Section: Anaesthesia

Original Research Article

EFFECT OF INHALED NITROUS OXIDE ON INDUCTION TIME AND DOSE REQUIREMENT OF PROPOFOL: A PROSPECTIVE RANDOMISED STUDY

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Received *: 02/04/2025*
Received in revised form *: 16/05/2025*
Accepted *: 03/06/2025*

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DOI: 10.70034/ijmedph.2025.2.483

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2025; 15 (2); 2663-2668

ABSTRACT

Background: Propofol induction can cause hemodynamic instability at higher doses. Nitrous oxide (N_2O) may reduce propofol requirements and improve induction. **Objective:** To evaluate the effect of N_2O on propofol induction dose, induction time, and hemodynamic stability in elective surgery patients.
Materials and Methods: Patients were randomized into two groups: Group N (N_2O + oxygen + propofol) and Group O (oxygen + propofol). Induction dose, time, and hemodynamics (HR, BP, MAP and SpO_2) were recorded.
Results: Group N showed a significant reduction in mean induction dose of propofol (70.67 mg) compared to Group O (121.33 mg). Induction time was also significantly shorter in Group N. Hemodynamic parameters (HR, SBP, DBP, MAP, and SpO_2) remained stable throughout the peri-induction period in both groups, with Group N demonstrating better maintenance of blood pressure. No adverse effects or complications related to hemodynamic instability were observed.
Conclusion: Coadministration of N_2O during propofol induction significantly reduces the induction dose and time, improving safety by minimizing propofol-related adverse effects.
Keywords: Anaesthesia; Hemodynamics; Induction Time; Nitrous Oxide; Propofol; Stability.

INTRODUCTION

General anaesthesia is a medically induced state of unconsciousness characterized by the loss of defensive reflexes, achieved through the use of various anesthetic agents. It ensures immobility, analgesia, and amnesia during surgical procedures. However, it can be accompanied by challenges such as airway obstruction, inadequate ventilation requiring mechanical support, and potential cardiovascular impairments.[1] To mitigate these issues, a thorough understanding of anesthetic agents and their interactions is critical.

Propofol (2,6-diisopropylphenol) remains the most widely used intravenous agent for induction of general anaesthesia due to its rapid onset, smooth induction, and favorable recovery profile. It is particularly suited for procedures requiring quick psychomotor recovery, such as ambulatory and neurosurgical cases, where reduced postoperative cognitive dysfunction and faster discharge times are crucial.[2] Propofol is known for its ability to provide superior intubating conditions while maintaining upper airway integrity. It is versatile, being used not only as an induction agent but also for procedural sedation during monitored anaesthesia care and in intensive care units for sedation of mechanically ventilated patients.

Despite these advantages, propofol's dose-dependent cardiovascular effects, including significant reductions in arterial blood pressure and heart rate, necessitate careful dosing, particularly in elderly or high-risk patients with limited cardiovascular reserve.[3] Additionally, its narrow therapeutic index and the potential for apnea upon induction demand

close monitoring and titration. Propofol's preparation in a lipid emulsion, which contributes to its characteristic milky white appearance, poses risks such as pain on injection and the rare occurrence of propofol infusion syndrome (PRIS) during prolonged administration, especially in critically ill patients. Nonetheless, its favorable pharmacokinetic and pharmacodynamic profile, including rapid redistribution and metabolism, short context-sensitive half-life, and low incidence of postoperative nausea and vomiting, makes it indispensable in modern anaesthesia practice.[3]

Efforts to optimize propofol dosing have led to the exploration of adjuvants like nitrous oxide (N_2O), an inhalational anesthetic widely recognized for its potent analgesic properties and minimal respiratory and hemodynamic effects. Unlike other volatile anesthetics, N_2O provides analgesia without causing significant muscle relaxation, making it a valuable adjunct in multimodal anaesthesia strategies.[4] Additionally, the use of N_2O has been associated with a reduction in the induction dose of propofol, potentially mitigating its cardiovascular side effects.[5]

Studies have demonstrated that combining N_2O with propofol not only maintains stable hemodynamic parameters but also shortens induction time and improves overall anaesthesia outcomes6. This prospective, randomized study specifically aims to evaluate the effects of inhaled N_2O on the induction dose and time of propofol, alongside its impact on hemodynamic variations. By exploring the synergistic potential of this combination, the findings could provide valuable insights into optimizing anaesthesia protocols for safer and more effective clinical outcomes.

MATERIALS AND METHODS

Study Design and Population

This prospective, randomized study was conducted at School of Medicine, D.Y. Patil Hospital, D.Y. Patil University Navi Mumbai, to evaluate the effects of inhaled N_2O on induction time, dose requirements of propofol, and associated hemodynamic variations. The study included a total of 60 patients who were randomly allocated into two groups (Group N and Group O) using the closed envelope technique, with 30 patients in each group. Ethical clearance was obtained from the Institutional Ethics Committee (Ref No:DYP/IECBH/2021/048; Dated 4/3/2021), and written informed consent was secured from all participants. A detailed Patient Information Sheet (PIS) outlining the study protocol and potential risks was provided to ensure comprehensive understanding and voluntary participation.

Sample Size Estimation

The sample size was calculated based on data reported by Jain et al., 2016 regarding the induction dose of propofol with and without N_2O inhalation5. The induction time for propofol without N_2O was 81.67 ± 17.64 seconds, while with N_2O it was 56.10 ± 13.92 seconds. Using a two-sample test to compare independent means, an estimated sample size of 9 per group was sufficient to achieve 90% power at a significance level of 0.05 (Type I error). To enhance the robustness of the study, 30 patients were included in each group, resulting in a total sample size of 60.

Eligibility Criteria and Study Parameters

The study included patients aged 18 to 60 years with American Society of Anesthesiologists (ASA) physical status I or II, who were scheduled for elective minor to major surgeries requiring general anaesthesia. Patients were excluded if they were pregnant, morbidly obese, had a history of bronchial asthma, diabetes mellitus with complications, drug allergies, or had contraindications to the use of N_2O during anaesthesia induction, such as intestinal obstruction, middle ear disease, pneumothorax, air embolism, or were undergoing sinus or middle ear surgery. The study was conducted over a three-year period from 2020 to 2023. Primary outcomes assessed were the induction dose of propofol and induction time. Secondary outcomes included hemodynamic parameters such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), oxygen saturation (SpO_2), and respiratory rate (RR). Demographic data including age, weight, gender, ASA physical status, and operative procedure details were also recorded.

Procedure

All patients underwent a thorough preanesthetic evaluation, during which the anaesthesia technique was explained, and written informed consent was obtained. They were kept nil per oral overnight, and tablet Alprazolam 0.25 mg was administered the night before surgery to reduce anxiety. Upon arrival in the operating theatre, standard monitors were attached, and HR, MAP, SBP, DBP, and SpO_2 were recorded. After securing intravenous access, patients were premedicated with glycopyrrolate 4 µg/kg, ondansetron 0.1 mg/kg, and fentanyl 2 µg/kg. Both groups received 3 minutes of preoxygenation with 100% oxygen. In Group N, the closed circuit was primed with 4 L/min N_2O and 2 L/min oxygen for 1 minute, and patients breathed this mixture via a face mask. Group O received 6 L/min oxygen only. Propofol was administered at a titrated rate of 20 mg every 10 seconds until loss of verbal response (i.e., inability to open eyes), which was recorded as the induction time; the total amount of propofol given was noted as the induction dose. Hemodynamic parameters (HR, MAP, SBP, DBP, SpO_2) were monitored at specific intervals: baseline (T0), after preoxygenation (T1), after induction (T2), and at 2, 4, 6, and 10 minutes after the start of propofol administration (T3-T6). Any complications, such as apnea, vomiting, laryngospasm, or involuntary movements, were documented. Intubation was performed using atracurium, and general anaesthesia

was maintained with oxygen, N_2O, and sevoflurane. At the end of surgery, neuromuscular blockade was reversed with glycopyrrolate and neostigmine, followed by extubation.

Statistical Analysis

Data was verified for accuracy before analysis using MedCalc Statistical Software version 19.0.6 (MedCalc Software bvba, Ostend, Belgium). Continuous variables such as induction time and dose were expressed as means with standard deviations, while categorical and nominal data were presented as frequencies and percentages. Group comparisons for continuous variables were performed using an unpaired t-test, and ranked data was analyzed using the Mann-Whitney U test. Vital parameters were analyzed using repeated measures ANOVA, considering treatment groups as the main factor, time as a repeated measure, and age and ASA class as covariates. Categorical variables were compared using the chi-square test. Statistical significance was determined using two-sided tests with an alpha level of 0.05.

RESULTS

The demographic characteristics of participants in Groups N and O were comparable. Age-wise distribution showed no significant difference between the groups ($p = 0.85$), with most participants falling within the 18–30 years age group. The mean age was 34.46 ± 12.43 years in Group N and 32.06 ± 10.21 years in Group O, which was not statistically significant ($p = 0.12$) (Table 1). Gender distribution was also similar across the groups, with 36.67% males and 63.33% females in Group N, and 46.67% males and 53.33% females in Group O, indicating no significant difference ($p = 0.710$). In terms of induction time, Group N exhibited significantly shorter induction times compared to Group O (37.03 ± 6.53 seconds vs. 57.27 ± 11.64 seconds; $p = 0.0001$). Additionally, the induction dose required in Group N (70.67 ± 14.37 mg) was significantly lower than that in Group O (121.33 ± 30.71 mg; $p = 0.0000$) (Table 1).

Table 1: Demographic Characteristics, Induction Time, and Dose Comparison Between Group N and Group O

Parameter	Group N	Group O	p-value	Significance
Age-wise distribution				
18 to 30 years	15 (50%)	16 (53.33%)	0.85	Not Significant
31 to 40 years	8 (26.67%)	8 (26.67%)		
41 to 50 years	2 (6.67%)	4 (13.33%)		
51 to 60 years	5 (16.67%)	2 (6.67%)		
Mean ± SD	34.46 ± 12.43	32.06 ± 10.21	0.12	Not Significant
Gender-wise distribution				
Males	11 (36.67%)	14 (46.67%)		
Females	19 (63.33%)	16 (53.33%)	0.710	Not Significant
Induction time (seconds)				
Mean ± SD	37.03 ± 6.53	57.27 ± 11.64	0.0001	Significant
Induction dose (mg)				
Mean ± SD	70.67 ± 14.37	121.33 ± 30.71	0.0000	Significant

The comparison of hemodynamic parameters, including HR, SBP, and DBP, revealed notable differences between Groups N and O (Table 2). HR remained comparable between the groups across all time intervals, with no statistically significant differences observed. In contrast, Group O demonstrated significantly lower SBP at several post-induction intervals, including at 2 minutes (110.2 ± 17.6 mmHg vs. 119.2 ± 12.3 mmHg; $p = 0.02$), 6 minutes (111.0 ± 18.1 mmHg vs. 119.6 ± 13.5 mmHg; $p = 0.04$), and 10 minutes (107.5 ± 21.8 mmHg vs. 117.5 ± 11.9 mmHg; $p = 0.03$) when compared to Group N. Baseline DBP values were similar between the groups; however, Group O showed a trend toward lower DBP at later time points, with statistical significance approached at 4 minutes post-induction (65.0 ± 15.0 mmHg vs. 71.2 ± 9.0 mmHg; $p = 0.05$) (Table 2). These findings highlight significant differences in the SBP and trends in DBP between the two groups, while HR remained unaffected.

Table 2: Comparison of Hemodynamic Parameters Across Different Time Intervals in Groups N and O

Time Interval	HR		p	SBP		p	DBP		p
	Group N	Group O		Group N	Group O		Group N	Group O	
T0 Baseline	90.8 ± 16.9	91.3 ± 18.8	0.91	127.3 ± 14.1	123.5 ± 16.6	0.65	77.8 ± 8.2	75.2 ± 12.2	0.34
T1 Post Preoxy	88.2 ± 15.1	90.1 ± 15.8	0.62	125.7 ± 15.0	120.6 ± 12.2	0.15	77.0 ± 9.5	77.5 ± 11.3	0.84
T2 Induction	89.3 ± 17.5	91.7 ± 16.7	0.60	122.0 ± 10.8	114.0 ± 19.5	0.05	77.0 ± 10.8	71.3 ± 15.7	0.10
T3 2 mins	85.6 ± 16.9	89.8 ± 17.8	0.35	119.2 ± 12.3	110.2 ± 17.6	0.02	74.8 ± 9.5	68.6 ± 17.0	0.08
T4 4 mins	85.9 ± 11.5	88.4 ± 19.4	0.53	117.0 ± 12.3	109.8 ± 18.3	0.07	71.2 ± 9.0	65.0 ± 15.0	0.05
T5	85.4 ± 11.9	89.7 ± 15.9	0.24	119.6 ± 13.5	111.0 ± 18.1	0.04	72.5 ± 10.2	67.6 ± 18.5	0.20

6 mins									
T6 10 mins	86.1 ± 11.5	90.2 ± 17.9	0.30	117.5 ± 11.9	107.5 ± 21.8	0.03	72.2 ± 9.9	69.6 ± 14.0	0.41

The comparison of MAP and SpO_2 between Groups N and O revealed notable differences in MAP, with Group O consistently showing significantly lower values across all time intervals, including baseline, post-preoxygenation, and during the observation period. The differences were most pronounced after induction and at subsequent intervals. In contrast, SpO_2 levels remained stable at 100% in both groups throughout, indicating no differences in oxygenation. These findings highlight a significant reduction in MAP in Group O while maintaining adequate oxygen saturation in both groups.

Table 3: Comparison of MAP and SpO_2 Across Different Time Intervals in Groups N and O

Time Interval	MAP		p	SpO_2		p
	Group N	Group O		Group N	Group O	
T0 Baseline	95.03 ± 10.54	86.27 ± 13.99	0.008	100 ± 0	100 ± 0	1
T1 Post Preoxy	93.63 ± 13.32	86.10 ± 12.95	0.030	100 ± 0	100 ± 0	1
T2 Induction	93.00 ± 10.32	81.23 ± 18.23	0.003	100 ± 0	100 ± 0	1
T3 2 mins	90.33 ± 10.42	77.40 ± 16.31	0.000	100 ± 0	100 ± 0	1
T4 4 mins	87.20 ± 9.77	75.03 ± 16.36	0.000	100 ± 0	100 ± 0	1
T5 6 mins	89.27 ± 10.91	78.27 ± 19.31	0.008	100 ± 0	100 ± 0	1
T6 10 mins	86.77 ± 9.84	79.23 ± 15.22	0.026	100 ± 0	100 ± 0	1

DISCUSSION

The essential components of anaesthesia include immobility, unconsciousness, and suppression of autonomic responses, often achieved through a combination of inhaled and intravenous agents. Combining drugs allows for a reduction in individual drug dosages, minimizing adverse effects and enhancing safety. N_2O has been extensively documented to reduce the requirements of intravenous anesthetics such as propofol, thereby improving induction characteristics and minimizing the risks associated with higher doses, including significant hemodynamic changes.[7-9] Propofol, a widely used intravenous induction agent, is favored for its smooth and rapid induction, better intubating conditions, and rapid recovery. However, at higher doses, it is associated with profound hypotension and other hemodynamic alterations that often necessitate vasopressor support.[9-11] The addition of N_2O during induction has been shown to reduce propofol requirements by 30–50%, leading to less cardiovascular and respiratory depression, as well as cost savings.[12-16] Despite its declining use in some Western European countries, N_2O remains a key anaesthetic agent in developing countries due to its cost-effectiveness and ability to enhance induction outcomes, including faster onset and improved oxygenation.[39-43] This study was designed to evaluate the effects of inhaled N_2O on reducing the induction dose and time of propofol while assessing hemodynamic variations and adverse effects.

The age distribution was comparable between groups N and O in this study. The mean ages of groups N and O were 34.46 and 32.06 years, respectively. These findings are consistent with previous literature who reported mean ages of 39.8 and 39.35 years for the N2O and O2 groups, respectively5. Similar results were noted by Singh et al. (37.05 and 37.9 years) and Ng JM et al. (39 years for both groups), reinforcing the demographic similarities across studies.[17,18]

Gender distribution was also balanced, with 36.67% of group N and 46.67% of group O being male. These findings align with Jain K et al., who observed comparable gender distribution5. Singh et al. reported equal male representation (45%) in both groups, while Ng JM et al. noted differences, with 23.07% males in the N2O group and 41.02% in the O2 group.[17,18]

The mean induction time in this study was significantly shorter in group N compared to group O. This aligns with findings from Jain K et al., who also reported significantly reduced induction times in the N2O group compared to the O2 group5. Similarly, Ng JM et al. observed induction times of 133 seconds for the N2O group and 226 seconds for the O2 group ($p < 0.05$).[18] Other studies, including those by Singh et al. and Sunil et al., corroborate these results, consistently showing a shorter induction time with N2O administration.[17,19] The reduction in induction time can be attributed to the rapid onset of action associated with the anaesthetic properties of N2O. Also, this study revealed a significantly lower mean induction dose of propofol in group N (70.67 mg) compared to group O (121.33 mg). These findings are consistent with those of Jain K et al., who reported mean induction doses of 56.10 mg and 81.67 mg for the N2O and O2 groups, respectively.[5] Similarly, Ng et al. found induction doses of 75 mg in the N2O group and 133 mg in the

O2 group, while Singh et al. and Sunil et al. reported reductions in induction dose with N2O use.[17-19]

The reduction in induction dose with N2O can be attributed to its analgesic, anxiolytic, and hypnotic properties, which augment the effects of propofol. Studies by Peacock et al., Ng, and Hwang have highlighted the role of slower propofol infusion rates (20 mg/min) in minimizing the total dose required while maintaining an acceptable induction time.[18,20] Furthermore, Kumar et al. demonstrated a 27.48% reduction in propofol requirement with priming techniques, although their study noted hypotension in the control group, a complication not observed in this study.[21] The findings collectively suggests the dual advantage of N2O in reducing both induction time and the dose of propofol required, enhancing the efficiency and safety of the induction process. Additionally, the absence of significant cardiovascular complications in this study emphasizes the role of careful dose administration and supports the feasibility of using N2O to optimize anesthetic protocols.

In this study, the HR remained stable across different time intervals in both groups. In Group N, the mean HR at T0 (Baseline) was 90.83, and it gradually decreased to 86.17 by T6 (10 mins). Similarly, in Group O, the mean HR ranged from 91.30 at T0 to 90.20 at T6. No statistically significant differences were observed between the two groups at any time interval. These findings align with those reported by Jain et al., where baseline HR in N2O and O2 groups was comparable, with no significant rise observed after propofol administration ($P > 0.05$)5. Contrary to this, Singh et al. observed a significant increase in HR in the N2O group following induction, with a peak at 5 mins (99.35 bpm).[17] In this study, while there was a transient rise in HR post-intubation, it lacked clinical significance, likely due to the balancing effects of propofol-induced bradycardia and the sympathetic stimulation induced by N2O. Literature supports this phenomenon, suggesting that N2O, while a direct myocardial depressant, stimulates the sympathetic nervous system and catecholamine release, maintaining stable HR and hemodynamic parameters. Mckinney and Fee's findings further highlight the influence of age, where elderly patients with reduced cardiovascular responsiveness exhibited a decrease in HR22. This reflects the multifactorial nature of HR regulation during anaesthesia.

SBP showed a noticeable decline in both groups post-induction, consistent with the vasodilatory effects of propofol. Group N exhibited a gradual decline from 127.30 mmHg at T0 to 117.50 mmHg at T6. Conversely, Group O showed a sharper decline, from 123.53 mmHg at T0 to 107.53 mmHg at T6. Statistical analysis revealed significantly lower SBP in Group O at T3, T5, and T6. DBP, however, showed no significant intergroup differences, maintaining a stable decline in both groups. Our findings echo those of Jain et al., who reported a significant, though clinically non-significant, drop in SBP and DBP at the end of propofol induction in both groups5. Similarly, Singh et al. documented a more pronounced SBP reduction in the O2 group compared to the N2O group, highlighting the stabilizing effects of N2O on blood pressure.[17] The observed stability in Group N's SBP may be attributed to N2O's sympathetic stimulation, which counters the myocardial depressant effects of propofol.

The MAP followed a similar trend, with a significant decline observed in Group O across time intervals. Group N maintained higher MAP values, reflecting better hemodynamic stability. Our findings are consistent with those of Sunil R. et al., who reported comparable pre-induction MAP values between groups but significantly higher MAP in N2O-treated patients at induction and subsequent time points19. These results align with prior studies suggesting that N2O mitigates the hypotensive effects of propofol through sympathetic stimulation. However, the variations in MAP stabilization observed across studies could stem from differences in study populations, propofol dosing, and adjunctive agents used.

Both groups maintained 100% SpO_2 across all time intervals, reflecting adequate oxygenation during the perioperative period. Our findings are consistent with those reported by Jain et al. and Singh et al., where SpO_2 levels remained stable without complications or desaturation during propofol induction.[5,17] This further supports the use of N2O in conjunction with oxygen as an effective method for preoxygenation and safe anaesthesia induction. Studies by Khoo et al. corroborate our results, emphasizing that the use of 50% N2O with oxygen during slow propofol induction does not compromise oxygenation23. Kumar et al. noted rare instances of hypotension with no hemodynamic instability, which aligns with our observation of no adverse events in either group.[21]

The limitations of the study are its single-center design, limited patient attendance, and exclusion of high-risk and extreme age groups, restricting the generalizability of the findings.

CONCLUSION

The coadministration of N_2O during the induction of anaesthesia with propofol offers significant clinical advantages. It reduces both the induction dose and time of propofol, thereby minimizing its associated adverse effects such as profound hypotension and hemodynamic instability. This reduction not only enhances patient safety but also contributes to cost-effective anaesthesia management. Our study demonstrated that the inclusion of N_2O leads to stable hemodynamic parameters, including HR, SBP, DBP, MAP, and SpO_2, with no observed complications or adverse effects. These findings indicate the efficacy and safety of N_2O in elective

surgical procedures. However, careful consideration is warranted when selecting patients for N_2O use. It should be avoided in individuals with anticipated difficult intubation or compromised cardiorespiratory reserve to mitigate potential risks. While these results are encouraging, further multi-center studies with larger, more diverse populations are recommended to better validate and expand these findings. Such studies would provide a more comprehensive understanding of the risk-benefit profile of N_2O in various clinical scenarios, ensuring its judicious and optimal use in anaesthesia practice.

Conflict of Interest Statement

Authors declares no conflict of interest

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