	276.7–296.1	5

Data are presented as means ± SD or ranges

$F_{I,S}$ inspired concentration of sevoflurane, $F_{A,S}$ alveolar concentration of sevoflurane, CI confidence interval

scheme has acceptable intra- and inter-subject variability. The parallel rising pattern of $F_{A,S}$ and $F_{I,S}$ (Fig. 3) shows that the wash-in scheme has enough power to drive both $F_{A,S}$ and $F_{I,S}$ to the desired target of both groups within 4.5 and 5 min, as reflected in the rising $F_{A,S}/F_{I,S}$ ratio pattern (Fig. 4). The rising $F_{A,S}/F_{I,S}$ ratio pattern reflects the onset of volatile anesthetic: the more rapid the rise the shorter the onset. The rapidly rising $F_{A,S}/F_{I,S}$ ratio of the 1-1-8 wash-in scheme in both groups underscores the efficacy of this scheme. The higher $F_{A,S}/F_{I,S}$ ratio of the group N_2O reflects the second gas effect [11].

The changes in heart rate and blood pressure during the wash-in process are similar to the 1-1-12 wash-in scheme for desflurane [15, 16] (i.e., slightly increasing initially then gradually decreasing as presented in Fig. 5). The changes are statistically but not clinically significant.

The 1-1-8 wash-in scheme has many advantages: (a) simplicity – just a one-step setting; (b) coverage – includes every $F_{A,S}$ target from 1 to 3.5% used in daily practice both in balanced anesthesia and pure inhalation anesthesia; (c) swiftness – accomplishing the desired target within 1 to 4.5 or 5 min; (d) safety – no clinically significant change in heart rate and blood pressure; (e) economy – just 2 $L \cdot \text{min}^{-1}$ of FGF; and (f) applicability – can be applied with both N_2O and Air. When the target $F_{A,S}$ is achieved, the FGF can be reduced to 1 $L \cdot \text{min}^{-1}$ and the $F_{A,S}$ can simply be maintained by setting the $F_{V,S}$ above the desired $F_{A,S}$ by 50 to 60% [17]. The current study used Litholyme as the CO_2 absorbent to guarantee the safety of sevoflurane LFA.

Most hospitals in developed countries have an anesthetic gas analyzer in the operating theatre, making any wash-in scheme unnecessary during low-flow

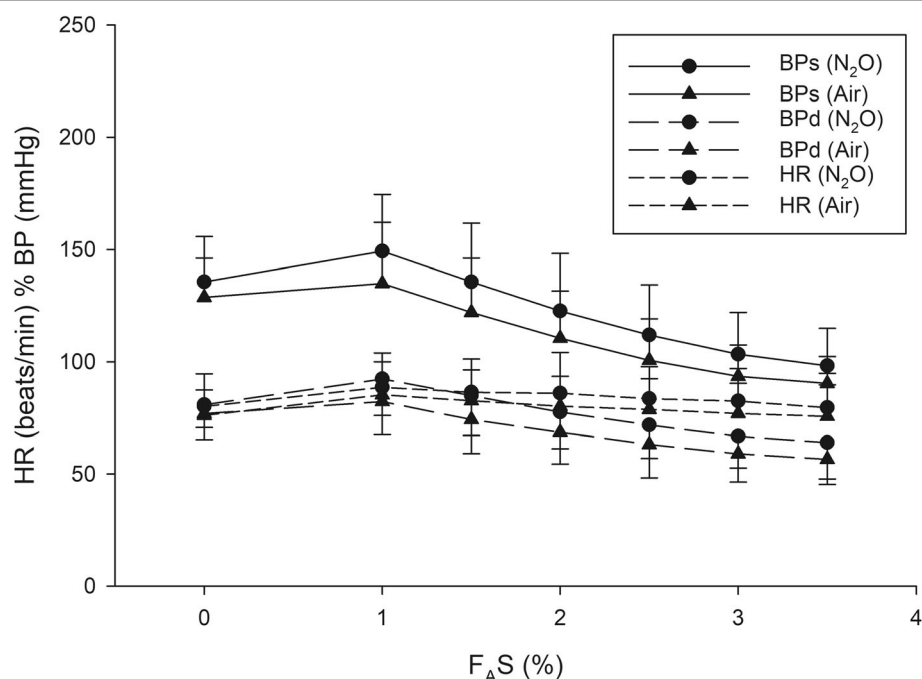


Fig. 5 Pattern of changes in heart rate and blood pressure of group N_2O and group Air at each $F_{A,S}$. $p < 0.001$ for all values. $F_{A,S}$, alveolar concentration of sevoflurane; BPs, systolic blood pressure; BPD, diastolic blood pressure; HR, heart rate

anesthesia. Many operating theatres in less developed areas, however, still lack such equipment. The tested wash-in scheme may thus be applied as guidance to perform sevoflurane LFA provided that an inspired oxygen concentration monitor is available.

Limitations

Since we excluded patients with a BMI > 30 kg m⁻²; having pulmonary or cardiac disease; or, being pregnant, this wash-in scheme may not be applied in those groups of patients. Further studies are required.

Conclusions

In patients requiring general anesthesia with endotracheal intubation and controlled ventilation, the 1-1-8 wash-in scheme for sevoflurane LFA yields a respective F_AS of 1, 1.5, 2, 2.5, 3, and 3.5% at 1, 1.5, 2, 3, 3.5, and 4.5 min when used with N₂O and at 1, 1.5, 2, 3, 4, and 5 min when used with Air. This technique uses a one-step setting for O₂: N₂O or O₂:Air 1:1 L·min⁻¹ with sevoflurane 8%. There were statistically but not clinically significant changes in heart rate and blood pressure during the wash-in process.

Abbreviations

ASA: American Society of Anesthesiologists; CI: Confidence interval; CO₂: Carbon dioxide; F_AS: Alveolar concentration of sevoflurane; FGF: Fresh gas flow; F_IS: Inspired concentration of sevoflurane; F_V: Vaporizer concentration of volatile anesthetic; F_VS: Vaporizer concentration of sevoflurane; N₂O: Nitrous oxide; O₂: Oxygen; SD: Standard deviation

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Authors' contributions

ST and TS designed the study, performed the study, performed the statistical analysis and wrote the manuscript. NV, MT, DN, and WS performed the study and collected data. All authors read and approved the final manuscript.

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Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics approval and consent to participate

The current study was approved by the Khon Kaen University Ethics Committee in Human Research (HE601228). All participants gave written informed consent before being recruited into the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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