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ORIGINAL ARTICLE

An Entropy Based Observational Study to Assess the Dosage of Propofol Required for Induction of Anaesthesia by Varying the Time Intervals between Fentanyl and Propofol Administration

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Background: Propofol is the preferred drug for the induction of anesthesia in many centers. However, its ubiquitous use is hampered by adverse effects. The rationale behind our study is to prove that whether the administration of an opioid drug before propofol induction, lowers the amount of propofol requirement for balanced anesthesia, and enhances hemodynamic stability. **Aim:** The present study intends to know the consequence of the differing time intervals between the administration of fentanyl and propofol on the dosage of propofol required to achieve induction of general anesthesia. **Methods:** In this observational study, 84 patients were included in the study. Patients who received propofol immediately after fentanyl injection were included in Group 1, whereas patients who received propofol at 3 min and 6 min after fentanyl injection, respectively, were grouped as Group 2 and Group 3. The total propofol required, the hemodynamic variations and the entropy values were recorded. SSPS version 25.09 (IBM) was used for statistical analysis. **Results:** In this study, it was observed that there was a significant reduction in propofol requirement in Group 2 and Group 3 compared with Group 1. The incidence of hypotension was seen in about 42.9% of Group 1 when compared to Group 2 and 3, which was 28.6% and 17.8%, respectively. Furthermore, the entropy values in Group 3 were initially higher and later were comparable in all the groups. **Conclusion:** Our study concluded that as the duration between the administration of propofol and fentanyl increases, the hemodynamic stability also increases and there is no variation in the depth of anesthesia attained in the distinct study population.

Key words: Propofol, anesthesia, entropy, fentanyl, hemodynamic

INTRODUCTION

Propofol acts at gamma-aminobutyric acid receptors as a selective modulator.[1] It is the preferred drug when immediate and complete awakening is desirable.[2]

The use of this medication as the sole induction agent is hampered by additional side effects, the most notable of which is a considerable decrease in stroke volume with an accompanying reduction in blood pressure.[3] It also fails to sufficiently lessen the hemodynamic and hypertensive response to intubation. Opioids are administered as a part of balanced anesthesia with the aim of decreasing propofol consumption and attaining stable hemodynamics.[4]

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Fentanyl is a commonly used opioid and it is a μ receptor agonist.[5] Despite the quick onset of fentanyl, a noticeable delay between its peak plasma concentration and the effect on the electroencephalogram (EEG) can be noted. This lag corresponds to blood–brain effect-site equilibration duration of 6.4 min for fentanyl.[6]

Entropy is a monitor used to measure the depth of anesthesia. It has a sensor with 3 electrodes and is used to get an EEG recording. From this, the module calculates two

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values: one between 0 and 91 for *"state entropy"* (SE), which reflects cortical activity for frequencies between 0.8 and 32 Hz and, a second between 0 and 100 for *"response entropy"* (RE) for frequencies between 0.8 and 47 Hz. It is recommended that both values should be between 40 and 60 during surgery under general anesthesia.[7]

The primary objective of our study was to measure the amount of propofol required for induction of anesthesia when used along with fentanyl at varying time intervals between the administration of the drugs. The secondary objective was to measure the hemodynamic variations and compare the entropy values among these patients.

MATERIALS AND METHODS

Institutional ethics and scientific committee clearance were obtained before the commencement of the study. The study was registered under CTRI/2021/03/031878, India. Eighty-four under the American Society of Anesthesiology I and II were included in the study. The patients were of the age group between 18 and 65 years, undergoing elective surgery under general anesthesia.

Exclusion criteria included patients refusing consent to participate in the study, patients with a known history of allergic reactions, patients with body mass index >30 kg/m^2, patients with a difficult airway, and patients receiving any drugs which were likely to interfere with induction agent or hemodynamic parameters and patients posted for emergency surgery.

The sample size of 84 was determined by the following calculation.

$$n = \frac{2(Z_{1-\frac{\alpha}{2k}} + Z_{1-\beta})^2 \sigma^2}{d^2}$$

$$= \frac{2\left(2.39 + 0.84\right)^2 \left(0.346\right)^2}{0.44^2}$$

=28. Where,

$Z_{1-\alpha/2k}$ is a Z score adjusted to α level of significance (Bonferroni correction), i.e., 2.39, $Z_{1-\beta}$: Z score for (1−β) at 80% power: 0.84, σ = standard deviation = 0.346,

d is clinically significant difference = 0.44.

Each group 28;

Total sample size: 84.

The method used was convenience nonprobability sampling. Every participant underwent a thorough preanesthetic evaluation and preoperative orders were given. In the operating room, intravenous access was secured and standard monitors were connected to record the vitals such as heart rate, blood pressure, and oxygen saturation. Baseline vitals were recorded. Spectral entropy electrodes (GE Health care, Helsinki, Finland) were attached to the forehead and baseline SE and RE were recorded. Intravenous fluid infusion with Ringer's lactate was started. Preoxygenation was done for all the patients for 3 min with 100% oxygen. Intravenous fentanyl 2 μg/kg (Verefen 50 μg/mL) was administered as bolus.

The patients were administered propofol (Neorof 1% w/v, Neon pharmaceuticals) after the fentanyl injection. Those patients who received propofol immediately after fentanyl administration were grouped as 1. Those patients who received propofol 3 min after the fentanyl injection were named Group 2, and those patients who received propofol 6 min after the fentanyl injection became Group 3.

Propofol was injected slowly while communicating verbally with the patient. When there was no verbal response, entropy values were noted and were recorded every 2 min until 10-min postinduction and every 5 min after that for a total duration of 30 min. The time at which there was loss of verbal response was noted as T_0. Propofol was administered until the loss of verbal response was noted. The patients were monitored during and after propofol injection. Saturation, heart rate, and blood pressure were recorded every 2 min, from the time of fentanyl administration for 10 min and after that vitals were recorded every 5 min for a total of 30 min.

If bucking, movement, or vocalization were observed during mask ventilation, additional doses of propofol at 20 mg aliquots were given. The total dose requirement of propofol was also noted (loss of verbal response dose plus additional boluses). Neuromuscular blockade was achieved by administering rocuronium 0.6 mg/kg (Rocunium 50 mg/5 mL) after confirming adequate mask ventilation. Trachea was intubated and the endotracheal tube was fixed after confirming with capnography. After the procedure, patients were reversed and extubated. In the event of hypotension, a 300 mL intravenous bolus of fluids was administered. A 100 μg bolus of phenylephrine was given intravenously to treat hypotension that did not respond to a fluid bolus. Bradycardia was treated with 0.6 mg of intravenous atropine. Hypotension, bradycardia, and the need for drugs to treat hypotension were all recorded.

Data analysis was done using one-way analysis of variance (ANOVA). SSPS version 25.09 (IBM) Armonk, NY; USA was used for statistical analysis.

RESULTS

Eighty nine patients were assessed for eligibility and eighty four patients were included in the study [Flow chart 1]. Demographic data showed that there was no statistical significance between the variables [Table 1]. The dosage of fentanyl administered to the groups was similar

and was not statistically significant. The mean initial dosage of propofol required to achieve the loss of verbal response was statistically significant among the three groups. The amount of propofol consumed was more in Group 1 and least in Group 3. *P* value for Group 1: Group 2 was 0.013 and Group 1: Group 3 was 0.00, respectively [Figure 1]. The mean initial propofol consumption in Group 1 was 101.79 mg, Group 2 was 89.64 mg, and Group 3 was 73.21 mg. The total dose requirement of propofol was more in Group 1 when compared to Groups 2 and 3 and was statistically significant with a $P < 0.00$. The total propofol consumption was 1.68 mg/kg in Group 1, 1.43 mg/kg in Group 2, and 1.23 mg/kg in Group 3 [Table 2]. In this study, it was seen that there was a drop in mean arterial pressure between T2 and T6 in Group 1 as compared to other groups and was statistically significant [Table 3]. The depth of anesthesia was monitored using entropy. Both RE and SE values were low at T2, T4, and T6 in group 1 (SE at T2:T4: T6: 60.43:43.25:34.86 and RE at T2:T4: T6: 64.29, 46.79, 38.46) as compared to Group 2 and Group 3. Group 3 had a higher value and had a gradual sloping

Table 1: Demographic data

	Group 1	Group 2	Group 3	Significance level
Age				ANOVA
n	28	28	28	*P*=0.738
Mean	40.6	40.6	38.4	NS
SD	13.34	13.34	13.31	
Sex				
Female	12	7	15	Chi-square test
Male	16	21	13	*P*=0.0896
				NS
ASA				
1	23	24	24	Chi-square test
2	5	4	4	*P*=0.182
				NS
BMI				
n	28	28	28	ANOVA
Mean	23.75	23.09	21.43	*P*=0.1
SD	2.57	3.33	3.36	NS

SD=Standard deviation; BMI=Body mass index; ASA=American Society of Anesthesiologist; NS=Not significant; ANOVA=Analysis of variance

Table 2: Total dosage of propofol

	n	Mean	SD	95% CI		ANOVA *P*	Significance level
				Lower Bound	Upper Bound		
Total propofol							
Group 1	28	1.68	0.16	1.61	1.74	<0.001	HS*
Group 2	28	1.43	0.18	1.36	1.50		
Group 3	28	1.29	0.15	1.23	1.35		

SD=Standard deviation; CI=Confidence interval; ANOVA=Analysis of variance; HS=Highly significant

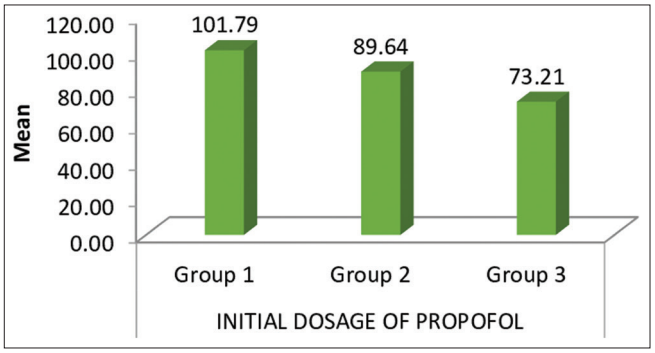


Figure 1: Mean initial dose of propofol

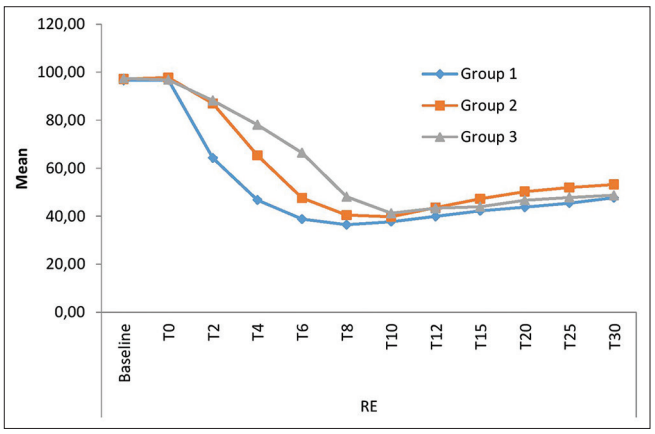


Figure 2: Response entropy

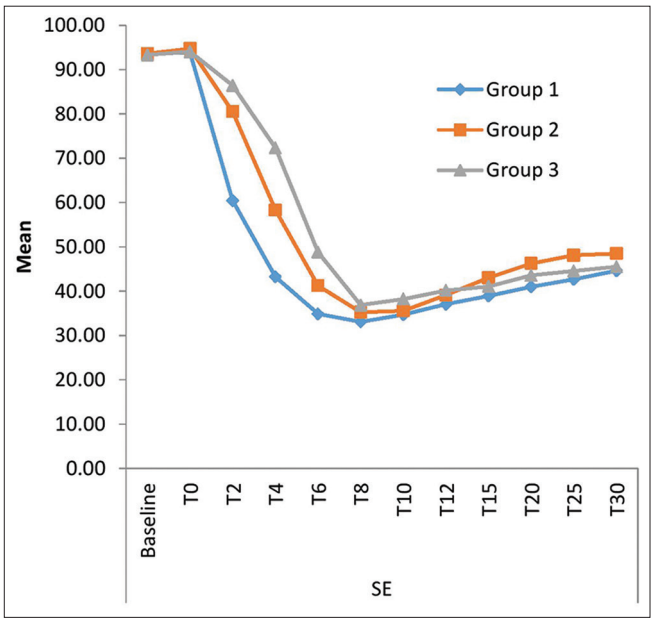


Figure 3: State entropy

on the graph as shown [Figures 2 and 3]. The values of RE and SE at T2, T4, and T6 were statistically significant between the groups and clinically significant between Groups 2 and 3. The entropy values at the other time intervals were comparable, with Group 1 values being lower than Group 2 and 3, but at any given time interval they were statistically not significant. The comparison of mean heart rate between the groups showed no statistically significant difference [Figure 4].

The incidence of vocalization/bucking/movement was more in Group 1 (28.6%) when compared to Group 2 (10.7%) and 3 (10.7%). The incidence of hypotension was seen in about 42.9% of Group 1 participants when compared to Group 2 and Group 3 which were 28.6% and 17.8%, respectively. The fall in blood pressure was managed with intravenous fluid boluses. Vasopressors were not required to maintain the blood pressure in the different groups.

In our study, the primary outcomes measured included the total dosage of propofol required for induction of anesthesia, when the propofol fentanyl mixture was given at varying time intervals. The secondary outcomes measured included the initial dose of propofol required for induction, the entropy values, the incidence of vocalization/bucking/movement after the initial dose of propofol, the incidence of oxygen saturation, heart rate, and blood pressure variations in these patients.

Table 3: Comparison of mean arterial pressure between the groups

	Post hoc analysis by Bonferroni test -*P*			Significance level
	Group 1 versus 2	Group 1 versus 3	Group 2 versus 3	
MAP				
Baseline	1.000	1.000	1.000	
T0	1.000	1.000	1.000	
T2	0.000	0.003	0.273	HS*
T4	0.000	0.000	0.984	HS*
T6	0.000	0.004	1.000	HS*
T8	0.146	0.081	1.000	
T10	1.000	0.612	1.000	
T12	0.206	0.788	0.012	
T15	0.006	1.000	0.056	

HS=Highly significant: MAP=Mean arterial pressure

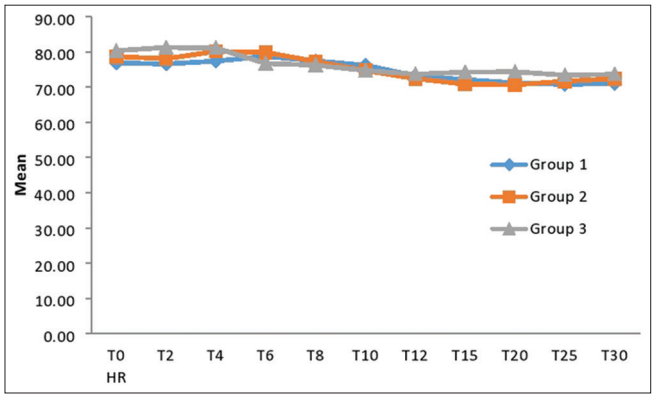


Figure 4: Comparison of Mean heart rate between the 3 groups

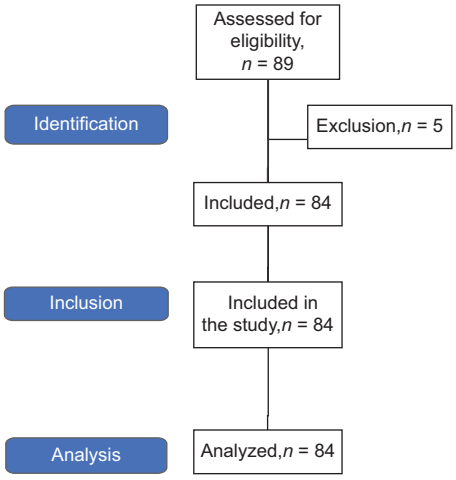
DISCUSSION

In our study, we selected a dose of 2 μg/kg dose of fentanyl as this concentration provides better hemodynamic stability and adequate analgesia. These findings were observed in the study conducted by Choudhary *et al*. In their study, 2, 3, and 4 μg/kg dose of fentanyl was used for premedication in Functional endoscopic sinus surgery surgeries and it was found that patients receiving 2 μg/kg dose were more stable.[8]

Our findings were comparable to the outcomes observed by Darlong *et al*. In their study, the duration between fentanyl and propofol administration was 2, 3, and 5 min, respectively. They found that the total propofol dose required for induction was higher when the time intervals between the administration of both drugs were reduced. They also found that the incidence of hemodynamic instability was also high in the group in which the drugs were administered in 2 min.[9]

In another study, the induction of anesthesia was based on the entropy values in 60 patients undergoing coronary artery bypass graft. It was observed that entropy monitoring reduced the induction dose of propofol and offered better hemodynamic stability compared to the induction following "no response to verbal commands". These findings were contradicting our observation. In our study, we found that a higher dosage of propofol was required in Group 1 which had lower entropy values initially compared to the other groups.[10]

Our findings were comparable to the findings made by Kaur *et al*. In their study patients were compared with 2 μ/kg fentanyl, 20 and 40 μ/kg butorphanol, respectively, as premedication.



Flowchart 1: Strobe flow chart

They observed that the premedication with these drugs reduced the induction dose of propofol. Furthermore, they found that the loss of response to verbal commands occurred at a higher entropy value, which was similar to our observations.[11]

In our study, we found that patients receiving a higher dose of propofol had a sudden fall in entropy values and were more hemodynamically unstable. Furthermore, we found that when the duration of fentanyl and propofol was increased as seen in Group 3, induction was possible at higher entropy values. This discrepancy can be explained by the following study.

In this study, the effect of opioids including fentanyl on propofol induction and the effect of site concentration was compared using BIS and sedation score. It was found that there was a higher BIS value and lower propofol consumption in the propofol fentanyl group which was similar to our findings. One reason for this observation could be that opioids at lower doses may produce minimal EEG changes in the cerebral cortex.[12]

Thus, we observed that increasing the duration of fentanyl and propofol administration has favorable outcomes concerning hemodynamic parameters and the depth of anesthesia.

There was a noticeable lag between the peak plasma concentration of fentanyl and the maximum slowing on the EEG, despite the clinical sense that fentanyl has a rapid onset of action. This delay is due to the fentanyl's 6.4-min effect-site equilibration period between blood and the brain. Hence, when propofol is given with a time lag of more than 3 min after fentanyl administration, it was found that consumption of propofol was reduced. Hence, this can be taken as an advantage to provide more hemodynamically stable anesthesia.

Fall in systolic blood pressure (SBP) was statistically significant between Groups 1 and 2 and between Groups 1 and 3. However, Group 2 and Group 3 did not statistically differ from one another. As a result, Group 1 experienced a greater decrease in SBP than Groups 2 and 3. This variation can be attributed to the administration of boluses of propofol and increased initial doses of propofol. Furthermore, we found that the entropy values were at an elevated level of the desired range of anesthesia in the groups, especially Groups 2 and 3 which proved that the correlation between depth of anesthesia and entropy values can vary. The entropy values were maintained between 40 and 60 throughout the surgery.

Thus the depth of anesthesia after varying the time interval could not be proven in our study.

The strength of our study was that we included entropy values to measure the depth of anesthesia and this association was linked to the patient's hemodynamic status, while most of the previous studies did not consider entropy monitoring in their research work. One limitation of the study was that the correlation between the entropy values and the depth of anesthesia could not be satisfactorily proven in our study. We could have included the recovery details of the patient. Another limitation was that we failed to confirm our findings in correlation with the plasma concentration of drugs, due to organizational issues. Finally, we could have included patients with poor cardiac performance.

These observations can be included in future studies on similar topics. The effect of varying the duration of the drug administration can be studied in hemodynamically unstable patients. Furthermore, randomized controlled trials with different dosages of fentanyl and at different time intervals between fentanyl propofol administrations can be undertaken.

CONCLUSION

The groups receiving propofol after 3 min of fentanyl infusion had a lesser requirement of propofol, lesser incidence of hypotension, and a more gradual drop in entropy. Hence, it is preferable to administer propofol at least 3 min after fentanyl administration during induction which helps us to achieve stable hemodynamics. Furthermore, there is no variation in the depth of anesthesia attained in the distinct study population.

Data availability statement

The data that support the findings of this study are available from the corresponding author, Neeta Santha, upon reasonable request.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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