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Research Article

EFFECT OF VARYING TIME INTERVALS BETWEEN FENTANYL AND PROPOFOL ADMINISTRATION ON PROPOFOL REQUIREMENT FOR INDUCTION OF ANESTHESIA - AN OBSERVATIONAL STUDY

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ABSTRACT

Objective: The objective of the study is to determine the dose of propofol required for induction when fentanyl was administered just before, 3 min, and 5 min before propofol administration. Furthermore, to determine changes in heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP), when fentanyl was given at varying time intervals.

Methods: A prospective observational study was conducted in a tertiary care teaching hospital for 12 months. A total of 150 patients belonging to ASA 1 and 2 in the age group of 18–60 years scheduled for elective surgery under general anesthesia were allocated into three groups. Group 1 received propofol immediately after a 2 mcg/kg fentanyl injection and Group 2 and Group 3 received propofol 3 and 5 min, respectively, after the administration of fentanyl. The total dose of propofol required for induction is noted. Heart rate, systolic, diastolic, and MAPs after induction were also noted. Data analysis was done using SPSS version 25.

Results: All three groups were comparable concerning demographic variables. The total dose of propofol required for induction was highest in Group 1, where propofol was given immediately after fentanyl, followed by Group 2, and lowest in Group 3 where propofol was given 5 min after fentanyl. Fall in heart rate, SBP, DBP, and MAP after propofol administration was highest in Group 1, followed by Group 2, and least in Group 3 where fentanyl was administered 5 min before propofol. The results were statistically significant.

Conclusion: Administering fentanyl 5 min before propofol causes a marked reduction in the dose requirement of propofol along with a significantly decreased incidence of hypotension after induction.

Keywords: Propofol, Fentanyl, Anesthesia.

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INTRODUCTION

Propofol can be used for induction and maintenance of anesthesia. It is the most widely used anesthetic today. It acts by facilitation of inhibitory neurotransmission mediated by $GABA_A$ receptor binding. This receptor is coupled to the chloride channel, and receptor activation leads to hyperpolarization of the nerve membrane. The onset of action after a dose of 2.5 mg/kg is rapid, within one arm brain circulation time. Its peak effect is seen at 90–100 s [1]. Propofol is generally known for its hemodynamic depressant effects. The myocardial depressant effect and vasodilation depend on the dose and plasma concentration. An induction dose of 2–2.5 mg/kg produces a 25–40% reduction in systolic blood pressure (SBP). Mean and diastolic blood pressure (DBP) decreases similarly. The decrease in arterial blood pressure is associated with a decrease in cardiac output and cardiac index (±15%), stroke volume index (±20%), and systemic vascular resistance (15%–25%). The left ventricular stroke work index also is decreased (±30%). Propofol has a high extraction ratio of 0.79–0.92. This suggests that the metabolic clearance of propofol may be susceptible to changes in hepatic perfusion and not affected by enzyme inhibition.

The inclusion of an opioid as a component of balanced anesthesia decreases somatic and autonomic responses to airway manipulations reduces preoperative pain and anxiety, lowers the requirement of anesthetic agents, improves hemodynamic stability, and provides postoperative analgesia.

Fentanyl is the most widely used intravenous opioid for intraoperative analgesia in most parts of the world. Pharmacokinetic and pharmacodynamic interactions exist between fentanyl and propofo1. Alfentanil and remifentanil have been shown to increase blood propofol concentrations by reducing the elimination and distribution clearance of propofol [2].

Administration of opioids before propofol as a part of a balanced anesthetic induction technique has been shown to decrease the dose of propofol required for induction [3]. This study was done by comparing the effect of varying time intervals between fentanyl and propofol administration on the dose of propofol required for induction of general anesthesia. We hypothesized that there could be a significant reduction in the dose of propofol when fentanyl is given 5 min before propofol administration during induction of anesthesia.

METHODS

This was a prospective study done over a period of 1 year in a tertiary care teaching hospital. The study was started after getting clearance from the Institutional Review Board. One hundred and fifty patients (American Society of Anesthesiologists [ASA 2]) of either sex aged 18–60 years scheduled for elective surgery under general anesthesia were randomly allocated to one of the three groups using a computer-generated random numbers chart. Group 1 received propofol immediately after the fentanyl injection. Group 2 and Group 3 received propofol 3 and 5 min after administration of 2 mcg/kg fentanyl, respectively. An informed written consent was taken from all patients included in the study.

Inclusion criteria

ASA 1 and ASA 2 patients undergoing elective surgery under general anesthesia aged between 18 and 60 years.

Exclusion criteria

Include patients allergic to propofol or fentanyl, emergency surgery, patients with cardiovascular, respiratory, hyperthyroidism, hypothyroidism, cerebrovascular disease, renal disease including hypertension, history of alcohol or drug abuse, obese BMI >30 kg/m^2, patients with anticipated difficult airway, patients taking any drugs likely to affect the requirement of propofol or hemodynamic parameters.

Methodology

No sedative premedication was given to the patient. In the operating room, standard preinduction monitors including pulse oximetry, electrocardiography, and non-invasive blood pressure were recorded, followed by recordings at 1-min intervals. Intravenous infusion of ringer lactate 10 mL/kg was started. Patients were preoxygenated with 100% oxygen for 3 min. Group 1: Received propofol immediately after 2 mcg/kg fentanyl injection. Group 2: Received propofol 3 min after 2 mcg/kg fentanyl injection. Group 3: Received propofol 5 min after 2 mcg/kg fentanyl injection.

Propofol was taken in a 10 mL syringe at 10 mg/mL. Propofol was injected slowly at a rate of 1 mL/s while communicating verbally with the patient.

Induction was considered complete when there was a loss of verbal contact, fixed eyeballs, regular and rhythmic respiration, and loss of muscle tone. After confirmation of mask ventilation vecuronium, 0.1 mg/kg was administered to facilitate endotracheal intubation. In case of any movement, bucking, or vocalization noted at the initiation of mask ventilation additional dose of propofol as 20 mg bolus was administered. The total dose of propofol required was noted. Heart rate, SBP, DBP, and mean arterial pressure (MAP) recording were done every minute from fentanyl administration till completion of induction. In the case of hypotension which is defined as a fall of SBP of more than 20% of baseline, an intravenous bolus of 300 mL of ringer lactate was administered. Hypotension not responding to fluid boluses was treated with 100 µg boluses of intravenous phenylephrine. Occurrences of hypotension, bradycardia, and requirement of fluid bolus and vasopressors were noted.

Statistical analysis

Data were coded and entered into MS EXCEL software and analyzed using IBM SPSS version 25. Analysis of various factors was done using Chi-square test for qualitative variables and the F-test or Analysis of Variance test for quantitative variables. Appropriate non-parametric tests were applied wherever required. Results were considered statistically significant for $p<0.05$.

RESULTS

Age distribution among groups

Group	n	Mean	Standard deviation	F	p-value
Age					
Group 1	50	40.18	11.982	0.645	0.526
Group 2	50	38.48	12.831		
Group 3	50	37.38	12.441		
Total	150	38.68	12.393		

No statistical significance could be ascertained in age distribution among groups p=0.5 (*p>0.05).

Sex distribution among groups

Sex distribution was comparable among groups (*p>0.05).

ASA PS grading among groups

ASA-PS were comparable among groups p=0.13 (*p>0.05).

Comparison of the total dose of propofol required for induction

It was found that the amount of propofol required for induction was highest in Group 1 (115.3±12.3 mg) and lowest in Group 3 (81.2±12.2 mg). In Group 2, the dose required was 97.8±7.6 mg,

Sex	Group			Total	Chi-square	p-value
	Group 1	Group 2	Group 3			
Female						
Count	25	24	25	74	0.053	0.974
%	33.8	32.4	33.8	100.0		
Male						
Count	25	26	25	76		
%	32.9	34.2	32.9	100.0		
Total						
Count	50	50	50	150		
%	33.3	33.3	33.3	100.0		

ASA physical status	Groups			Total	Chi-square	p-value
	1	2	3			
ASA PS						
1						
Count	36	31	40	107	3.977	0.137
% Within ASA PS	33.6	29.0	37.4	100.0		
2						
Count	14	19	10	43		
% Within ASA PS	32.6	44.2	23.3	100.0		
Total						
Count	50	50	50	150		
% Within ASA PS	33.3	33.3	33.3	100.0		

ASA PS: American Society of Anesthesiologists physical status

Groups	n	Mean	Standard deviation	F	p-value
TD propofol					
Group 1	50	115.30	12.306	121.385	0.000
Group 2	50	97.80	7.637		
Group 3	50	81.20	12.229		
Total	150	98.10	17.701		

which was less than in Group 1. The p-value obtained is 0.00 (**p<0.01), hence statistically significant.

Comparison of dose of propofol (mg/kg) among groups

Groups	n	Mean	Standard deviation	F	p-value
Dose per kg					
Group 1	50	1.8210	0.1311	324.500	0.000
Group 2	50	1.5418	0.097660		
Group 3	50	1.2870	0.079056		
Total	150	1.54993	0.242327		

The dose of propofol per kg body weight was lowest in Group 3, 1.28±0.07 mg/kg, and highest in Group 1 (1.82±0.13 mg/kg). In Group 2, the dose of propofol required was 1.54±0.097 mg/kg which is less than that required in Group 1. The p-value obtained is 0.00 (**p<0.01), hence statistically significant.

Comparison of heart rate per minute among groups

The heart rate slightly increased from baseline after fentanyl in Group 1 and in Group 2 and Group 3, heart rate decreased after fentanyl. After propofol heart rate decreased in all groups, with more decrease from baseline in Group 1, followed by Group 2 and then Group 3. The results are statistically significant (*p<0.05).

Comparison of SBP among groups

The SBP decreased from baseline in Group 1 and Group 3 after fentanyl administration with more decrease in Group 3. After propofol

HR	n	Mean	Standard deviation	F	p-value
Baseline					
Group 1	50	79.68	6.953	1.627	0.200
Group 2	50	77.70	9.558		
Group 3	50	77.00	6.197		
Total	150	78.13	7.738		
After fentanyl					
Group 1	50	81.04	6.785	21.632	0.000
Group 2	50	73.40	9.293		
Group 3	50	71.86	5.932		
Total	150	75.43	8.446		
After propofol					
Group 1	50	65.84	5.223	4.438	0.013
Group 2	50	68.22	8.221		
Group 3	50	69.90	5.963		
Total	150	67.99	7.003		

Measured in mmHg					
Systolic blood pressure	**n**	**Mean**	**Standard Deviation**	**F**	**p-value**
Baseline					
Group 1	50	124.20	8.751	0.837	0.435
Group 2	50	123.50	8.469		
Group 3	50	122.12	7.244		
Total	150	123.27	8.172		
After fentanyl					
Group 1	50	121.44	8.142	10.824	0.000
Group 2	50	124.42	6.408		
Group 3	50	117.70	7.054		
Total	150	121.19	7.699		
After Propofol					
Group 1	50	100.34	5.819	50.792	0.000
Group 2	50	107.96	6.866		
Group 3	50	113.52	6.949		
Total	150	107.27	8.480		

administration, SBP decreased in all groups with more decrease from baseline in Group 1, followed by Group 2, and least in Group 3. The results are statistically significant (*p<0.05).

Comparison of DBP among groups

Diastolic blood pressure is measured in mmHg					
Diastolic blood pressure	**n**	**Mean**	**Standard Deviation**	**F**	**p-value**
Baseline					
Group 1	50	73.44	5.380	2.739	0.068
Group 2	50	75.82	4.835		
Group 3	50	74.66	5.025		
Total	150	74.64	5.144		
After fentanyl					
Group 1	50	70.14	3.264	48.804	0.000
Group 2	50	78.20	5.182		
Group 3	50	70.88	4.847		
Total	150	73.07	5.778		
After Propofol					
Group 1	50	57.96	4.125	68.425	0.000
Group 2	50	64.38	3.989		
Group 3	50	67.96	4.832		
Total	150	63.43	5.978		

After propofol administration, DBP decreased in all groups, with more decrease from baseline in Group 1, followed by Group 2 and then Group 3. The results are statistically significant (*p<0.05).

Comparison of MAP among groups

After propofol administration, MAP decreased in all 3 groups, with greater decrease noted in Group 1 (72.2±3.7), followed by Group 2 (78.7±4.6) and then Group 3 (83.2±4.6). The results are statistically significant (*p<0.05).

Mean arterial pressure	n	Mean	Standard Deviation	F	p-value
Baseline					
Group 1	50	90.54	5.853	0.711	0.493
Group 2	50	91.66	5.386		
Group 3	50	90.52	5.156		
Total	150	90.91	5.462		
After fentanyl					
Group 1	50	87.24	4.312	34.730	0.000
Group 2	50	93.64	4.881		
Group 3	50	86.52	4.892		
Total	150	89.13	5.668		
After Propofol					
Group 1	50	72.20	3.720	80.530	0.000
Group 2	50	78.76	4.662		
Group 3	50	83.20	4.634		
Total	150	78.05	6.270		

Intergroup comparison of hypotension requiring fluid bolus during induction

Hypotension during induction was managed by an intravenous fluid bolus of ringer lactate [Table 1].

Hypotension during induction requiring fluid bolus was more in Group 1 (28%) than in Group 2 (6%). There was no incidence of hypotension requiring fluid bolus in Group 3. The results are statistically significant (**p<0.01).

DISCUSSION

Administering opioids before propofol as a part of a balanced anesthetic induction technique has been shown to decrease the dose of propofol required for induction [4,5]. The combination of fentanyl and propofol has been studied extensively and their effects are found to be synergistic [6,7].

Numerous studies are comparing the effect of fentanyl administration on the dose of propofol required for induction. However, studies establishing their temporal relationship are fewer. Hence, this study was done comparing the effect of varying time intervals between fentanyl and propofol administration on the dose of propofol required for induction of general anesthesia.

The demographic profile of our patients was comparable concerning age, weight, sex, and ASA physical status and there were no statistically significant differences among the groups (p>0.05). The sample size was calculated based on the study conducted by Darlong *et al*. [8].

In our study, the total dose of propofol required for induction was highest in Group 1 where propofol was given immediately after fentanyl, followed by Group 2, and lowest in Group 3 where propofol was given 5 min after fentanyl. The findings were statistically significant. Our findings were consistent with the study conducted by Darlong *et al*.

Fall in heart rate, SBP, DBP, and MAP after propofol administration was higher in Group 1, followed by Group 2, and least in Group 3 where fentanyl was administered 5 min before propofol. The results were statistically significant. This is consistent with the study by Kumar *et al* [9]. The study by Kumar *et al*. showed that administering intravenous fentanyl 2 mcg/kg, 5 min before induction was found to be most effective in attenuating hemodynamic response.

The incidence of hypotension during induction and requirement of fluid bolus was higher in Group 1 patients who received propofol immediately after fentanyl (28%), followed by Group 2 (6%). There was no incidence of hypotension in Group 3. The results were statistically significant.

Table 1: Intergroup comparison of the requirement of fluid bolus

Groups	Fluid bolus		Total	Chi-square	p-value
	No	Yes			
Group 1					
Count	36	14	50	21.62	0.000
%	72.0	28.0	100.0		
Group 2					
Count	47	3	50		
%	94.0	6.0	100.0		
Group 3					
Count	50	0	50		
%	100.0	0.0	100.0		
Total					
Count	133	17	150		
%	88.7	11.3	100.0		

No patient in any group had bradycardia or needed phenylephrine injection for refractory hypotension.

Kaur *et al*. [10] studied the effect of fentanyl and 2 doses of butorphanol pre-treatment on the induction dose of propofol. Butorphanol and fentanyl 2 mcg/kg pre-treatment reduced the induction dose of propofol and conferred hemodynamic stability at induction and intubation.

Vullo *et al*. [11] studied the hemodynamic impact of the increasing time interval between fentanyl and propofol administration during anesthesia induction. Patients undergoing non-cardiac surgery with endotracheal intubation were randomized into 6-time dose groups (1 or 2 min/1, 1.5 or 2 mg/kg of propofol). He concluded that in patients under 55 years, increasing the time between administration of fentanyl and propofol to 2 min does not generate hemodynamic benefits. In patients over 55 years, the 2-min 2 mg/kg group showed the greatest SBP reduction (36±12%) at pre-intubation. Increasing the time interval between fentanyl and propofol administration to 3–5 min and also using titrated doses of propofol as in our study would have resulted in greater hemodynamic stability.

There are a few limitations to the study. Plasma concentrations of fentanyl and propofol were not measured. The endpoint of induction of anesthesia was assessed; only clinically, encephalography-based monitors were not used.

CONCLUSION

When fentanyl was administered 5 min before propofol, there was a significant reduction in the dose requirement of propofol along with a significantly decreased incidence of hypotension during induction. That is, injection of propofol, after the peak effect of fentanyl is achieved, will lead to a significant reduction in propofol dose and associated side effects.

AUTHOR'S CONTRIBUTION

All the authors contributed to the preparation of the final manuscript.

CONFLICT OF INTEREST

Authors state that there is no conflict of interest.

FUNDING INFORMATION

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