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Original Research Article

Effect of Varying Time Interval between Fentanyl and Propofol Administration, On Propofol Requirement for Induction of Anaesthesia

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Abstract:

Introduction: Fentanyl synergistically enhances propofol effects and reduces hemodynamic response during induction. Fentanyl and propofol administration timing affects propofol dose and associated side effects.

Aim and objectives: Primary objective is to calculate the total dose of propofol required to achieve loss of consciousness during induction of anesthesia. Secondary objective is to examine the Incidence of hypotension during induction and to examine any Incidence of any movement or Bucking or Any vocalization after initial dose of propofol.

Materials & Methods: After institutional ethical clearance, 68 ASA status I & II patients, aged 18-65 years, undergoing elective surgery under general anesthesia were randomized into two groups; Fentanyl 2 mcg/kg was administered immediately prior to, 5 and 7 min before induction with propofol in Groups A and B, respectively. The requirement of propofol induction dose and hemodynamic parameters was recorded. Statistical analysis was performed using software SPSS, P-value <0.05 was considered statistically significant.

Results: Demographic characteristics were comparable in both the groups. Total dose of propofol required for induction was higher in Groups A than group B (Group A vs. 85.88±14.221mg vs. 56.52±12.530 mg). Incidence of movement, vocalization, bucking is higher in Group A than Group B (P=<0.000001, P=0.002, P=0.007 respectively). Incidence of hypotension during induction was significantly lower in Group B (5.9%) than Group A (94.1%; P =<0.00001).

Conclusion: Administering fentanyl 7 min prior to propofol causes marked reduction in the dose requirement of the propofol along with a significantly decreased incidence of hypotension during induction.

Keywords: Anesthesia; Fentanyl; Hemodynamic parameters; Propofol.

Introduction

Anesthesia induction is a critical component of modern surgical practice, necessitating a precise and effective transition from a state of consciousness to unconsciousness, ensuring both patient safety and comfort. The induction phase often utilizes a combination of anaesthetic agents to achieve the desired depth of Anesthesia while minimizing adverse effects. Among these agents, propofol and fentanyl are frequently used due to their synergistic effects, which enhance the induction process and improve patient outcomes.

Propofol, an intravenous anesthetic agent, is widely favored for its rapid onset and short duration of action, which allows for precise control over the induction and maintenance of anesthesia. [1] Despite its efficacy, propofol administration is associated with several adverse effects, including hypotension, bradycardia, and respiratory depression, particularly when used in higher doses. [2] These side effects necessitate careful titration and, ideally, the use of adjunct medications to minimize propofol dosage without compromising anesthetic depth.

Fentanyl, a potent synthetic opioid, is often used in conjunction with propofol due to its powerful analgesic properties and its ability to enhance the hypnotic effects of other anesthetic agents. [3] When used in combination with propofol, fentanyl can significantly reduce the required dose of propofol for induction, thereby mitigating some of the adverse hemodynamic effects associated with propofol. [4] The interaction between fentanyl and

propofol is of particular interest in anesthesia research. The synergistic effects of these two drugs have been well-documented, indicating that the administration of fentanyl prior to propofol can reduce the dose of propofol required to achieve adequate anesthesia. [5]

However, the optimal timing for the administration of fentanyl relative to propofol remains a subject of on-going investigation. Understanding this timing is crucial, as it can influence the efficiency and safety of the induction process.

Previous studies have explored various aspects of the propofol-fentanyl interaction. For instance, studies have demonstrated that pre-administration of fentanyl can significantly reduce propofol requirements for induction. [6]

The lack of consensus highlights the need for more rigorous investigation to determine the optimal time interval that maximizes the synergistic effects of fentanyl and propofol while minimizing the risk of adverse events. Propofol is a relatively expensive anesthetic agent, and reducing the required dose using adjuncts like fentanyl can lead to significant cost savings, particularly in high-volume surgical centers. [7]

The present study aims to address the gap in the existing literature by systematically investigating the effect of varying the time interval between fentanyl and propofol administration on the propofol dose required for anesthesia induction.

Aim and Objectives

Primary objective is to calculate the total dose of propofol required to achieve loss of consciousness during induction of anesthesia.

Secondary objective is to examine the Incidence of hypotension during induction and to examine any Incidence of any movement or Bucking or Any vocalization after initial dose of propofol.

Materials & Methods

The study was done as a randomized, controlled study at the Department of Anaesthesiology, Sri Siddhartha Medical College and Research Centre, located in Tumkur, Karnataka, India. Patients aged 18-65 years, classified as ASA Class I & II, who were undergoing elective upper abdominal surgery under general anaesthesia, were recruited for the research after obtaining clearance from the institutional ethics committee (Ref No.: (SSMC/MED/IEC-127/July-2022) and informed consent from the patients.

Patients with known allergy to study drugs, pre-diagnosed systemic illness, expected difficult airway, pregnant or locational mothers, having BMI >30 kg/m^2, or unwilling to give consent were excluded from the study. Patients receiving medications that could affect the requirement of propofol or fentanyl or alter hemodynamic parameters were also excluded to minimize drug interaction effects.

Sample size calculation was done by employing Consecutive sampling method & the formula for calculating the sample size was $n = 2[Z(1-\alpha/2) + Z(1-\beta)]^2 x \sigma^2/d^2$. After considering the non-response rate of 10%, the minimum sample size required was 34 in each group (total – 68).

All the selected 68 patients were randomly assigned to one of two study groups using a computer-generated randomization schedule after pre-anaesthetic evaluation and routine work-up.

- **Group A:** received fentanyl at a dose of 2 mcg/kg followed by propofol after a 5-minute interval.
- **Group B:** received fentanyl at a dose of 2 mcg/kg followed by propofol after a 7-minute interval.

All the hemodynamic variables were observed before, during and immediately afterward the induction at regular intervals. Any deviations from baseline values, such as hypotension or bradycardia, were noted.

Study parameters:

Primary Parameter:

- **Propofol Dose Requirement**: The total dose of propofol required to achieve induction of anesthesia, defined as the loss of verbal contact with the patient.

Secondary Parameters:

- **Hemodynamic Stability**: Continuous monitoring of blood pressure (SBP, DBP, and MAP) and heart rate before and after drug administration, during induction, and immediately post-induction.
- **Adverse Events**: The incidence of hypotension, bradycardia, and other potential side effects such as respiratory depression.
- **Additional Propofol Requirements**: Documentation of any additional boluses of propofol required if patients exhibited movement, vocalization, or bucking during mask ventilation.
- **Interventions**: The need for fluid boluses or vasopressors to manage hypotension or other hemodynamic instabilities.

All collected data were reviewed for completeness and accuracy before being entered into a secure electronic database for analysis.

Statistical Analysis: Data analysis was conducted using SPSS software to ensure rigorous statistical evaluation of the study outcomes. Continuous

variables, such as the total dose of propofol required for induction and hemodynamic parameters, were analyzed using independent samples t-tests or ANOVA to compare differences between the two groups.

Categorical variables, such as the incidence of adverse events, were analyzed using chi-square tests or Fisher's exact test as appropriate.

Descriptive statistics, including means, standard deviations, and proportions, were calculated to summarize the baseline characteristics and outcomes. The primary endpoint, the difference in propofol dosage between groups, was assessed with a significance level set at $p < 0.05$. Secondary outcomes, including hemodynamic stability and adverse event incidence, were also evaluated to provide a comprehensive understanding of the clinical implications of varying the time interval between fentanyl and propofol administration.

Results

The demographic characteristics among the groups were found to be similar and comparable ($p>0.05$). [Table 1]

Table 1: Demographic data

Variables		Group A	Group B	P- Value
Age (years) (Mean±SD)		44.65±12.694	41.27±13.947	0.30 **(NS)**
Gender	Male	24 (61.5%)	15 (38.5%)	0.18 **(NS)**
	Female	10 (35.7%)	18 (64.3%)	
Weight (kg) (Mean±SD)		54.03±6.147	53.55±6.235	0.75 **(NS)**

NS- Non Significant

The results show that the mean dose of fentanyl administered in Group A was 108.06±12.294 mcg and in Group B was 107.33±12.467, P = 0.912. The mean dose of propofol required was significantly different between groups, with Group A requiring 72.35±8.549 mg and Group B requiring 54.09±8.790 mg, P = 0.491. Baseline HR and SBP showed no significant differences between the groups. However, DBP and MAP were significantly different, P = 0.023 and 0.039, respectively. These results suggest that while fentanyl doses and some baseline hemodynamic parameters were similar, the time interval between fentanyl and propofol significantly influenced propofol requirements and certain blood pressure parameters.

The study further examines the final hemodynamic parameters between the two groups. The heart rate (HR-F) showed no significant difference between Group A (65.35±6.040 bpm), and Group B (69.91±5.270 bpm) (P = 0.606). However, significant differences were observed in systolic blood pressure (SBP-F), with Group A (114.71±10.797 mmHg) and Group B (117.27± mmHg) (P = 0.004). Diastolic blood pressure (DBP-F) also showed a significant difference, with Group A (3.53±6.458 mmHg) and Group B (76.67± 4.787 mmHg) (P = 0.029). Additionally, mean arterial pressure (MAP-F) was significantly lower in Group A (87.18±7.392 mmHg) compared to Group B (90.09±3.900 mmHg) (P < 0.0000001). These findings suggest that the varying time intervals between fentanyl and propofol administration affect final hemodynamic parameters, with Group A generally showing lower values.

After administration of propofol, the heart rate post-induction did not show a significant difference between Group A and Group B (P = 0.245). However, significant differences were found in SBP, DBP and MAP after propofol induction (P = 0.000). These results indicate that the time interval between fentanyl and propofol administration significantly affects post-induction hemodynamic parameters, with Group A showing generally lower values compared to Group B. [Figure 1]

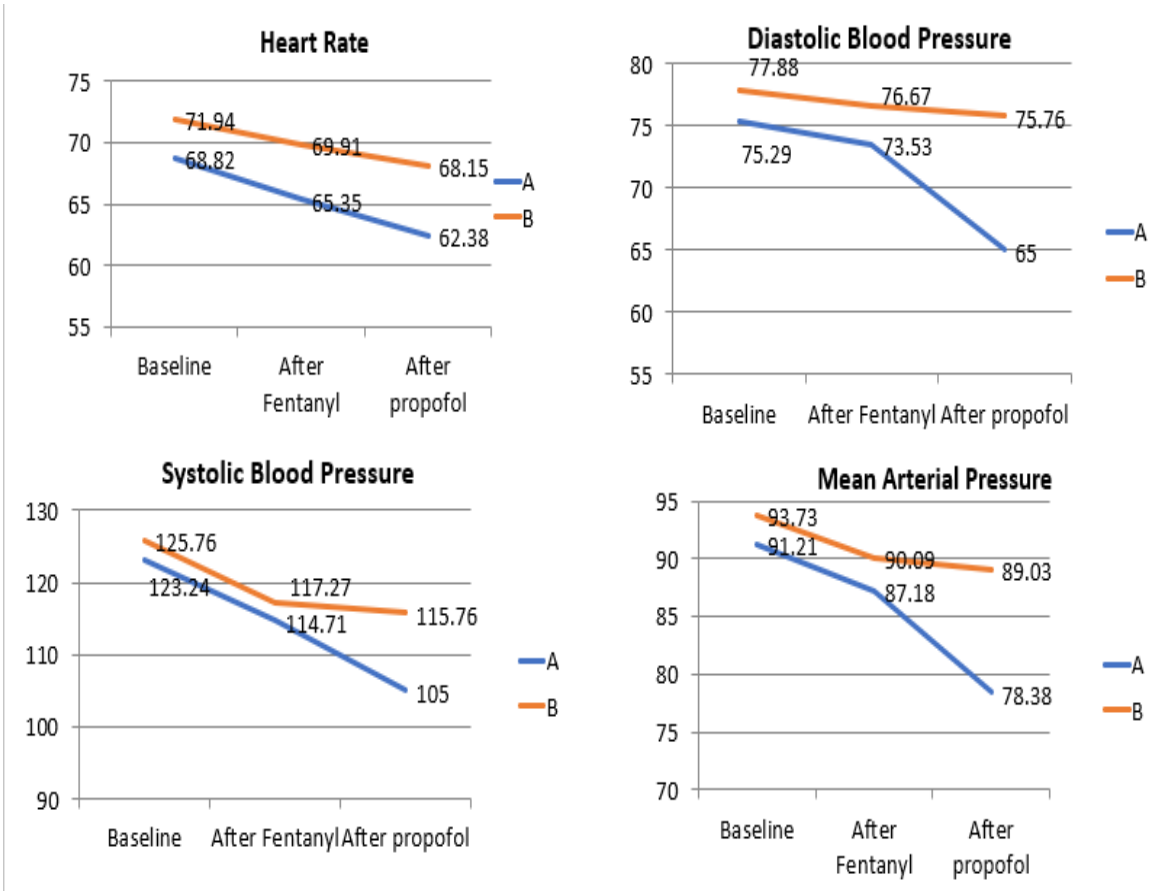

Figure 1:

Table 2 demonstrates that both groups experienced a reduction in HR, SBP, DBP and MAP following the administration of fentanyl and propofol, with Group A demonstrating a more significant decrease compared to Group B.

Table 2: Changes in vital parameters

Parameters	**Group A**			**Group B**		
	Baseline	After Fentanyl	After propofol	Baseline	After Fentanyl	After propofol
Mean values of HR	68.82	65.35	62.38	71.94	69.91	68.15
Mean values of SBP	123.24	114.71	105	125.76	117.27	115.76
Mean values of DBP	75.29	73.53	65	77.88	76.67	75.76
Mean values of MAP	91.21	87.18	78.38	93.73	90.09	89.03

Table 3 and Figure 2,3 compares various parameters between Group A and Group B, highlighting significant differences.

Table 3: Comparison of different outcome indicators among groups

Parameters	**Group A**	**Group B**	**P value**
Total propofol dose	85.88±14.221	56.52±12.530	0.2 **(NS)**
Movement	89.5%	10.5%	<0.000001 **(S)**
Vocalization	91.7%	8.3%	0.002 **(S)**
Bucking	90.0%	10.0%	0.007 **(S)**
Additional propofol requirement	50%	6.4%	<0.02 **(S)**
Hypotension, Fluid bolus	94.1%	5.9%	<0.00001 **(S)**

NS- Non Significant, S- Significant

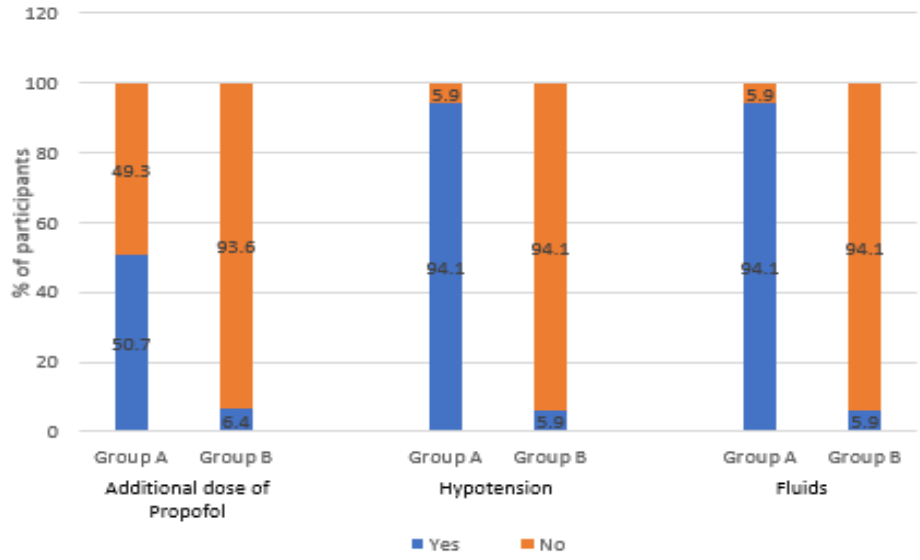

Figure 2:

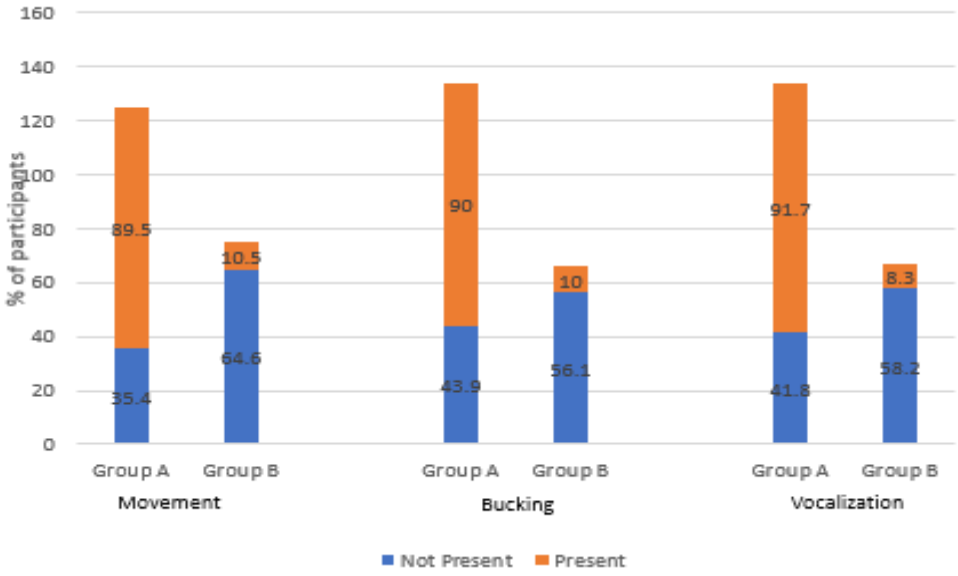

Figure 3:

Discussion

Using fentanyl and propofol together is a widely accepted method for initiating anesthesia. This combination has been found to work well together, improving the overall effectiveness of anesthesia and potentially allowing for lower doses of each drug. Administering fentanyl, an opioid analgesic, before propofol, a short-acting hypnotic agent, is recognized for its ability to enhance the induction process and minimize potential side effects. Nevertheless, there is still uncertainty regarding the ideal timing for administering fentanyl and inducing propofol. This study explores the impact of adjusting the time interval between the administration of fentanyl and propofol on the overall propofol dosage needed for a successful anesthesia induction. Through the identification of the most optimal time interval, our goal is to enhance anesthetic protocols, resulting in enhanced safety and comfort for patients. Darlong et al. [8] discovered that the administration of fentanyl five minutes prior to the administration of propofol resulted in a considerable reduction in the amount of propofol that was required for induction.

The mean doses of fentanyl were 59.98 mg when it was supplied prior to the delivery of the drug, whereas the mean doses for immediate administration were 86.28 mg (Darlong et al.) [8]. In a study that was conducted not too long ago by Vullo et al. [9], researchers looked at the effects of prolonging the amount of time that passed between the administration of fentanyl and propofol.

According to the findings, a two-minute gap led to significant reductions in systolic blood pressure, particularly among participants who were of an older age. The group that participated in the 2-minute exercise had a systolic blood pressure drop that was, on average, 36% lower (Vullo et al.) [9]. In a study that was carried out not too long ago by Ganesh and colleagues [10], the effects of dexmedetomidine and fentanyl on the levels of propofol that were required were investigated. When compared to fentanyl, the data demonstrated that dexmedetomidine had a more significant impact on the reduction of the effective concentration of propofol. In the study conducted by Ganesh et al. [10], the average doses of propofol administered to patients were 1.14 mg/kg for dexmedetomidine and 2.15 mg/kg for fentanyl.

The outcomes of the study reveal significant differences in the required dosage of propofol and specific hemodynamic parameters that were detected. These differences were observed between the two groups. These findings agree with the research that was carried out by Hayakawa-Fujii and colleagues [11]. That study indicated that the administration of propofol and fentanyl at intervals that were precisely timed can successfully stabilize hemodynamic variables. On the other side, immediate administration might not produce the same level of stability as traditional administration. These findings are consistent with the findings of Vullo et al. [9], who found that increasing the amount of time that passed between the administration of fentanyl and propofol led to a reduction in the amount of hemodynamic instability that occurred. Particularly noteworthy is the fact that their study groups displayed considerable variability in the readings of their blood pressure (Vullo et al.) [9]. In a similar vein, a study that was carried out by Ganesh and colleagues [10] discovered that the combination of dexmedetomidine and propofol led to a considerable reduction in the needed dose of propofol and greater stabilization of hemodynamic parameters when compared to fentanyl. According to Ganesh et al. [10], this further emphasizes the need of combining medications and timing them in a suitable manner.

In a recent study that was carried out by Shetabi and colleagues [12] that the utilization of remifentanil in conjunction with propofol resulted in enhanced stability in hemodynamics when compared to the utilization of propofol separately.

In a study conducted by Eldemrdash and Al-Azhary [13], it was found that combining ephedrine with propofol and fentanyl had a significant impact on minimizing hemodynamic changes. This resulted in a reduction in hypotension and helped maintain stable blood pressure levels. There are notable variations in movement observed after the use of propofol in the two groups. The results align with a study conducted by Joshi et al. [14], indicating that the use of fentanyl prior to treatment notably decreased the occurrence of movements during induction. In a study conducted by Smith et al. [15], it was found that higher concentrations of fentanyl significantly decreased the amount of propofol needed to prevent movement during anesthesia induction. In a study conducted by Ghabash et al. [16], it was noted that the administration of fentanyl before propofol induction resulted in a significant reduction in excitatory movements, leading to a more seamless induction process.

According to the results of this study, it is advised to administer fentanyl 7 minutes before propofol induction. This can help decrease the necessary amount of propofol and lower the occurrence of hypotension, movement, and vocalization during anesthesia induction. The timing of this approach seems to be ideal for maintaining stable hemodynamics, as indicated by the decreased occurrence of significant drops in blood pressure and the reduced requirement for additional doses or fluid boluses. It is highly recommended that clinicians incorporate this timing protocol into their anesthesia practice to improve patient safety and comfort.

Limitation of study: The sample size, although sufficient, was relatively small and may not accurately reflect the wider patient population undergoing different surgical procedures. The study also failed to consider potential variations in patient responses caused by underlying co-morbidities or different anesthetic techniques. In addition, the study only focused on a particular dosage of fentanyl and propofol. The study's design also did not incorporate a long-term follow-up to evaluate potential delayed effects of the timing differences on postoperative recovery and outcomes.

Conclusion

Administering fentanyl 7 min prior to propofol compared to 5min causes marked reduction in the dose requirement of the propofol along with a significantly decreased incidence of hypotension during induction. These findings emphasize the significance of proper timing in medical practice. Implementing this timing protocol can result in improved anesthetic management, decreased drug needs, and better patient outcomes. It is advisable to conduct additional research involving larger and more diverse populations, as well as different dosing regimens, to confirm and build upon these findings.

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