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Improving Induction Safety: Effect of Fentanyl Timing on Propofol Dose and Hemodynamic Outcomes: A Randomized Clinical Trial

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Abstract

Background and Aim: Propofol is a widely used intravenous induction agent known for its rapid onset and smooth recovery. However, its use is often associated with hypotension and apnea, especially at higher doses. Opioids like fentanyl are frequently used as adjuncts to reduce the propofol requirement and attenuate hemodynamic fluctuations. This study aimed to evaluate the effect of varying time intervals between fentanyl and propofol administration on the dose of propofol required for induction and the associated hemodynamic outcomes.

Methods: This prospective, randomized, double-blind clinical trial was conducted on 108 ASA I–II patients aged 18–65 years undergoing elective surgeries under general anaesthesia. Patients were randomly divided into three groups (n = 36 each): Group 1 received propofol immediately after fentanyl (2 mcg/kg), Group 2 after 5 minutes, and Group 3 after 7 minutes. Propofol was administered at a controlled infusion rate of 300 mL/hr until loss of verbal response. The primary outcome was the mean induction dose of propofol (mg/kg). Secondary outcomes included incidence of hypotension, apnea, vocalization, and additional propofol requirement. Data were analyzed using SPSS v24, with ANOVA and Chi-square tests applied where appropriate.

Results: The mean propofol requirement was significantly different among groups (Group 1: 1.23 ± 0.22 mg/kg; Group 2: 1.08 ± 0.36 mg/kg; Group 3: 0.90 ± 0.26 mg/kg; $p < 0.001$). Although Group 3 required the lowest dose, it had a higher incidence of hypotension (13.9%) compared to Group 1 (5.6%) and Group 2 (11.2%) ($p = 0.001$). Apnea occurred most frequently in Group 2 (97.3%), while vocalization and movement were more common in Group 1 (16.7%).

Conclusion: Administering fentanyl 5 minutes before propofol induction optimally reduces the required propofol dose and minimizes hemodynamic disturbances. Delaying propofol administration beyond this interval offers no additional advantage and may increase the risk of hypotension. Timing the administration of induction agents is thus critical for achieving safe and effective anaesthesia induction.

Keywords: Propofol, Fentanyl, Induction dose, Anaesthesia, Hypotension, Apnea, Opioid co-induction, Time interval, Hemodynamic stability

Introduction

Propofol, a 2,6-diisopropylphenol, is an intravenous anaesthetic agent widely used for the induction and maintenance of general anaesthesia. Its popularity stems from its rapid onset, smooth induction, and quick recovery characteristics, which make it ideal for short surgical procedures and outpatient anaesthesia settings [1,2]. Compared to older agents like thiopentone or ketamine, propofol provides better suppression of airway reflexes and superior intubating conditions, albeit at the cost of significant cardiovascular and respiratory depression, especially when used at higher induction doses of 2–2.5 mg/kg [3].

However, the major limitation of propofol remains its tendency to cause dose-dependent hypotension, bradycardia, and apnea due to its vasodilatory and negative inotropic effects [4]. To mitigate these adverse effects, anaesthesiologists often employ a co-induction strategy using adjuncts such as opioids or benzodiazepines. Among opioids, fentanyl—a potent μ-opioid receptor agonist—is frequently co-administered due to its profound analgesic effects and ability to blunt sympathetic responses to laryngoscopy and intubation [5].

The co-administration of fentanyl has been shown to reduce the induction dose requirement of propofol and decrease the incidence of adverse cardiovascular effects [6]. Furthermore, administering propofol via a controlled infusion rather than as a bolus has been demonstrated to reduce both the total dose required and the associated hemodynamic disturbances [7]. For example, Peacock et al. demonstrated that administering propofol at a slower infusion rate (300 mL/h) not only decreased the induction dose but also significantly reduced the incidence of hypotension and apnea compared to faster infusion rates [8].

Despite the well-documented benefits of fentanyl-propofol co-induction, limited literature exists on the optimal timing between the administration of fentanyl and propofol. The pharmacokinetics of fentanyl suggest that its peak effect occurs approximately 5–6 minutes after intravenous administration [9]. Administering propofol too early—before fentanyl has reached its peak effect—may not fully exploit fentanyl's synergistic potential, while excessive delays may risk hypotension due to overlapping vasodilatory effects or altered drug synergy [10].

Previous studies have attempted to explore this temporal relationship. For instance, Vanlal Darlong et al. showed that increasing the interval between fentanyl and propofol from 0 to 5 minutes significantly reduced the required propofol dose for induction, thereby improving hemodynamic stability [11]. However, there remains a lack of consensus on whether extending this interval beyond 5 minutes provides any additional benefit or potentially worsens outcomes due to delayed peak synchrony.

In this context, our study was designed to evaluate the effect of varying time intervals—specifically 0, 5, and 7 minutes—between fentanyl and propofol administration on the propofol dose required for induction. We hypothesized that a 5-minute interval would optimize the pharmacodynamic synergy between fentanyl and propofol, reducing the propofol requirement and minimizing hemodynamic perturbations during induction.

Methodology

This study was designed as a randomized, prospective, double-blind clinical trial and was conducted at the Department of Anaesthesiology, Chettinad Hospital and Research Institute, Tamil Nadu, over a period of four months from August to Novermber 2022. After obtaining ethical clearance from the Institutional Human Ethics Committee and informed written consent from all participants, 108 patients scheduled for elective surgeries under general anaesthesia were enrolled. Inclusion criteria comprised adult patients aged 18 to 65 years with American Society of Anesthesiologists (ASA) physical status I or II. Patients were excluded if they had ASA grade III or IV, a body mass index (BMI) greater than 35 kg/m², anticipated difficult airway, pregnancy, allergy to study drugs, contraindication to general anaesthesia, history of substance abuse or alcoholism, or were undergoing emergency procedures.

Participants were randomly assigned into three equal groups (n = 36 each) using a computer-generated randomization code and the serially numbered opaque sealed envelope (SNOSE) method to maintain allocation concealment. Group 1 received intravenous fentanyl (2 mcg/kg) followed immediately by propofol administration. Group 2 received propofol 5 minutes after fentanyl, while Group 3 received propofol 7 minutes after fentanyl. Propofol was administered using an infusion pump at a standardized rate of 300 mL/hr until the loss of verbal response was noted, indicating induction. If required, additional boluses of 20 mg propofol were given for inadequate induction, and the total dose was recorded.

Standard preoperative fasting guidelines were followed, and all patients received oral ranitidine 150 mg the night before and the morning of surgery. In the operating room, after securing intravenous access, patients were connected to standard monitoring devices including ECG, non-

invasive blood pressure (NIBP), and pulse oximetry. They were preoxygenated with 100% oxygen for 3 minutes, followed by fentanyl administration as per group allocation. An independent anaesthesiologist, blinded to the study protocol, administered propofol, while another observer recorded the dose, induction characteristics, and intraoperative events.
Following induction, neuromuscular blockade was achieved using either atracurium (0.5 mg/kg) or vecuronium (0.1 mg/kg). Hemodynamic parameters were recorded at baseline, after induction, and at 1 and 3 minutes post-induction. The incidence of hypotension (MAP < 65 mmHg), apnea, vocalization or movement, fluid bolus requirements, and vasopressor use (phenylephrine) were also recorded.
Statistical analysis was conducted using SPSS version 24.0. Continuous variables were expressed as mean ± standard deviation (SD) and analyzed using ANOVA. Categorical variables were expressed as frequencies and percentages, and compared using Chi-square test. A p-value of <0.05 was considered statistically significant.

Results

Study Population- A total of 108 patients were enrolled and randomized equally into three groups (n = 36 each). The groups were comparable in terms of age, gender, ASA physical status, BMI, and baseline hemodynamic parameters (p > 0.05).

Table 1: Demographic Characteristics of the Study Groups

Parameter	**Group 1 (Immediate)**	**Group 2 (5 min)**	**Group 3 (7 min)**	**p-value**
Age (mean ± SD)	38.1 ± 12.5	36.8 ± 11.9	37.3 ± 13.1	0.958
Gender (M/F)	14 / 22	14 / 22	15 / 21	0.347
ASA I / II	16 / 20	17 / 19	19 / 17	0.056
BMI (mean ± SD)	26.2 ± 3.1	25.9 ± 2.9	26.5 ± 3.3	0.353

Table 1 shows the baseline demographic characteristics of patients enrolled in the three study groups. Variables compared include age, gender distribution, ASA physical status classification, and body mass index (BMI). The data indicate no statistically significant differences between the groups, confirming effective randomization and comparability of cohorts (p > 0.05 for all parameters).

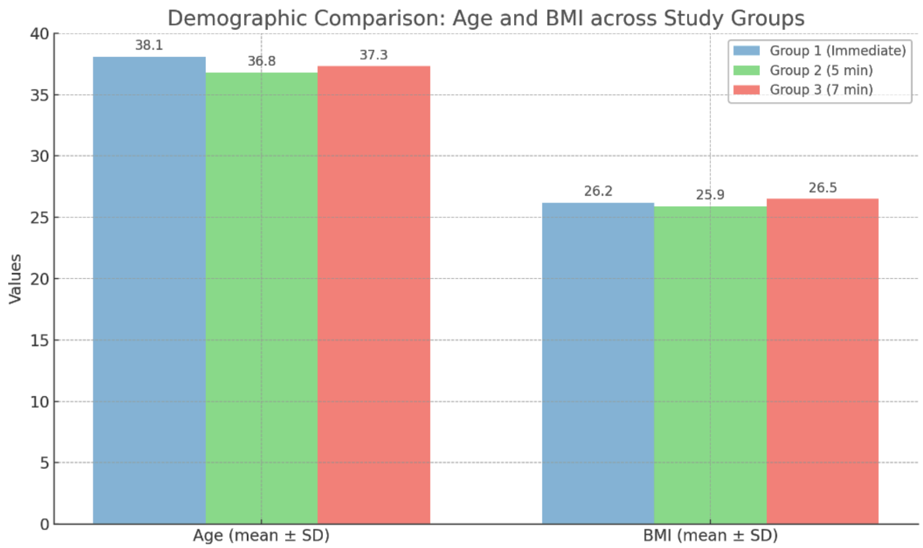

Figure 1: The image depicts bar graph comparing Age and BMI (mean ± SD) across the three study groups.

Propofol Dose Requirement- Group 3 (7 min interval) required the lowest mean dose of propofol for induction, followed by Group 2 and then Group 1. The differences were statistically significant ($p < 0.001$).

Table 2: Mean Propofol Dose Required for Induction

Group	**Mean Propofol Dose (mg/kg) ± SD**	**p-value**
Group 1 (0 min)	1.23 ± 0.22	**<0.001**
Group 2 (5 min)	1.08 ± 0.36	
Group 3 (7 min)	0.90 ± 0.26	

Table 2 presents the average propofol dose required to induce anaesthesia in each group. Group 1 received propofol immediately after fentanyl, Group 2 after 5 minutes, and Group 3 after 7 minutes. The data demonstrate a statistically significant reduction in propofol dose with increasing time intervals, with Group 3 requiring the least amount of propofol. This supports the hypothesis that delaying propofol administration allows fentanyl to reach peak effect and enhance induction efficiency ($p < 0.001$).

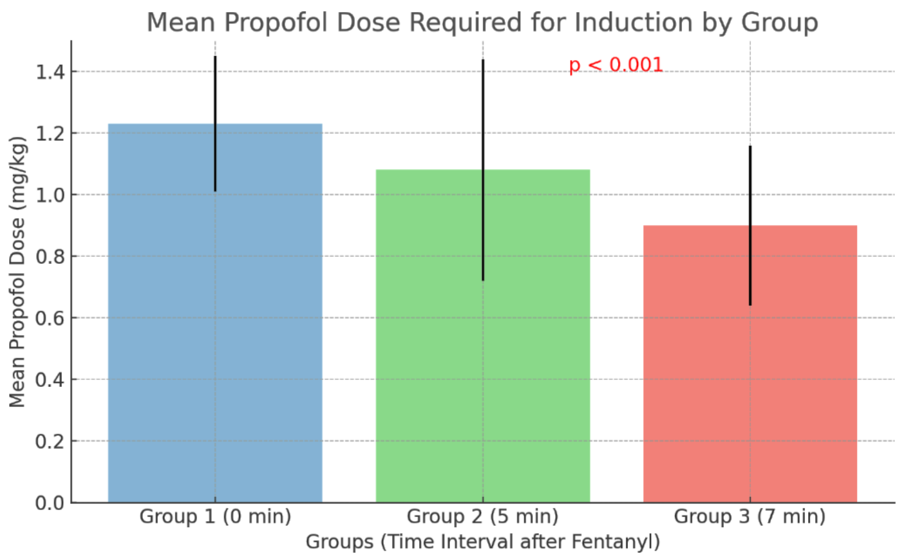

Figure 2: The bar graph shows the mean propofol dose required for induction in each group, with error bars representing the standard deviation. The significant reduction in dose with increasing time after fentanyl administration is highlighted by the p-value < 0.001.

Hemodynamic Parameters Post Induction- Mean arterial pressure (MAP) showed a more significant drop-in Group 3 compared to Group 1 and 2 after induction.

Table 3: Incidence of Hypotension (MAP < 65 mmHg)

Group	**Hypotension Cases (n)**	**Percentage (%)**	**p-value**
Group 1 (0 min)	2	5.6%	**0.001**
Group 2 (5 min)	4	11.2%	
Group 3 (7 min)	5	13.9%	

Table 3 compares the number and percentage of patients who developed hypotension, defined as a mean arterial pressure (MAP) less than 65 mmHg, following anaesthesia induction. Although Group 3 required the lowest propofol dose, it exhibited the highest incidence of hypotension, suggesting that a 7-minute delay may increase the risk of hemodynamic instability. This difference was statistically significant (p = 0.001).

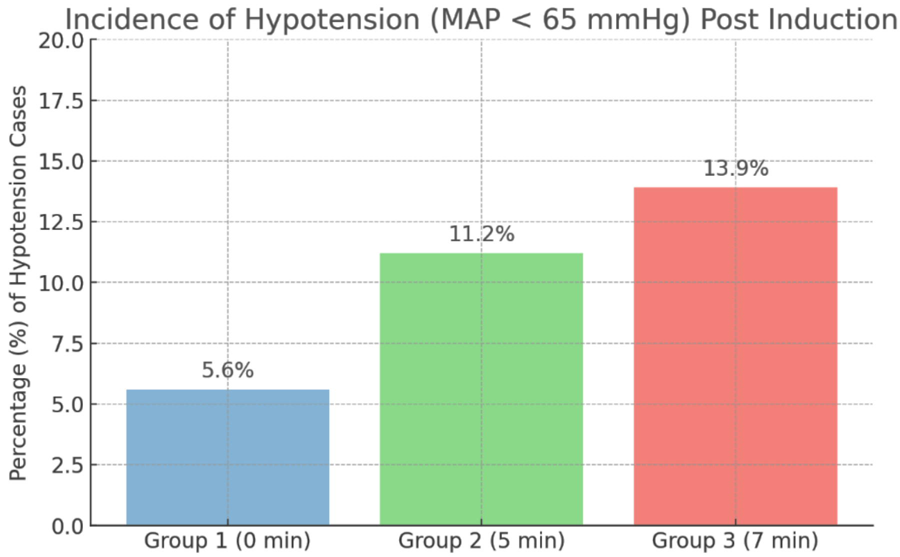

Figure 3: The bar graph shows the incidence of hypotension (MAP < 65 mmHg) post induction in the three groups. Group 3 shows the highest percentage of hypotension cases (13.9%), followed by Group 2 (11.2%), and Group 1 (5.6%). The difference is statistically significant (p = 0.001).

Apnea, Vocalization, and Additional Propofol Use- Apnea was observed most frequently in Group 2, while vocalization and movement were slightly higher in Group 1.

Table 4: Incidence of Apnea and Vocalization

Group	Apnea (%)	Vocalization/Movement (%)	Additional Propofol Needed (%)
Group 1 (0 min)	88.9%	16.7%	19.4%
Group 2 (5 min)	97.3%	13.9%	16.7%
Group 3 (7 min)	91.7%	13.9%	13.9%

Table 4 details the frequency of specific post-induction events across the three study groups, including apnea, patient movement or vocalization during induction, and the need for additional boluses of propofol. Apnea occurred most frequently in Group 2, possibly due to a synergistic peak effect of fentanyl and propofol. Group 1 showed the highest rate of vocalization/movement, indicating suboptimal induction due to early propofol administration. These findings further illustrate the importance of timing in achieving smooth and stable induction.

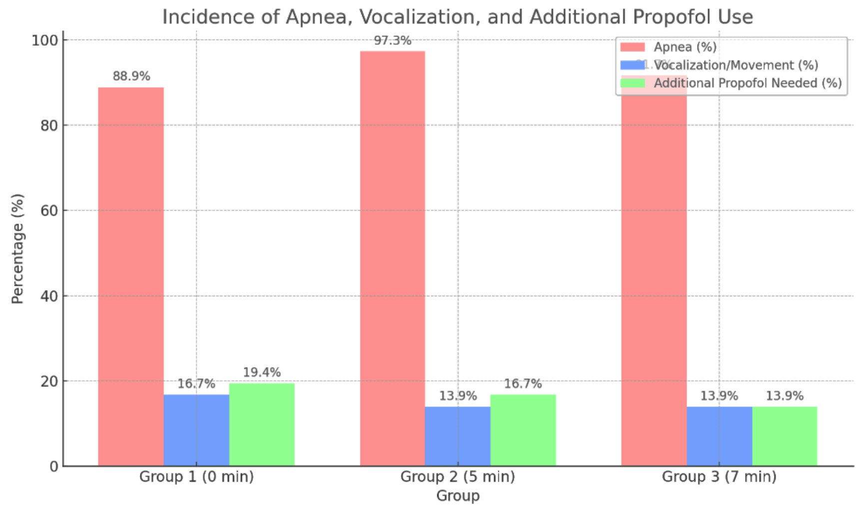

Figure 4: Incidence of Apnea, Vocalization, and Additional Propofol Use Across Groups;Apnea was most prevalent in Group 2 (5-minute delay), supporting the hypothesis of peak fentanyl-propofol synergy. Group 1 (immediate induction) had higher vocalization and additional propofol requirements, indicating suboptimal sedation timing. These results underscore the clinical relevance of induction timing in optimizing procedural sedation.

Discussion

This randomized clinical trial assessed the effect of varying time intervals between fentanyl and propofol administration on the propofol dose required for induction and its associated hemodynamic consequences. Our findings revealed that a 5-minute interval between fentanyl and propofol (Group 2) resulted in a significant reduction in propofol dose requirements while maintaining more stable hemodynamic parameters compared to immediate administration (Group 1) or a longer 7-minute interval (Group 3). These observations support the hypothesis that the pharmacodynamic interaction between fentanyl and propofol is time-dependent and optimized at approximately 5 minutes post-fentanyl injection.

The mean dose of propofol required for induction was highest in Group 1 (1.23 ± 0.22 mg/kg) and lowest in Group 3 (0.90 ± 0.26 mg/kg), with Group 2 (1.08 ± 0.36 mg/kg) serving as the optimal compromise between dose reduction and hemodynamic stability. This is consistent with previous studies that have shown opioid premedication reduces the induction dose of propofol by enhancing its sedative and hypnotic effects [5,6]. Our results closely align with those of Vanlal Darlong et al., who demonstrated a similar stepwise reduction in propofol requirements when fentanyl was administered 0, 3, and 5 minutes before propofol [11].

Interestingly, although Group 3 required the least dose of propofol, it also had the highest incidence of hypotension (13.9%), suggesting that delaying propofol administration beyond the optimal fentanyl peak time may lead to undesirable cardiovascular effects due to overlapping vasodilatory actions. This phenomenon is likely attributable to fentanyl's peak effect, which typically occurs around 5–6 minutes post-administration, after which its synergistic effect on reducing propofol requirement may plateau or even reverse due to compounded vasodilation [9,10]. Our findings indicate that the clinical benefit of dose reduction must be weighed against the increased risk of hypotension.

Apnea was most frequently observed in Group 2 (97.3%), followed by Group 3 (91.7%) and Group 1 (88.9%). This somewhat paradoxical finding may be explained by the deeper synergistic hypnotic effect in Group 2 at the time of induction. While this may not be clinically concerning under controlled ventilation conditions, it underscores the need for vigilant respiratory monitoring during co-induction. Vocalization and movement were most commonly seen in Group 1 (16.7%), suggesting suboptimal sedation due to premature administration of propofol before peak fentanyl effect.

The hemodynamic parameters—particularly systolic and diastolic blood pressures and mean arterial pressure—were better preserved in Group 2, suggesting a hemodynamically favorable window when fentanyl's sympatholytic effects are maximal but not yet compounded by prolonged vasodilation. These results support earlier pharmacokinetic modeling by Peacock et al., who noted that slower propofol infusions and optimized opioid timing reduced fluctuations in blood pressure and apnea incidence [8].

Our study also reinforces the importance of infusion technique in propofol administration. Using a standardized infusion rate of 300 mL/hr likely contributed to the reduced propofol requirement and lower incidence of pain on injection, as observed in other infusion-based protocols [7,8].

Strengths and Limitations:

This randomized, adequately powered study incorporated standardized drug dosages and controlled infusion protocols to ensure methodological consistency. Blinding of both participants and investigators, along with strict inclusion criteria, helped reduce potential bias and enhance internal validity. However, the single-center design and restriction to ASA I–II patients undergoing elective surgeries limit the generalizability of the findings to broader populations, including high-risk or emergency surgical cases. Furthermore, the study did not account for the influence of concurrent medications or the effect of varying fentanyl doses, which may impact anaesthetic requirements.

A notable limitation was the absence of bispectral index (BIS) monitoring to objectively assess anaesthetic depth. While clinical signs were used to determine loss of consciousness, BIS would have provided a more precise and quantifiable measure of hypnotic depth, potentially improving the consistency of induction depth assessment across patient groups.

Clinical Implications

The findings suggest that administering fentanyl approximately 5 minutes before propofol provides an optimal balance between reduced propofol dose and hemodynamic stability. This has practical relevance in routine anaesthesia induction, especially in patients with borderline cardiovascular reserve, where minimizing drug dose and avoiding hypotension are crucial.

Future Directions

Future studies may explore varying fentanyl doses, different opioids (e.g., remifentanil), and broader patient populations, including those with cardiovascular comorbidities. Additionally, the use of BIS monitoring may provide more objective endpoints for depth of anaesthesia in timing-based induction protocols.

Conclusion

Administering fentanyl 5 minutes before propofol induction minimizes propofol requirement while maintaining hemodynamic stability. Extending this interval to 7 minutes offers minimal additional benefit and increases hypotension risk.

Ethical Considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Human Ethics Committee (IHEC) of Chettinad Hospital and Research Institute, Tamil Nadu, India, under reference number IHEC-I/0910/22. Written informed consent was obtained from all participants after explaining the study protocol, risks, and benefits. Participants were ensured that their participation was voluntary and that they could withdraw from the study at any time without any impact on their clinical care. Confidentiality and anonymity of participant data were strictly maintained throughout the research process. The trial was registered with CTRI before commencement (CTRI/2022/07/043932).

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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