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Research Article

Effect of Nitrous Oxide–Oxygen Mixture versus Oxygen Alone on Propofol Induction Dose, Induction Time, and Haemodynamic Response to Laryngoscopy: A Randomised, Single-Blinded Trial

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Abstract

Background and Aims: Propofol is a widely used induction agent but produces dose-related cardiovascular depression. Nitrous oxide (N_2O), through its analgesic and second-gas effects, may reduce propofol requirements. We compared the effect of an inhaled N_2O–O_2 mixture with oxygen alone on the induction dose of propofol, induction time, oxygen saturation and haemodynamic response to laryngoscopy in adults undergoing elective surgery under general anaesthesia.

Methods: Sixty adults (American Society of Anesthesiologists [ASA] physical status I–II, aged 20–60 years) were randomised by a block-of-four schedule into Group PN (67% N_2O + 33% O_2 at 6 L/min, n=30) or Group PO (100% O_2 at 6 L/min, n=30). After 3 min of preoxygenation and 1 min of gas exposure, propofol was infused at 10 mg every 20 s (30 mg/min) until loss of eyelash reflex. Heart rate (HR), systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP) and peripheral oxygen saturation (SpO_2) were recorded at eight time points (T0–T7). The primary outcome was propofol induction dose; secondary outcomes were induction time, SpO_2 and haemodynamic parameters. Statistical analysis was performed with SPSS v21 using Student's t-test, Mann–Whitney U, Chi-square or Fisher's exact test; $p<0.05$ was significant.

Results: Groups were comparable at baseline. The mean induction dose of propofol was significantly lower in Group PN (69.23 ± 10.23 mg) than in Group PO (98.97 ± 16.87 mg; $p<0.001$), a reduction of approximately 30%. Induction time was also shorter in Group PN (138.47 ± 20.46 s vs 197.93 ± 33.73 s; $p<0.001$). HR and MAP after laryngoscopy and intubation were more stable in Group PN, with a maximal MAP rise of 9% versus 14% in Group PO ($p<0.001$ at T3–T7). SpO_2 remained ≥99% throughout in both groups, with no episodes of desaturation.

Conclusion: Co-administration of an N_2O–O_2 mixture during propofol induction

significantly reduced the induction dose and induction time of propofol and attenuated the haemodynamic response to laryngoscopy, without compromising oxygenation. N_2O remains a useful adjunct during intravenous induction in ASA I–II adults, with particular relevance to cost-constrained settings.

Keywords: Propofol; Nitrous oxide; Anaesthesia induction; Laryngoscopy; Haemodynamics; Oxygen saturation.

Introduction

General anaesthesia is a composite state requiring unconsciousness, amnesia, analgesia, suppression of autonomic responses and immobility. These endpoints are rarely achieved safely with a single agent; balanced anaesthesia combines drugs so that each is used at a lower, safer dose. Propofol is the most widely used intravenous induction agent because of its smooth, rapid onset, favourable recovery profile, antiemetic action and depression of airway reflexes. However, propofol has no meaningful analgesic effect and produces dose-related decreases in systemic vascular resistance, myocardial contractility and arterial blood pressure, together with transient apnoea. These effects are particularly undesirable in elderly and high-risk patients.[1,2]

Nitrous oxide (N_2O) has been part of anaesthetic practice since the mid-nineteenth century. Although a weak anaesthetic, it possesses analgesic, anxiolytic and sympathomimetic properties, and, through the second-gas and concentration effects, augments the uptake of concurrently administered agents.[3,4] Reported N_2O–propofol combinations have shown reductions in propofol requirements of 30–50%, with attenuation of haemodynamic swings and potential cost savings.[1,5,6] The use of N_2O has declined in several high-income countries because of environmental and haematological concerns, but it remains widely used in developing countries owing to its cost-effectiveness and safety profile in appropriately selected patients.[7,8]

Laryngoscopy and endotracheal intubation elicit a stress response with tachycardia and hypertension that may be hazardous in patients with limited cardiovascular reserve. Deeper planes of anaesthesia—often achieved by rapid or higher-dose propofol bolus—blunt this response but at the cost of hypotension.[9] Adjuncts such as opioids, lignocaine and inhaled agents are commonly used to reconcile this trade-off. Whether pre-induction exposure to an N_2O–O_2 mixture can achieve the same balance—reducing propofol requirements, attenuating the pressor response and preserving oxygenation—has been studied in relatively few trials, particularly using clinically pragmatic slow-infusion techniques.[10–13]

The present randomised, single-blinded study was undertaken to compare an inhaled mixture of 67% N_2O and 33% O_2 with 100% oxygen during induction of general anaesthesia with slow-infusion propofol. We hypothesised that pre-induction inhalation of an N_2O–O_2 mixture would reduce the induction dose and induction time of propofol and blunt the haemodynamic response to laryngoscopy, without compromising peripheral oxygen saturation.

Methods

Ethics and registration

After approval by the Institutional Ethics Committee, Dr. S. N. Medical College, Jodhpur (Ref. No. SNMC/IEC/2020/Plan/314) and prospective registration with the Clinical Trials Registry–India (CTRI/2020/11/028928), the study was conducted in the Department of Anaesthesiology and Critical Care at Dr. S. N. Medical College and Associated Group of Hospitals, Jodhpur. Written informed consent was obtained from every participant.

The study was conducted in accordance with the Declaration of Helsinki and ICMR/GCP guidelines.

Study design and participants

This was a single-blinded, parallel-group, randomised controlled trial. Sixty adults aged 20–60 years, of either sex, ASA physical status I or II, body mass index (BMI) 20–35 kg/m², Mallampati class I or II, scheduled for elective non-cardiac surgery under general anaesthesia with tracheal intubation, were enrolled. Exclusion criteria were patient refusal, pregnancy, anticipated difficult airway (Cormack–Lehane view III or IV), morbid obesity, shock, chronic obstructive lung disease, bronchial asthma, interstitial lung disease, uncontrolled hypertension, allergy to study drugs, and any relative contraindication to N_2O (intestinal obstruction, middle-ear surgery, pneumothorax, air embolism).

Randomisation and blinding

Participants were randomised in a 1:1 ratio to Group PN (N_2O + O_2) or Group PO (100% O_2) using block randomisation with a block size of four, yielding 15 balanced blocks. Allocation was concealed by sequentially numbered sealed opaque envelopes and revealed only at induction by the attending anaesthesiologist who administered the gas mixture. The participant was blinded to group allocation (single-blind design).

Sample size

Sample size was calculated using the formula for comparison of two means:

$$n = 2 \times (Z_{1-\alpha/2} + Z_{1-\beta})^2 \times \sigma^2 / (\mu_1 - \mu_2)^2$$

Taking $\alpha = 0.05$ ($Z = 1.96$), power = 90% ($Z = 1.28$), pooled standard deviation $\sigma = 15.78$ mg and expected difference in mean propofol induction dose $\mu_1 - \mu_2 = 25.57$ mg from the reference study by Jain et al.,[6] the minimum sample size was calculated as 9 per group. To improve precision, this was expanded to 30 per group (n = 60 total).

Anaesthetic protocol and intervention

All patients received oral alprazolam 0.5 mg on the night before surgery and were kept fasting overnight. On arrival in the operating room, standard monitoring (electrocardiography, non-invasive blood pressure, pulse oximetry) was established and baseline parameters recorded (T0). Two 20-G intravenous cannulae were secured, and Ringer's lactate was started. Premedication consisted of intravenous glycopyrrolate 4 µg/kg, ondansetron 80 µg/kg and fentanyl 1 µg/kg.

Preoxygenation was performed with 100% O_2 at 6 L/min via a tight-fitting facemask and a closed circuit with CO_2 absorber for 3 min (T1). Group PN then received 67% N_2O (4 L/min) + 33% O_2 (2 L/min) for 1 min, while Group PO continued to receive 100% O_2 at 6 L/min (T2). Propofol 1% was then infused at 10 mg every 20 s (30 mg/min) until loss of response to verbal command; loss of eyelash reflex confirmed the endpoint. The propofol dose consumed and the time from start of infusion to loss of response were recorded as the induction dose and induction time, respectively (T3). Succinylcholine 2 mg/kg (in the original protocol; atracurium 0.5 mg/kg was used where succinylcholine was contraindicated) was given, and direct laryngoscopy with a Macintosh blade and tracheal intubation with an appropriately sized cuffed tube were performed after approximately 1 min. Anaesthesia was maintained with O_2, N_2O and a volatile agent. At the end of surgery, neuromuscular blockade was reversed with neostigmine 50 µg/kg and glycopyrrolate 10 µg/kg intravenously, and the trachea was extubated.

Outcomes and measurement time points

The primary outcome was the induction dose of propofol (mg). Secondary outcomes were induction time (s), peripheral oxygen saturation (SpO_2, %), and haemodynamic parameters (heart rate [HR], systolic [SBP], diastolic [DBP] and mean arterial pressure

[MAP], mmHg). These were recorded at eight time points: baseline (T0), after 3 min of preoxygenation (T1), after 1 min of study gas inhalation/pre-induction (T2), immediately after loss of response (T3), immediately after intubation (T4), and at 2, 5 and 10 min after intubation (T5–T7). Adverse events (hypoxia, respiratory depression, allergic reactions) were monitored throughout.

Statistical analysis

Data were entered in Microsoft Excel and analysed using SPSS v21 (IBM Corp., Armonk, NY, USA). Normality was assessed by the Shapiro–Wilk test. Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range) and were compared using the unpaired Student's t-test or Mann–Whitney U test as appropriate. Categorical variables were compared using the Chi-square test or Fisher's exact test. A two-tailed p value <0.05 was considered statistically significant.

CONSORT flow

Sixty consecutive eligible patients were assessed, all consented, and all were randomised (30 per group). All 60 participants received the allocated intervention, were followed through the intraoperative period and were included in the final analysis (no post-randomisation exclusions or losses to follow-up). A CONSORT flow diagram should accompany the manuscript at submission.

Results

Sixty patients were randomised and all completed the study. The two groups were comparable in age, sex, weight, BMI and ASA physical status (Table 1). Approximately 60% of participants in each group were ASA I, and women accounted for 53–60% of participants.

Table 1. Baseline demographic and clinical characteristics of the two study groups.

Variable	Group PN (n=30)	Group PO (n=30)	p value
Age (years), mean ± SD	43.50 ± 11.88	38.53 ± 12.86	0.10
Sex (M/F), n	14 / 16	12 / 18	0.60
Weight (kg), mean ± SD	68.13 ± 9.16	68.80 ± 8.85	0.77
BMI (kg/m²), mean ± SD	24.71 ± 2.38	25.21 ± 1.59	0.34
ASA I / II, n	18 / 12	18 / 12	1.00

Group PN, propofol + nitrous oxide–oxygen mixture; Group PO, propofol + 100% oxygen; SD, standard deviation; ASA, American Society of Anesthesiologists physical status.

Primary outcome: induction dose of propofol

The mean induction dose of propofol was significantly lower in Group PN (69.23 ± 10.23 mg) than in Group PO (98.97 ± 16.87 mg; p<0.001), corresponding to a reduction of approximately 30%. When expressed as a weight-adjusted dose, 46.7% of patients in Group PN required only 0.5–1.0 mg/kg for induction, and only 13.3% required more than 1.5 mg/kg. In Group PO, no patient was induced with less than 1.0 mg/kg and 56.7% required more than 1.5 mg/kg (p<0.001) (Table 2).

Secondary outcomes

Induction time was significantly shorter in Group PN (138.47 ± 20.46 s) than in Group PO (197.93 ± 33.73 s; p<0.001). Loss of response was achieved in less than 150 s in 76.7% of Group PN patients versus 10% of Group PO patients (Table 2).

Baseline SpO_2 was 98.93 ± 0.91% in Group PN and 98.60 ± 1.16% in Group PO (p=0.22). After preoxygenation and throughout induction, laryngoscopy and the post-intubation period, SpO_2 remained at 99.7–100% in both groups with no between-group difference at any time point (Table 2). No episode of desaturation was recorded

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Table 2. Primary and secondary outcomes: induction dose of propofol, induction time and peripheral oxygen saturation.

Outcome	Group PN (n=30)	Group PO (n=30)	p value
Induction dose of propofol (mg), mean ± SD	69.23 ± 10.23	98.97 ± 16.87	<0.001
Induction dose <1.0 mg/kg, n (%)	14 (46.7)	0 (0.0)	<0.001
Induction dose 1.01–1.5 mg/kg, n (%)	12 (40.0)	13 (43.3)	—
Induction dose >1.5 mg/kg, n (%)	4 (13.3)	17 (56.7)	—
Induction time (s), mean ± SD	138.47 ± 20.46	197.93 ± 33.73	<0.001
Induction time <150 s, n (%)	23 (76.7)	3 (10.0)	<0.001
Baseline SpO_2 (%), mean ± SD	98.93 ± 0.91	98.60 ± 1.16	0.22
SpO_2 after preoxygenation (%)	99.70 ± 0.53	99.60 ± 0.50	0.46
SpO_2 after induction (%)	99.90 ± 0.30	100.00 ± 0.00	0.08
SpO_2 post-intubation (T4–T7) (%)	100.00 ± 0.00	100.00 ± 0.00	1.00

SD, standard deviation; SpO_2, peripheral oxygen saturation.

Haemodynamic response

Baseline HR, SBP, DBP and MAP were comparable between groups (p>0.05 at T0–T2) (Table 3). Immediately after induction (T3), MAP fell by approximately 9% in Group PN and 14% in Group PO. In Group PO, the fall in DBP after induction was 17%, whereas in Group PN it was 10%. Following laryngoscopy and intubation (T4), Group PO showed a pronounced pressor and tachycardic response: mean HR rose from a preinduction value of 79.33 ± 3.41 beats/min to a peak of 96.33 ± 6.91 beats/min at T5 (approximately 13% rise from baseline), and MAP rose to 102.13 ± 3.26 mmHg at T6. In Group PN, the corresponding rises were smaller: HR peaked at 88.60 ± 3.83 beats/min at T5 (about 5% rise) and MAP peaked at 96.57 ± 3.76 mmHg at T6. Between-group differences at T3–T7 were statistically significant for HR, SBP, DBP and MAP (p<0.001). No clinically significant hypotension or bradycardia requiring intervention occurred in either group

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Table 3. Heart rate and arterial blood pressures at each measurement time point (mean ± SD). Between-group p values were >0.05 at T0–T2 and <0.001 at T3–T7 for HR, SBP, DBP and MAP.

Time point	HR (bpm) PN	HR (bpm) PO	SBP (mmHg) PN	SBP (mmHg) PO	DBP (mmHg) PN	DBP (mmHg) PO	MAP (mmHg) PN	MAP (mmHg) PO
T0 Baseline	84.33±6.11	83.50±7.24	129.10±5.86	130.57±4.74	84.43±4.71	86.33±4.43	99.33±5.01	101.13±4.32
T1 Post-preoxygenation	83.30±4.97	81.43±4.19	130.30±5.49	130.53±6.59	82.70±4.92	84.07±3.88	98.60±4.80	100.20±3.96
T2 Pre-induction	81.33±5.23	79.33±3.41	126.20±5.10	126.73±5.26	81.13±4.12	83.03±3.71	96.07±3.80	97.57±3.39
T3 Post-induction	83.03±4.59	88.43±7.49	121.43±3.76	117.10±5.42	75.67±2.82	70.53±3.99	90.90±2.43	86.01±3.50
T4 Immediate post-intubation	87.87±3.73	94.87±7.40	124.57±3.81	132.23±6.04	78.43±4.50	83.20±4.12	93.77±3.32	99.53±3.46
T5 2 min post-intubation	88.60±3.83	96.33±6.91	126.83±4.08	134.07±5.39	78.23±5.90	82.10±3.59	94.37±4.38	99.43±3.05
T6 5 min post-intubation	86.80±5.55	90.37±5.78	127.87±5.53	136.17±4.20	80.90±4.86	85.07±3.88	96.57±3.76	102.13±3.26
T7 10 min post-intubation	84.01±6.22	89.83±5.41	123.83±7.12	130.53±6.59	80.47±5.84	84.23±4.55	94.90±4.66	99.67±3.10

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PN, propofol + N_2O–O_2; PO, propofol + 100% O_2.

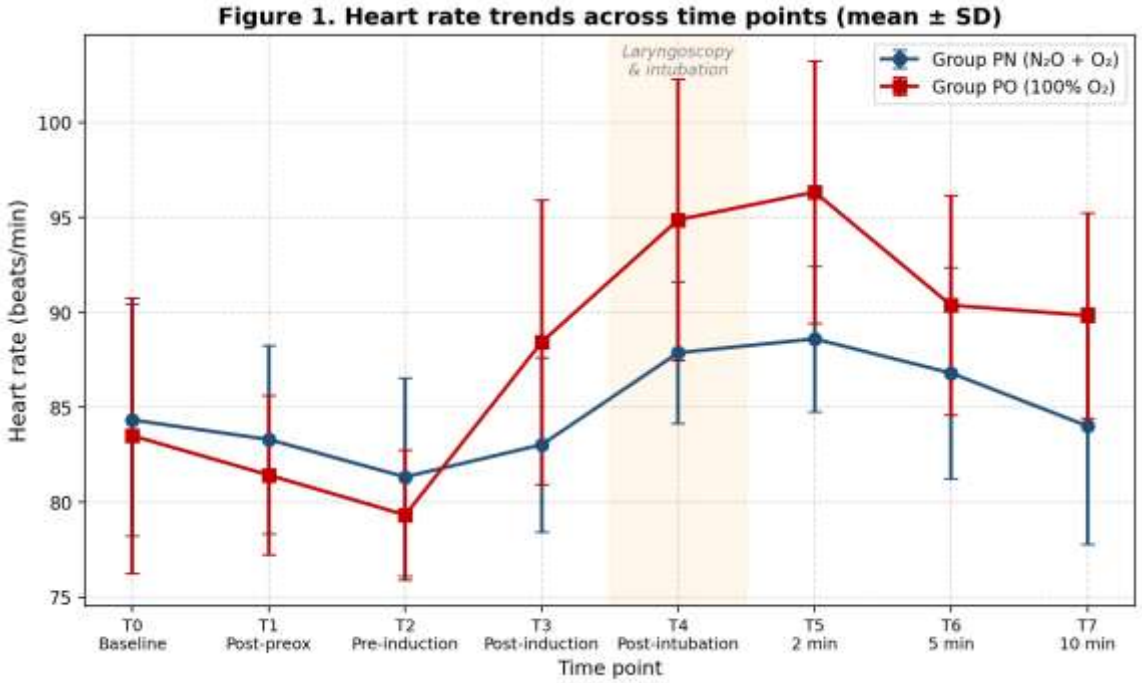

Figure 1. Heart rate (mean ± SD) at each measurement time point (T0–T7) in Group PN (propofol + N_2O–O_2 mixture) and Group PO (propofol + 100% O_2). Between-group differences were non-significant at T0–T2 and statistically significant at T3–T7 ($p<0.001$).

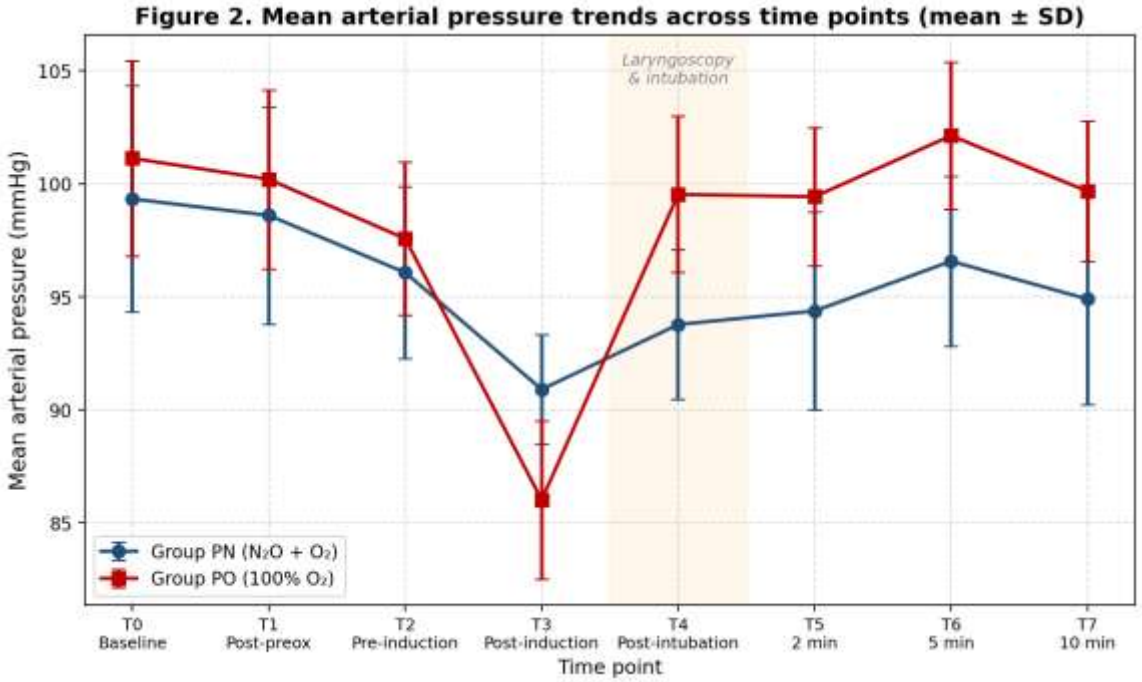

Figure 2. Mean arterial pressure (mean ± SD) at each measurement time point (T0–T7) in Group PN and Group PO. The pressor response to laryngoscopy and intubation (T4–T7) was markedly attenuated in Group PN. Between-group differences were significant at T3–T7 ($p<0.001$).

Discussion

The principal finding of this randomised trial is that pre-induction inhalation of a 67% N_2O – 33% O_2 mixture, combined with a slow-infusion propofol technique (30 mg/min), reduced the induction dose of propofol by approximately 30% and shortened induction time by approximately 60 s compared with 100% oxygen. Haemodynamic response to laryngoscopy and intubation was attenuated in the N_2O group, and SpO_2 remained above 99% throughout in both groups. These results support the continued use of N_2O as an inexpensive, effective adjunct to propofol during induction of general anaesthesia in ASA I–II adults.

The observed 30% reduction in propofol dose is broadly consistent with earlier work. Ng and Hwang reported that inhalation of N_2O for one minute before slow propofol infusion (20 mg/min) reduced propofol requirements and induction time.[1] Jain et al. compared 67% N_2O + 33% O_2 with 100% O_2 during propofol induction in 80 patients and found a significantly lower induction dose and time with N_2O, with stable haemodynamics.[6] Sanjeev et al. observed 35–40% dose reduction and shorter induction time with a similar protocol.[9] Ranjan et al., in 150 patients, likewise demonstrated a substantially lower propofol dose (30.4 ± 26.17 mg) and induction time (1.52 ± 1.3 min) in the N_2O group compared with 101.87 ± 26.17 mg and 5.09 ± 1.3 min in the oxygen-only group.[12] Peacock et al. demonstrated that a slower propofol infusion rate reduces the total induction dose, and our slow-infusion protocol likely amplified the dose-sparing effect of N_2O.[10]

Two mechanisms plausibly underlie these observations. First, the second-gas and concentration effects accelerate the alveolar and cerebral uptake of any concurrently administered agent; although these classical

Fink phenomena apply most obviously to inhaled agents, an analogous pharmacodynamic potentiation is seen when N_2O is co-administered with intravenous hypnotics, reducing the plasma concentration required for loss of consciousness. Second, N_2O itself contributes analgesic and mild hypnotic effects mediated by activation of periaqueductal grey opioid receptors and descending noradrenergic inhibition, as well as antagonism of NMDA receptors. Propofol acts primarily via allosteric potentiation of GABA_A receptors, and the combination of GABAergic hypnosis with N_2O-mediated NMDA antagonism yields additive hypnotic–anaesthetic effect at reduced propofol doses.[1,3]

The haemodynamic pattern we observed is also mechanistically coherent. Propofol produces dose-related reductions in systemic vascular resistance and myocardial contractility, typically decreasing MAP by up to 15–25% at conventional bolus doses.[10] In our study, the post-induction fall in MAP was 9% in Group PN versus 14% in Group PO, consistent with the lower propofol dose in the N_2O group and with the mild sympathomimetic action of N_2O, which increases central sympathetic outflow and catecholamine release. This offset the anticipated propofol-related decrease in HR, resulting in a small but significant post-induction tachycardia in Group PN. Following laryngoscopy and intubation, the pressor response was markedly attenuated in Group PN—consistent with the findings of Adachi et al., who showed that N_2O co-administered with propofol during slow infusion effectively prevents the pressor response to orotracheal intubation without adverse cardiovascular depression,[11] and Shiga et al., who reported minimal haemodynamic and Doppler-derived changes when N_2O was added to therapeutic-dose propofol.[13] Carlier et al.

did not find additional haemodynamic benefit from N_2O in a small trial using a bolus propofol technique,[14] a discrepancy likely explained by the different induction technique and higher propofol dose used in that study.

SpO_2 remained essentially unchanged throughout the study period in both groups. This mirrors the observations of Khoo et al., who found that a pre-induction inhalation of 50% N_2O in oxygen provided effective preoxygenation and augmented the propofol induction without compromising oxygenation.[15] Because our patients received 3 min of 100% oxygen preoxygenation before the study gas was switched on, any theoretical dilution of alveolar oxygen by 67% N_2O was more than offset by the very high initial FRC oxygen content.

Clinically, the observations have several implications. A 30% reduction in propofol induction dose translates into lower drug expenditure, an important consideration in resource-limited settings where the price differential between N_2O and propofol favours the former.[7] The attenuation of the intubation pressor response is likely to be of most benefit in patients with limited myocardial reserve, cerebrovascular disease or raised intracranial pressure, in whom hypertensive surges are especially undesirable. The shorter induction time—albeit of small absolute magnitude—may improve operating-room throughput. Finally, the stable oxygenation profile supports the safety of an N_2O–O_2 mixture as an adjunct during induction in appropriately selected patients.

Balancing these benefits against known concerns is essential. Prolonged or repeated exposure to N_2O inactivates methionine synthase via oxidation of vitamin B_{12}, with the potential for megaloblastic changes, hyperhomocysteinaemia and, in the

postoperative context, an association with wound and cardiovascular complications in some observational data. N_2O also expands closed gas-containing spaces and is a greenhouse gas. Our study was confined to a short induction window in healthy adults; the ENIGMA-II trial and subsequent European Society of Anaesthesiology consensus concluded that short-duration N_2O use during induction and maintenance in elective surgery has an acceptable safety profile.[4] The present data support that view within their scope of application.

Limitations

This study has several limitations. It was single-centre, single-blinded and included a modest sample of ASA I–II adults undergoing elective non-cardiac surgery; the findings should not be extrapolated to higher-risk populations, emergency settings or paediatric patients. Bispectral index or other objective measures of anaesthetic depth were not used, and loss of eyelash reflex was the only endpoint for induction. Long-term outcomes, postoperative nausea and vomiting, and haematological parameters were not evaluated. Finally, the observed difference in induction dose (29.74 mg) closely matched the assumption used in the sample size calculation (25.57 mg), providing internal consistency, but replication in larger and more heterogeneous populations is warranted.

Conclusion

In ASA I–II adults undergoing elective surgery, pre-induction inhalation of a 67% N_2O + 33% O_2 mixture, combined with slow-infusion propofol, reduced the induction dose of propofol by approximately 30% and shortened induction time compared with 100% oxygen. Peripheral oxygen saturation was preserved, and the haemodynamic response to laryngoscopy and intubation was attenuated. N_2O remains a useful, low-cost adjunct during propofol induction of general anaesthesia in appropriately selected patients.

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