Single-breath vital capacity high concentration sevoflurane induction in children: with or without nitrous oxide?

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Editor’s key points

- This study found that for single-breath vital capacity inhalation induction with high concentration sevoflurane in children, the addition of N₂O resulted in faster loss of consciousness and reduced excitatory movements.
- Differences in the time to return of ‘regular breathing’ and ‘conjugate gaze’ were not statistically significant.
- Patients receiving N₂O had less excitatory movements.

Background. Single-breath vital capacity inhalation induction with high concentration sevoflurane (SBVC-HC) is a rapid and ‘needleless’ technique, preferred and well tolerated in the cooperative child. The addition of nitrous oxide may speed up induction by its second gas effects. Previous studies done in children looking at the effect of N₂O on this technique lacked power and showed conflicting results. This study aims to investigate the effect of N₂O on induction time for SBVC-HC sevoflurane induction in children.

Methods. Eighty unpremedicated, ASA I and II children, aged 5–15 yr having elective surgical procedures under general anaesthesia, were recruited and randomized to: Group A: 8% sevoflurane in O₂ 6 litre min⁻¹, and Group B: 8% sevoflurane in N₂O 4 litre min⁻¹ and O₂ 2 litre min⁻¹. The primary outcome was the time to ‘loss of eyelash reflex’. The time to return of ‘regular respiration’ and ‘conjugate gaze’ were also noted.

Results. The difference in the ‘time to loss of eyelash reflex’ was small but statistically significant. Group B: mean duration 53.6 s, standard deviation (SD) 16.1, compared with Group A: 63.5 s, SD 16.1 (mean difference 9.9, 95% confidence interval 2.5–17.3, P=0.01). Differences in the time to return of ‘regular breathing’ and ‘conjugate gaze’ were not statistically significant. Patients receiving N₂O had less excitatory movements (P=0.007), but incidence of other adverse events was low and did not differ significantly between both groups. More than 94% of children would choose this method of induction again in both groups.

Conclusions. We conclude that for SBVC-HC sevoflurane induction in children, the addition of N₂O resulted in faster loss of consciousness and reduced excitatory movements.

Keywords: anaesthesia, paediatric; anaesthetics gases, nitrous oxide; anaesthetics volatile, sevoflurane; inhalation anaesthesia

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Inhalation induction offers the possibility of ‘needleless induction’; hence, it is a preferred technique by many children, especially when cannulation is difficult.

Paediatric anaesthetists use different strategies for inhalation induction, which can vary from volatile agents delivered in a high inspired concentration or incrementally,²–⁴ by having the child to take a single vital capacity breath⁵ or normal tidal volume (TV) breaths.⁶

The introduction of sevoflurane,⁶ ⁷ with its low solubility and good acceptability even at high concentrations (HCs), has popularized the single-breath technique. It has been shown that single-breath vital capacity HC (SBVC-HC) inhalation induction with sevoflurane is more rapid and better tolerated by the cooperative child, compared with the conventional TV technique.² ⁶

As with any other drug, nitrous oxide has its advantages and disadvantages.

Despite its long history, there have been increasing concerns⁸ of its possible adverse effects on both patients⁹ ¹⁰ and the environment.¹¹ ¹² More recently, it has been implicated in contributing to increased postoperative nausea/vomiting, pulmonary complications,⁹ and possibly apoptosis in the developing brain¹³ (in animal studies). Previously associated with increased spontaneous abortions in the pre-scavenging era,¹⁴ it is still considered a potential health hazard to healthcare staff, as prolonged exposure may have repercussions on the reproductive, neurological, and haematological systems, by inhibition of methionine synthesis.¹⁵ On the environmental aspect, nitrous oxide also contributes to the greenhouse effect.¹⁶
Conversely, as an analgesic and weak anaesthetic, nitrous oxide is a useful adjunct to other anaesthetic agents, reducing their consumption, and saving costs. Its anaesthetic-sparing effect also results in a faster recovery. The addition of nitrous oxide can increase the rate of alveolar–capillary uptake of the volatile agent, and also oxygen, by the concentration and second gas effect. During inhalation induction, it may contribute to a smoother and marginally quicker induction, as shown by Hall and colleagues. This is especially useful in anaesthetizing children, even the uncooperative ones.

While this theoretical advantage has not been demonstrated in some adult studies, the uptake of anaesthetic gas in children differs from the adult, due to a larger ratio of alveolar ventilation to functional residual capacity, a larger fraction of cardiac output being delivered to vessel-rich organs, and different blood gas partition coefficients for inhaled anaesthetics. Responses to inhalation induction may also differ due to higher MAC requirements in children.

The assessment of concentrating and second gas effects of nitrous oxide may have been underestimated in the past (as end-expired concentrations rather than arterial partial pressures were used). Moreover, previous studies done in children included only small numbers and were not powered to evaluate the effect of nitrous oxide on SBVC-HC method of induction with sevoflurane. We decided to investigate the hypothesis that the concentrating and second gas effects of nitrous oxide can hasten, smoothen, or both this inhalation induction technique in children.

Methods

After ethics committee approval, informed written consent was obtained from the parent or legal guardian, and written assent from the child, if old enough. Eighty unpremedicated, ASA I and II paediatric patients, aged 5–15 yr undergoing elective day surgery procedures, for example, circumcision, herniotomy, and orchidopexy, underwent general anaesthesia, were recruited. Patients with a history of malignant hyperthermia, reactive airway disease, upper respiratory tract infection, or full stomach were excluded. Patients who preferred an i.v. induction or who could not take the facemask were also not included.

Upon recruitment, each child was taught the SBVC inhalation technique. He/she was instructed to take a vital capacity breath, and then breathe out fully, at the end of which, a facemask was applied; and the child was then told to inhale maximally and hold his/her breath for at least 20 s. This was practiced until the child was confident, in performing the technique. Once ready, the child was brought to the operating theatre and arterial pressure, ECG, and pulse oximetry monitoring were applied. Induction was performed using a circle-absorber breathing circuit primed with sevoflurane 8% with 6 litre min\(^{-1}\) of fresh gas flow (FGF).

Recruited patients were randomized into two groups by sealed envelope assignment: Group A without nitrous oxide (8% sevoflurane in O\(_2\) 6 litre min\(^{-1}\)), and Group B with nitrous oxide (8% sevoflurane in N\(_2\)O 4 litre min\(^{-1}\) and O\(_2\) 2 litre min\(^{-1}\)). The Datex-Ohmeda (GE) Aespire 700 anaesthetic machine (breathing system volume of 2.7 litre), with integrated haemodynamic and airway gas monitor system, was used in all cases. Before the facemask was placed on the patient’s face at the end of exhalation, the circle-absorber breathing circuit was primed with the required gas mixture by completely emptying the reservoir bag, and flushing the circuit with 6 litre min\(^{-1}\) of FGF and 8% sevoflurane delivered by a Datex Ohmeda Tec 7 vaporiser, with the patient’s Y piece occluded.

The volatile concentration was monitored by a Datex Ohmeda (GE) infra-red multi-gas analyser, with side-stream sampling at 200 ml min\(^{-1}\), from the Y piece at the patient’s end. A constant sevoflurane concentration of >7% with FGF 6 litre min\(^{-1}\) was ensured before proceeding.

For our study, the endpoints chosen were the loss of eyelash reflex, establishment of regular breathing, and return of conjugate gaze. The loss of eyelash reflex is most commonly used to identify the loss of consciousness and induction of anaesthesia, whereas regular tidal breathing and the return of conjugate gaze, in combination with other clinical signs such as heart rate (HR) and arterial pressure, are used to gauge the depth of anaesthesia. Based on experience, these endpoints are chosen because they are useful in identifying time to certain events during a paediatric inhalation induction. For example, it may be timely to send a parent out of the induction room with the ‘loss of eyelash reflex’. I.V. cannulation, jaw manipulation, and insertion of airway device may be timed with the establishment of ‘regular respiration’ and ‘return of conjugate gaze’.

For our study, three endpoints were chosen. The primary outcome was the time (in seconds) to ‘loss of eyelash reflex’, and secondary outcomes were the time to ‘return of regular breathing’ and ‘return of conjugate gaze’. Outcomes were assessed by an independent observer, familiar with the identification of all three endpoints and blinded to the gas mixture delivered. The ‘loss of eyelash reflex’ was assessed every 5 s by gentle brushing of the eyelashes of one eyelid with a finger. Breathing was considered regular once five regular tidal breaths were captured on capnography, in the absence of breathholding or apnoea. Conjugate gaze was assessed by lifting the eyelids to observe for centralization of pupils. All timings were measured from the time the facemask (connected to the primed circuit) was applied onto the child’s face (i.e. at the start of maximal inspiration from residual volume).

The onset of anaesthesia was taken as the time when eyelash reflex was lost. Therefore, the time to ‘loss of eyelash reflex’ defined induction time.

Vital signs such as systolic arterial pressure (SAP), HR, saturation (Sp\(_O_2\)), inspired sevoflurane concentration (\(F_{Sevo}\)), and end-tidal sevoflurane concentration (\(E_{Sevo}\)) were recorded just before induction, then at 1 min intervals. Adverse events such as excitatory movements, coughing, laryngospasm, breath-holding/apnoea, and the presence of secretions were also noted with graded severity (0, none; 1, mild; 2, moderate; 3, severe). In addition, desaturation...


\[ \text{SPO}_2 < 94\% \] and the need for rescue i.v. induction drugs was noted. Observations were made until the last endpoint ‘return of conjugate gaze’ was reached.

All timings were recorded using the same stopwatch each time. The primary and secondary endpoints were defined as above. The severity of excitatory movements were defined as (0, none; 1, mild, inconsequential; 2, moderate, more movement but does not interfere with induction; 3, severe, interferes with induction, requiring restraint).

On return to the day surgery ward, the patients were asked if they were satisfied with the technique and whether they would choose the same type of induction again.

Based on a local study\(^3\) where the mean SB-VC induction time was 50 s (SD 14), a 10 s difference in induction time was presumed significant, and a sample size of 62 (31 in each group) calculated, using a two-tailed test with \(\alpha\)-value of 0.05 and \(\beta\) of 0.2. SPSS version 16 was used for statistical analysis, where unpaired \(t\)-test and \(\chi^2\)/Fisher’s exact tests were used for continuous variables and categorical variables, respectively. \(P<0.05\) was presumed as significant.

**Results**

A total of 75 patients completed the study. Five patients (three in Group A, two in Group B) dropped out due to anxiety (three) and mask refusal upon reaching the operating theatre (two).

Baseline characteristics were similar in both Groups A and B (Table 1), and between patients who completed the study and those who did not complete the study.

The ‘time to loss of eyelash reflex’ was significantly shorter for the nitrous group (Group B) with a mean duration of 53.6 s (SD 16.1), compared with Group A which was 63.5 s (SD 16.1). This gave a mean difference of 9.9 s (95% confidence interval (CI) 2.5–17.3), \(P=0.01\).

Differences in secondary endpoints were not statistically significant. The time to return of regular breathing in Group A was 90.1 s (SD 18.4) and Group B was 81.5 s (SD 20.5), with a mean difference of 8.6 s (95% CI –0.4 to 17.7), \(P=0.06\).

<table>
<thead>
<tr>
<th></th>
<th>Group A ‘no nitrous’ ((n=37))</th>
<th>Group B ‘with nitrous’ ((n=38))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Excitatory movements</strong></td>
<td></td>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td>None</td>
<td>40.5% (15)</td>
<td>78.9% (30)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>29.7% (11)</td>
<td>13.2% (5)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>24.3% (9)</td>
<td>7.9% (3)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>5.4% (2)</td>
<td>0% (0)</td>
<td></td>
</tr>
<tr>
<td><strong>Cough</strong></td>
<td></td>
<td></td>
<td>0.489</td>
</tr>
<tr>
<td>None</td>
<td>83.8%</td>
<td>92.1%</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>8.1%</td>
<td>5.3%</td>
<td></td>
</tr>
<tr>
<td><strong>Laryngospasm</strong></td>
<td></td>
<td></td>
<td>0.321</td>
</tr>
<tr>
<td>None</td>
<td>100%</td>
<td>97.4%</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>0%</td>
<td>2.6%</td>
<td></td>
</tr>
<tr>
<td><strong>Breathholding</strong></td>
<td></td>
<td></td>
<td>0.321</td>
</tr>
<tr>
<td>None</td>
<td>100%</td>
<td>97.4%</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>0%</td>
<td>2.6%</td>
<td></td>
</tr>
<tr>
<td><strong>Secretions</strong></td>
<td></td>
<td></td>
<td>0.321</td>
</tr>
<tr>
<td>None</td>
<td>100%</td>
<td>97.4%</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>0%</td>
<td>2.6%</td>
<td></td>
</tr>
<tr>
<td><strong>Desaturation</strong></td>
<td></td>
<td></td>
<td>0%</td>
</tr>
</tbody>
</table>

The time to return of conjugate gaze in Group A was 160.6 s (SD 32.0) and Group B was 153.6 s (SD 41.3), with a mean difference of 7.0 s (95% CI –10.1 to 24.1), \(P=0.42\).

Patients receiving nitrous oxide (Group B) had less excitatory movements (\(P=0.007\)) (Table 2). The incidence of other adverse events (i.e. cough, laryngospasm, breathholding, secretions, desaturation) was low and did not differ significantly between the groups.

Changes in \(F_{\text{ISevo}}\) and \(E_{\text{Sevo}}\) recorded every minute from the start of induction were similar between both groups. The \(F_{\text{ISevo}}\) at baseline 0 min was \(8.7\%\) in all patients and notably higher in the non-nitrous Group A (mean inspired Sevo 8.08%, SD 0.53) compared with the nitrous Group B (mean inspired Sevo 7.64%, SD 0.49), with a mean difference of 0.44% (95% CI 0.20–0.18), \(P=0.001\).

Changes in vital signs such as SAP and HR after SBVC-HC induction did not differ significantly between the two groups (Table 3).

The difference between the two groups was not significant, with 94.7% of children in Group B and 94.3% of children in Group A (\(P=1.0\)) reporting that they would choose the same method of induction again.

**Discussion**

We found that the addition of nitrous oxide to the gas mixture hastened and smoothened SBVC-HC sevoflurane
induction in children. This supports our hypothesis that the concentration\textsuperscript{15} and second gas\textsuperscript{19, 20} effects of nitrous oxide make it an effective adjunct\textsuperscript{16} in improving the rate and quality of inhalation induction in children.

First described by Lamberty\textsuperscript{32} in 1988, the single-breath induction technique has been much evaluated in both adults and children, using HC administration of various types of volatile agents, for example, halothane\textsuperscript{5} or sevoflurane, delivered via carrier gas (with or without nitrous oxide). Studies have consistently shown that the SBVC\textsuperscript{6, 13–16}, HC\textsuperscript{2} technique results in faster induction of anaesthesia than incremental TV technique, in both adults and children.

The SBVC-HC sevoflurane technique has been shown to be an efficient and well-accepted technique in children as young as 4 yr old, with an acceptance rate up to 95% in older children.\textsuperscript{35} It is associated with few haemodynamic side-effects or airway complications,\textsuperscript{35, 36} and it remains very popular with paediatric anaesthetists.\textsuperscript{37}

However, the effect of nitrous oxide in the gas mixture remained equivocal. In our study, SBVC-HC inhalation induction using a circle system primed with >7% sevoflurane delivered by 6 litre min\textsuperscript{-1} FGF yielded an approximate induction time of 53.6 s with nitrous oxide, and 63.5 s without nitrous oxide. Similar induction timings were reported by Dubois and colleagues\textsuperscript{22} and Ho and colleagues.\textsuperscript{31} Two other paediatric studies\textsuperscript{5, 6} found shorter induction times, probably because patients were premedicated, and non-circle delivery systems with higher gas flows, such as the Ayre’s T-piece, were used.

Despite presenting a lower sevoflurane concentration in the nitrous oxide group, our study consistently showed a small but statistically significant faster induction time when nitrous oxide was used as a carrier gas using an SBVC-HC technique. This was also shown by Dubois and colleagues,\textsuperscript{22} although the TV technique was used in her study. These findings are in contrast to three adult studies by Yurino and Kimura\textsuperscript{38} (SBVC), Siau and Liu,\textsuperscript{25} and O’Shea and colleagues\textsuperscript{24} (TV technique for both), which failed to show a difference in time to induction of anaesthesia, although ’motor endpoints’ (time taken for the outstretched arm to drop, and cessation of finger tapping) were used in the latter two studies. The discrepancy may be due to different endpoints being chosen.

The effects of nitrous oxide on the incidence of excitation and involuntary limb movement in our study also differed from other studies. Fernandes and colleagues\textsuperscript{39} and O’Shea and colleagues\textsuperscript{26} found that excitation was more frequent in adults receiving nitrous oxide than those receiving oxygen only. Siau and Liu\textsuperscript{25} reported nitrous oxide conferred no benefit in the reduction in involuntary movements, whereas Dubois and colleagues\textsuperscript{22} found that nitrous oxide reduced the incidence of excitation. Our study found that the addition of nitrous oxide resulted in a smoother induction and a decreased incidence of excitatory movements. The difference between adult and paediatric studies may be explained by the fact that the minimum alveolar concentration (MAC) requirements decreases with age.\textsuperscript{29} At a similar end-tidal concentration of inhaled anaesthetic agent, a child may still be in stage 2, the excitatory stage of anaesthesia, when compared with an adult. Hence the addition of nitrous oxide, which allows a more rapid achievement of a higher MAC, would result in a smoother induction with less time in stage 2 of anaesthesia.

The use of nitrous oxide has been challenged due to its postulated deleterious effects on the haematological system and cardiovascular system after prolonged exposure, especially in patients at risk.\textsuperscript{40} The effects of raised plasma homocysteine levels after nitrous oxide anaesthesia in children warrant further investigation.\textsuperscript{41} However, we found that nitrous oxide still has significant advantages as a co-induction agent for sevoflurane inhalation induction using the SBVC-HC technique in children, resulting in a faster and smoother induction. This was achieved using a circle system with efficient scavenging, hence reducing theatre and environmental pollution. At the recommended

### Table 3 Changes in inspired sevoflurane ($F_{\text{sevo}}$), expired sevoflurane ($E_{\text{sevo}}$), SAP, and HR during SBVC-HC induction, with and without nitrous oxide

<table>
<thead>
<tr>
<th>Variables</th>
<th>Time from start of induction (min)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F_{\text{sevo}}$ (% ± SD)</td>
<td>Group A</td>
<td>8.08 (0.53)</td>
<td>7.67 (0.84)</td>
<td>7.33 (0.79)</td>
<td>6.44 (1.54)</td>
<td>5.30 (1.73)</td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td>7.64 (0.49)</td>
<td>7.46 (0.59)</td>
<td>7.28 (0.59)</td>
<td>6.57 (1.02)</td>
<td>5.07 (1.72)</td>
</tr>
<tr>
<td>$E_{\text{sevo}}$ (% ± SD)</td>
<td>Group A</td>
<td>3.60 (3.85)</td>
<td>5.85 (1.41)</td>
<td>5.93 (1.04)</td>
<td>5.45 (1.13)</td>
<td>4.59 (1.39)</td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td>3.67 (3.95)</td>
<td>5.50 (1.62)</td>
<td>6.08 (1.09)</td>
<td>5.64 (0.87)</td>
<td>4.59 (1.38)</td>
</tr>
<tr>
<td>SAP (mm Hg) (± SD)</td>
<td>Group A</td>
<td>99.06 (1.37)</td>
<td>99.37 (1.22)</td>
<td>99.71 (0.94)</td>
<td>99.60 (1.27)</td>
<td>99.79 (0.49)</td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td>98.11 (4.98)</td>
<td>99.05 (1.29)</td>
<td>99.32 (1.29)</td>
<td>99.22 (1.46)</td>
<td>99.47 (1.16)</td>
</tr>
<tr>
<td>HR (beats min\textsuperscript{-1} ± SD)</td>
<td>Group A</td>
<td>86.95 (14.22)</td>
<td>97.78 (16.60)</td>
<td>104.25 (21.97)</td>
<td>103.62 (28.71)</td>
<td>94.61 (23.04)</td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td>88.97 (16.54)</td>
<td>92.89 (17.07)</td>
<td>95.84 (20.87)</td>
<td>93.18 (23.45)</td>
<td>88.58 (24.32)</td>
</tr>
</tbody>
</table>
occupational exposure limits, there is no conclusive evidence for reproductive, genetic, haematological, or neurological occupational toxicity from nitrous oxide exposure. Nitrous oxide remains to be a useful inhalation analgesic and sedative that is cheap and has a long history of use in various clinical settings. Further research is needed to weigh the risk–benefit ratio of using this agent for anaesthesia in the paediatric population.

In conclusion, we found that the addition of nitrous oxide resulted in less excitement and marginally faster induction times, as defined by the time to loss of eyelash reflex. Overall, we also established that the SBVC-HC sevoflurane technique was pleasant with most children choosing to have it again.

Despite movement away from the use of nitrous oxide, it may still have a beneficial role in SBVC-HC sevoflurane induction in children. Further studies need to be done to evaluate if short exposure to nitrous oxide during induction alone has the same adverse effects as when used for a longer period during maintenance of anaesthesia, to the patients and healthcare personnel.

Declaration of interest
None declared.

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