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To Determine the Effect of Varying Time Intervals Between Fentanyl and PropofolAdministration on Propofol Requirement for Induction of Anesthesia- A ProspectiveObservational Study

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KEYWORDS

Fentanyl and Propofol, Anesthesia

ABSTRACT:

INTRODUCTION:

To determine the effect of varying time intervals between fentanyl and propofol administration on propofol requirement for induction of anesthesia- a prospective observational study

METHOD:

Propofol induction of anesthesia following fentanyl administration should facilitate a smooth induction with a reduction in propofol induction dose and side effects. After obtaining institutional ethical approval, 108 American Society of Anaesthesiologists physical status I–II patients aged 18–65 undergoing elective surgery under general anaesthesia were randomly allocated to one of three groups. In Groups 1, 2, and 3, 2 mcg/kg fentanyl was administered just prior, 3 minutes prior, and 5 minutes prior to propofol induction. Recorded hemodynamic parameters and the required propofol induction dose. Incidence of hypotension, fluid bolus requirement, need for vasopressor administration, incidence of movement or vocalization, and incidence of apnoea post-induction were recorded. The statistical analysis was conducted using SPSS version 24.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS:

The mean dose of propofol required for induction was highest in Group 1 and lowest in Group 3 (1.75 ± .22 for Group 1, 1.45 ± .36 for Group 2, and 1.25 ± .15 for Group 3.) Incidence of hypotension during induction and need for fluid bolus requirement was significantly higher in Group 1 (19%) and Group 2 (16.7%) than in Group 3 (7.1%) p = 0.001). 1 case among the whole study population required vasopressor post-induction in Group 3. Incidence of vocalization and movement post-induction was higher in group 1 (19%) than in group 2(16.7%) and group 3 (7.1%). Incidence of apnoea post-induction was highest in Group 2 (83.3%) than in Group 1 (76.2%) and Group 3 (59.5%).

CONCLUSION:

Administration of fentanyl five minutes prior to propofol reduces the amount of propofol required and significantly reduces the occurrence of hypotension compared to when given 3 minutes after fentanyl.

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1. INTRODUCTION:

Propofol is an ideal anesthetic agent with a rapid onset of hypnosis and rapid awakening with minimal excitation. Propofol has become the preferred induction agent during the past two decades because of its smooth induction and quick recovery. Compared to conventional induction drugs such as thiopentone and ketamine, propofol provides better intubating conditions, superior airway integrity, and the extra benefit of suppressing the airway reflex. However, the anaesthesiologist's primary concern is hemodynamic instability caused by the typical dose needed for induction of 2–3 milligrams per kilogram and the pain during drug injection.(1)Propofol doses often exceed 2.5 mg/kg when administered alone, which shall account for cardiovascular, and respiratory distress, increased apnoeic time, prolongation of sedation, and decrease in blood pressure. (2) Therefore, propofol as the sole anesthetic agent is unsatisfactory. (3) It has been studied that giving opioids before giving propofol shall lower the quantity of propofol and lower instability in hemodynamic parameters.

Apnoea is a frequently sighted adverse reaction after propofol is used for induction. Co-induction with opioids decreases the chances of apnoea.(4)To mitigate this problem, the concept of balanced anesthesia has been expanded to incorporate the administration of an opioid prior to propofol. Commonly used combination for induction: propofol with a short-acting opioid such as fentanyl. Fentanyl, a potent synthetic mu-receptor agonist, in bolus doses of up to 2 mcg/kg, has frequently been utilized for induction of anesthesia in order to provide analgesia during surgical procedures and reduce the sympathetic response to intubation.(6) Propofol if injected after the peak effect of fentanyl, it will lead to a significant reduction in propofol dose and thereby side effects. (7)

Administration of opioids before giving propofol reduces the dose requirement of propofol and provides better hemodynamic stability.

2. OBJECTIVES:

Primary Objective:

To study the optimal dose of propofol required for induction when given immediately, 3 min and 5 mins after fentanyl administration

Secondary Objective

- To compare the incidence of movement, vocalization
- Additional propofol requirement
- To compare post induction hemodynamic changes, incidence of hypotension and fluid bolus requirement

INCLUSION CRITERIA:

1. Adult patients between the age 18 and 65 years
2. ASA I and II physical status
3. Elective procedures under general anesthesia

EXCLUSION CRITERIA:

1. Patient not willing to be in the study group
2. Contraindication to GA
3. ASA-III & IV physical status
4. BMI > 35 kg/m^2
5. Anticipated difficult airway
6. Pregnant patients
7. History of allergy to study drug
8. Drug abuse including chronic alcoholics
9. Emergency procedures

4.METHODS:

Patients will be considered into 3 groups,42 in each group.

Group 1- propofol administered immediately after fentanyl, Group 2- propofol administered 3 min after fentanyl, Group 3- propofol administered 5 min after fentanyl. On arrival to the operative room an IV access

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with 18 or 20 Gauge IV cannula will be secured. In the operating room, standard ASA monitors including electrocardiography, pulse oximetry, and non-invasive blood pressure will be attached. Baseline heart rate and blood pressure will be recorded, followed by recordings at five-minute intervals. IV infusion with Ringer's Lactate will be started at 10 ml/kg/hr and preoxygenated with 100% of Oxygen (O2) for 3 minutes

Fentanyl 2 mcg/kg will be administered. Anaesthesiologist posted in the operating room will inject fentanyl and the time will be noted. Patients will receive propofol immediately after fentanyl administration,3min after fentanyl administration and 5 min after fentanyl administration according to the study group and the results will be observed. The anaesthesiologist who administers propofol will start the pre-loaded propofol while communicating verbally with the patient and will note the dose required to produce loss of verbal response. After checking for adequate ventilation, the patients will receive muscle relaxant – Inj. Atracurium 0.5mg/kg or Inj. Vecuronium 0.1mg/kg body weight IV. In case of movement or vocalization, additional doses of propofol in aliquots of 20 mg will be administered and the total dose administered will be noted by the researcher. Incidence of apnoea will be recorded. Pulse rate (PR), Systolic BP (SBP), Diastolic BP (DBP), Mean Arterial Pressure (MAP), and SpO2 will be noted every 2 minutes from fentanyl administration followed by every 5 minutes. Outcomes will be recorded and interpreted by the researcher. In case of hypotension following induction, an IV bolus of Ringer's lactate will be given. Hypotension not responding to fluid bolus will be treated using of IV Phenylephrine 1-2 mcg/kg. Occurrence of hypotension, bradycardia, requirement of fluid boluses, vasopressors and apnoea following induction will be recorded.

5.RESULTS:

Age, sex, ASA, total body weight, height, BMI, mean dose of propofol per kilogramme for induction, hemodynamics, frequency of hypotension, fluid bolus or vasopressor requirement for hypotension management, incidence of movement or vocalization and incidence of apnea following induction, if any were compared between 3 groups.

Age, gender, ASA, total body weight, height, and BMI had no significant statistically between groups ($p > 0.05$)

TABLE 1: COMPARISON OF MEAN PROPOFOL DOSE REQUIREMENT PER KG

Parameter	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	Group 3 (Mean ± SD)	p Value
MEAN DOSAGE OF PROPOFOL REQUIREMENT PER KG	1.75 ± 0.22	1.45 ± 0.36	1.25 ± 0.15	0.001

Mean propofol dose requirement per kg was compared between the groups and it was found statistically significant, p value <0.05. The mean propofol requirement per kg was 1.75 ± .22 for group 1, 1.45 ± .36 for group 2 and 1.25 ± .15 for group 3.

TABLE 2: ADDITIONAL PROPOFOL DOSE DISTRIBUTION

Additional Dose (mg)	Group 1 (n=42)	Group 2 (n=42)	Group 3 (n=42)	p Value
0	32 (76.2%)	34 (81.0%)	38 (90.5%)	**0.045**
20	10 (23.8%)	8 (19.0%)	4 (9.5%)	
Total	42 (100%)	42 (100%)	42 (100%)	

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The additional propofol dose requirement between 3 groups was statistically significant (p value 0.045) in which more no of cases in group 1 (10 cases) required additional propofol requirement.

TABLE 3: MEAN HEART RATE COMPARISON

Mean Heart Rate	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	Group 3 (Mean ± SD)	p Value
Baseline	85 ± 15.174	84 ± 17.466	86 ± 10.464	0.345
After Induction	105 ± 15.745	100 ± 19.515	95 ± 12.478	0.010
1 Minute	100 ± 16.264	97 ± 14.463	94 ± 10.729	0.015
3 Minute	90 ± 12.626	88 ± 13.537	85 ± 9.052	0.020

The mean heart rate comparison between 3 groups showed statistical significance after induction (p value 0.010), after 1 min (p value 0.015) and after 3 min (p value 0.020)

TABLE 4: MEAN SYSTOLIC BLOOD PRESSURE COMPARISON

Mean Systolic Blood Pressure	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	Group 3 (Mean ± SD)	p Value
Baseline	100 ± 11.200	99 ± 11.885	102 ± 12.706	0.203
After Induction	110 ± 10.459	109 ± 12.089	112 ± 14.255	0.017
1 Minute	95 ± 13.464	94 ± 15.543	97 ± 14.935	0.012
3 Minutes	100 ± 10.016	99 ± 11.410	102 ± 12.934	0.020

Mean systolic blood pressure comparison between 3 groups showed statistical significance after induction (p value 0.017), after 1 min (0.012) and after 3 min (0.020).

TABLE 5: MEAN DIASTOLIC BLOOD PRESSURE COMPARISON

Mean Diastolic Blood Pressure	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	Group 3 (Mean ± SD)	p Value
Baseline	75 ± 11.301	74 ± 12.718	77 ± 12.848	0.100
After Induction	85 ± 12.936	84 ± 13.285	87 ± 14.087	0.014
1 Minute	78 ± 10.678	77 ± 10.278	80 ± 13.609	0.019
3 Minutes	75 ± 9.429	74 ± 11.833	77 ± 12.411	0.027

Mean diastolic blood pressure comparison between 3 groups showed statistical significance after induction (p value 0.014) after 1 min (p value 0.019) and after 3 min (p value 0.027)

TABLE 6: MEAN OF MEAN ARTERIAL PRESSURE COMPARISON

Mean of Mean Arterial Pressure	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	Group 3 (Mean ± SD)	p Value
Baseline	80 ± 12.019	79 ± 13.77	81 ± 16.213	0.343
After Induction	95 ± 12.013	93 ± 15.426	96 ± 14.284	0.013
1 Minute	85 ± 10.479	83 ± 13.823	86 ± 10.933	0.019
3 Minute	80 ± 12.020	79 ± 15.797	82 ± 13.427	0.024

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The mean of mean arterial pressure was compared between groups during baseline, after induction, 1 minute and 3 minutes and it showed statistical significance after induction (p value 0.013),after 1 min (p value 0.019) and after 3 min (p value 0.024)

The mean oxygen saturation was compared between groups during baseline, after induction, 1 minute and 3 minutes. There was no statistical significance between the groups (p value > 0.05)

TABLE 7: INCIDENCE OF HYPOTENSION POST-INDUCTION (MAP < 65)

Hypotension	Group 1	Group 2	Group 3	p Value
Yes	8 (19.0%)	7 (16.7%)	3 (7.1%)	0.001
No	34 (81.0%)	35 (83.3%)	39 (92.9%)	
Total	42 (100%)	42 (100%)	42 (100%)	

The incidence of hypotension, when compared between 3 groups showed statistical significance, p value (0.001) with the incidence of hypotension higher in group 1.

TABLE 8: INCIDENCE OF VOCALIZATION – MOBILIZATION DISTRIBUTION

Vocalization – Mobilization	Group 1 (n=42)	Group 2 (n=42)	Group 3 (n=42)	p Value
Yes	8 (19.0%)	7 (16.7%)	3 (7.1%)	0.025
No	34 (81.0%)	35 (83.3%)	39 (92.9%)	
Total	42 (100%)	42 (100%)	42 (100%)	

Among the total cases, 8 patients in 1, 7 patients in 2 and 3 patients in 3 had an incidence of vocalisation/movement. Hence, an aliquot of 20 mg of propofol was administered. In group 1 the no of cases requiring additional propofol was more and it is statistically significant (p value 0.025)

TABLE 9: INCIDENCE OF FLUID BOLUS REQUIREMENT DISTRIBUTION

Fluid Bolus Requirement	Group 1 (n=42)	Group 2 (n=42)	Group 3 (n=42)	p Value
Yes	10 (23.8%)	8 (19.0%)	4 (9.5%)	0.045
No	32 (76.2%)	34 (81.0%)	38 (90.5%)	
Total	42 (100%)	42 (100%)	42 (100%)	

The incidence of fulid bolus requirement was statistically significant (p value 0.045) and the no of cases was lesser in group 3.

TABLE 10: INCIDENCE OF VASOPRESSOR REQUIREMENT DISTRIBUTION

Vasopressor Requirement	Group 1 (n=42)	Group 2 (n=42)	Group 3 (n=42)	p Value
Yes	4 (9.5%)	3 (7.1%)	1 (2.4%)	0.030
No	38 (90.5%)	39 (92.9%)	41 (97.6%)	
Total	42 (100%)	42 (100%)	42 (100%)	

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The requirement of vasopressor was statistically significant (p value 0.030) and the no of cases was more in group 1.

6.DISCUSSION:

In current study, administration of fentanyl 3 and 5 minutes prior to propofol resulted in considerable decrease in dosage of propofol on comparison with administration of propofol immediately after fentanyl. Propofol has many desirable characteristics as an induction drug (intravenously), including a quicker onset of action (one arm-brain circulation time) and a rapid recovery with minimal excitation. (9) (10). In addition to its antiemetic actions, propofol inhibits reflexes in airway, reduces intra cranial pressure & possesses anti-convulsant characteristics. (7). Propofol is contraindicated in subjects with unstable hemodynamic conditions, severe cardiovascular disease, and dehydration, which include a marked reduction in BP (25 to 40% decrease SBP) accompanied by a 15% drop in CI and a 15 - 25% drop in SVR. (7). It has been demonstrated that administering opioids before propofol, as a part of balance anaesthesia strategy, reduces the amount of propofol required for induction. The effects of combining propofol & fentanyl with other opioids have been widely explored and proven to have synergistic effects. (13). Administering propofol after peak effect of fentanyl, leads to marked reduction in propofol dosage required for induction of anaesthesia, possibly due to the synergistic action of both drugs. In our study, we recorded the following demographic variables: age, body weight, gender, and ASA PS. The primary outcome measure was the amount of propofol per kg of TBW required to induce anaesthesia. Secondary outcome measurements included hemodynamic parameters, the occurrence of movement and vocalisation, requirement of fluid bolus or vasopressor were recorded. Demographic parameters such as age, sex, ASA, total body weight, height, BMI were not significantly different in all 3 groups. Mean propofol dose requirement per kg was compared between the groups and the mean propofol dose required for induction was significantly higher in group 1 (1.75 ± .22 milligram/kg), compared to both Grp 2 (1.45 ± .36 milligram / kg) and Grp 3 (1.25 ± .15 milligram / kg). p value-0.001.

According to Smith et al. (12), co-administering fentanyl with propofol lowers the arterial concentration levels of propofol required to cause loss of responsiveness to verbal commands and incision to skin (reductions of 63 percentage and 89 percentage in propofol and fentanyl concentrations of 1 and 3 mcg/kg, respectively). In our study, 32 (76.2 %) cases in 1, 35 (83.3 %) cases in 2, and 25 (59.5 %) cases in 3 had incidence of apnoea post-induction and there was statistical significance (p 0.020). 8 patients in 1, 7 patients in 2 and 3 patients in 3 had incidence of vocalization or movement post-induction. Hence, an aliquot of 20 mg of propofol was administered and was significant statistically (p 0.025). In group 1, no of cases requiring additional propofol requirement was more compared to other two groups. Higher dose of opioid drugs than those typically used for analgesia have been shown to expedite loss of responsiveness. This was concluded by Lysakowski et al. (9) (10), who used a target-controlled infusion to achieve the desired effect-site concentration of opioids. They then used BIS index and sedation scores to determine amount of propofol necessary to achieve a loss of verbal response. This was accomplished by using the target-controlled infusion device. They came to the conclusion that the concentrations of analgesic opioids played a role in the early loss of consciousness. After seeing that patients lost consciousness at lower effect-site doses of propofol when it was coupled with opioids. In our study, the hemodynamic responses between the groups were recorded during

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baseline, after induction, one minute and three minutes, and showed statistical significance at various time intervals. Hypotension following intubation was more in group 1 compared to groups 2 and 3. According to our study, the Incidence of hypotension post-induction was compared between the groups and was significantly more in grp 1 (19%) in comparison with Group 2(16.7%) and Group 3 (7.1%). (p value- 0.001). 10 patients in 1, 8 patients in 2, and 4 cases in 3 had an incidence of the requirement of fluid bolus for treatment of hypotension and had significance statistically ($p < 0.05$). 4 cases in grp 1, 3 cases in grp 2, and 1 case in 3 among the whole study population had an incidence of the requirement of vasopressor for treatment of hypotension and was significant statistically (p value - 0.030). In another study related to hemodynamic response to induction and intubation by V.Billiard et al (15) concluded that maximal postintubation hypotension was observed with fentanyl administered with propofol rather than propofol being administered alone. The mean decrease in SBP after propofol alone was 28 mmHg and 53 mmHg when fentanyl 2 mcg/kg was co-administered. Pre intubation hypotension also was noted after fentanyl administration. Vanlal Darlong et al.(8) concluded that administering propofol after 5 minutes showed a decreased dose requirement for induction and a decreased incidence of hypotension following induction. This chronology supports the current study's conclusion that fentanyl administered 3 to 5 minutes before propofol reduces the dose of the latter. In the previous study by Vanlal Darlong et al.(8) one-third of the patients developed hypotension in patients receiving propofol immediately after fentanyl administration and required fluid boluses.

CONCLUSION:

The administration of fentanyl five minutes prior to propofol reduces the amount of propofol required during induction and significantly reduces the occurrence of hypotension compared to when given 3 mins after fentanyl. Hence it is ideal to administer propofol after 5 mins of fentanyl administration and at 2mg/kg.

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