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Effects of Fentanyl and Butorphanol on Induction Dose of Propofol in Adults

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Abstract
Background*: Propofol induction dose is reduced with concomitant use of opioids as a result of a possible synergistic action.*
Objective*: To study the effects of fentanyl and butorphanol on induction dose of propofol in adults.*
Methods:*Onetwentypatients of either sex, of ASA(American society of anesthesiologist) I and II, undergoing elective surgery under general anaesthesia was taken and randomly allocated into three groups of 40 each. Group I received intravenous fentanyl 2μg/kg, Group II 20μg/kg and Group III 40μg/kg butorphanol. Induction of anaesthesia was done with propofol (30mg/10s) till the loss of response to verbal commands. Patients hemodynamic were recorded before administration of study drugs, 5 minutes thereafter, at the time of induction, for 2 min post-induction and post-intubation for 5 min at 1 min interval. The study concluded 5 min after intubation.*
Results: *Fentanyl 2μg/kg reduces the induction dose of propofol to 1.01±0.25 mg/kg.Butorphanol20μg/kg reduces the induction dose of propofol to 0.95±0.18 mg/kg and butorphanol 40 μg/kg to 0.90±0.15 mg/kg. However, sedation was observed to a greater degree with butorphanol 40 μg/kg.*
Conclusion:*Fentanyl 2μg/kg, butorphanol20μg/kg and 40μg/kg reduces the induction dose of propofol comparably.However butorphanol 40 μg/kg was associated with more sedation.*
Keywords:*Butorphanol, Fentanyl, Propofol.*

I. Introduction

Intravenous anaesthetics have become the primary agents for induction of general anaesthesia. Propofol is one of the most popular drugs used in the induction of anaesthesia. It is a rapidly acting intravenous anaesthetic agent with a half life of only around 2 min and an efficient hepatic and extra hepatic clearance. Recovery from propofol is rapid and clear headed with almost no hangover effect.[1]Propofol's pharmacokinetic properties and low incidence of nausea and vomiting associated with it makes it particularly useful for short procedures and ambulatory surgery. However, propofol produces significant reduction in systemic vascular resistance and cardiac filling leading to a greater degree of hypotension as compared to other hypnotic agents.[2, 3] The most prominent cardiovascular effect of propofol is a decrease in arterial blood pressure during induction ofanaesthesia. At induction dose, it causes 25% to 40% reduction of systolic blood pressure, mean and diastolic blood pressure.

The incidence of cardiorespiratory depression appears to be higher than that of other induction agents.[1,2,4-6]The haemodynamic effects of propofol are magnified in hypovolemic or elderly patients and in patients with impaired left ventricular function. These patients will benefit from a reduced dose of propofol.Thedose of propofolrequired to induce anaesthesia in unpremedicated patients is 2.5mg/kg.[2,3,7]It has been found that the induction dose can be reduced by premedication with an opioid.Fentanyl is a potent opioid agonist which acts at mu receptor. It is 100 times more potent than morphine. It is added during induction of anaesthesia to provide analgesia and to decrease the hypertensive response to intubation[10].It also potentiates the hypnotic effect of propofol.Butorphanol is an analgesic possessing mixed agonist and antagonist activity at opiate receptor. It is a kappa-receptor agonist and mu-receptor antagonist[9]. Due to its receptor specificity, it has analgesic and sedative properties without causing respiratory depression or dependency. Its most prominent side effect is sedation. Butorphanol has been used as a preoperative sedative and analgesicandas a supplement to balanced anaesthesia. It has also been used for conscious sedation.It is suggested that butorphanol could also be used to reduce the requirement of propofol at induction.

The aim of our study is to compare the propofol induction dose with butorphanol and fentanyl pretreatment, using clinical end-points, and to identify the optimal dose of propofol that would augment the

hypnotic effect of propofol without causing undue adverse effects such as increased sedation and delayed post-operative recovery.

II. Materials And Methods

This study was randomized, prospective, double-blind one, conducted in the Department of Anaesthesiology,aTertiary Care Centre inImphal, Manipur, during October 2014 to September 2016. The "Patients of American Society of Anaesthesiologists (ASA)[12] physical status I or II, between 18 and 65 years of age, undergoing elective surgery under general anaesthesia were included in the study." Patients with history of cardiac,cardiovascular,respiratory,hepatic or renal disease, allergy to study drugs, risk of regurgitation,predicted difficult airway,obesity and pregnancy, alcohol or opioid abuse,onsedatives,anticonvulsants,antipsychotics and antihypertensives were excluded from the study.

Based on a previous study,[3] the estimated sample size with an α error of 0.05 and power of 80% for equivalence of groups was calculated to be 36 in each group, assuming the dose reductions in propofol with the two study drugs to be 20% and 50%. One twenty patients were recruited for this study. Patients were randomized into one of the following three groups(Group Ireceiving intravenous fentanyl 2μg/kg, Group IIreceiving butorphanol 20 μg/kg and Group IIIreceiving butorphanol40 μg/kg) on the basis of a computer-generated random number table. After obtaining approval for conducting the study from the institutional ethics committee, patients scheduled for elective surgery under general anaesthesia and fulfilling the inclusion criteria were explained about the purpose and procedure of the study and enrolled after getting written informed consent. The enrolled patients were kept fasting for 8 hours and they were not administered any sedative as premedication on the day of surgery. An intravenous line was secured in a peripheral vein. The baseline heart rate(HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), respiratory rate (RR) and oxygen saturation (SpO_2) wererecorded.The drugs were prepared in identical syringes and in equal volume by an anaesthesiologist and another anaesthesiologist who was blinded to the study drugadministered the drugs.

After administration of the study drug, the patient remains undisturbed for 5 min. The sedation level was then assessed using the observer's assessment of alertness scale(OAA/S).[13]Patient were observed for nausea, vomiting, pruritis, RR<8 min, and SpO_2<90%. Anaesthesia was induced with propofol (30 mg/10 sec) using a syringe pump till the loss of response to verbal commands. The anaesthesiologist performing the clinical observations was blinded to the study drug administered. Subsequent muscle relaxation was achieved with rocuronium 1mg/kg. The patient's lungs were manually ventilated with 100% O_2 for 2 min before endotracheal intubation. Following intubation, anaesthesia was maintained with 1% isoflurane in oxygen: nitrous oxide (35%:65%). Patient was not given any stimulation for 5 min after intubation. The HR, SBP,DBPand MAP were recorded before administration of study drugs, 5 minutes thereafter, at the time of induction, for 2 min post-induction and post-intubation for 5 min at 1 min interval.The study concluded 5 min after intubation.The data collected were entered in a computer and statistical analysis was performed using Statistical Pakage for Social Sciences (SPSS-version 20, Chicago, IL, USA).Numerical /continuous variables were presented as Mean ± SD (standard deviation) and for qualitative/categorical variables were again described as number of cases and percentages. The difference of three means, one each from each group, for each parameter were compared by *ANOVA (Analysis of Variance Ratio) test*, commonly known as *F-test* and formultiple comparisons of means, *Post Hoc Tests of Bonferroni* was advocated whenever applicable. For categorical variables,χ^2*-test(chi-square)* was applied if data permit. However in some table, asmost of the theoretical cell frequencies were found to be either less than 5 or nil the test statistic like χ^2 could not be applied and therefore interpretation was made based on percentages only. All comparisons were two-sided and the P-values of < 0.05 and < 0.01 was treated as the cut off values for significance and highly significance respectively.

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III. Results

All the 120 patients completed the study protocol. The patient demographics such as age ,sex ,height and weight were comparable and insignificant (P>0.05) in the three groups as shown in Table 1.

Table 1: Demographic profile

Para-Meters	Mean±SD				P-value
	Group I (fentanyl 2 □g/kg) (n=40)	Group II (butorphanol 20 □g/kg) (n=40)	Group III (butorphanol 40 □g/kg) (n=40)	Total (n=120)	
Age(years)	36.60±10.51	35.43±12.85	36.88±13.05	36.30±12.11	0.853
Weight(kg)	55.33±9.35	57.30±8.93	55.45±6.91	56.03±8.44	0.507

Height(cm)	157.20±4.59	158.28±5.23	157.20±2.59	157.56±4.28	0.436
Sex(M/F)	8/32	10/30	13/27	31/89	0.438

Mean ± SD: mean ± standard deviation; n: number of cases.

Changes in HR and MAP are shown in Table 2, 3 and Figure 1.In all the three groups, there was a fall in HR from baseline after administration of the study drug till two minutes after induction. An increase in HR was observed in all the groups 1minute after intubation which came to baseline within 4 minutes after intubation. We observed a fall in MAP in all the three groups after administration of the study drug till 2 minutes after induction. We also observed an increase in MAP in all the three groups 1minute after intubation which returned to baseline within 3 minutes. There was no significant difference of MAP among the three groups over the stages considered in the present study.

Table – 2: Group-wise mean±SD of heart rate (HR) at different stages

Para-meters	**Group I (fentanyl 2 □g/kg)**	**Group II (butorphanol 20 □g/kg)**	**Group III(butorphanol 40 □g/kg)**	**Total**	**df**	**F-value**	**P-value**
	Mean±SD	**Mean±SD**	**Mean±SD**	**Mean±SD**			
Baseline HR	79.83±11.21	86.00±16.17	86.28±13.48	84.03±13.98	(2,117)	2.804	0.065
Drug HR	77.33±13.18	82.98±15.44	83.58±10.20	81.29±13.31	(2,117)	2.763	0.067
I HR	74.85±12.42	78.03±12.05	78.03±9.54	76.97±11.41	(2,117)	1.031	0.360
PI1 HR	74.30±9.95	76.30±10.23	77.43±9.61	76.01±9.94	(2,117)	1.015	0.366
PI2HR	75.00±13.51	80.08±11.17	80.28±9.55	78.45±11.69	(2,117)	2.689	0.072
PIX1HR	97.08±15.45	99.35±12.43	97.18±10.48	97.87±12.88	(2,117)	0.394	0.675
PIX2HR	90.70±14.27	92.58±10.72	91.65±9.64	91.64±11.64	(2,117)	0.256	0.775
PIX3HR	86.80±13.31	87.08±10.78	88.95±9.04	87.61±11.13	(2,117)	0.438	0.647
PIX4HR	84.03±12.95	82.78±10.21	85.38±8.57	84.06±10.69	(2,117)	0.587	0.557
PIX5HR	82.03±11.63	81.03±9.36	82.98±9.56	82.01±10.18	(2,117)	0.363	0.696

Mean ± SD: mean ± standard deviation; n: number of cases; df: degree of freedom;
F: ANOVA (analysis of variance ratio); P: probability of difference due to chance factors.

Table – 3 Group-wise mean±SD of mean arterial pressure (MAP) at different stages

Parameters	**Group I (fentanyl 2 □g/kg)**	**GroupII (butorphanol 20 □g/kg)**	**GroupIII (butorphanol 40 □g/kg)**	**Total**	**df**	**F-value**	**P-value**
	Mean±SD	**Mean±SD**	**Mean±SD**	**Mean±SD**			
Baseline MAP	94.63±11.38	96.70±9.44	96.88±8.82	96.07±9.91	(2, 117)	0.634	0.532
Drug MAP	88.78±11.80	91.90±10.33	91.38±8.48	90.68±10.30	(2, 117)	1.056	0.351
I MAP	83.73±9.29	85.85±11.17	84.75±8.73	84.78±9.74	(2, 117)	0.471	0.626
PI1MAP	84.93±13.28	83.28±10.80	81.68±8.24	83.29±10.96	(2, 117)	0.877	0.419
PI2MAP	82.38±11.48	86.10±11.13	85.25±7.78	84.58±10.30	(2, 117)	1.445	0.240
PIX1 MAP	107.08±11.72	104.95±8.59	105.08±8.27	105.70±9.62	(2, 117)	0.610	0.545
PIX2 MAP	95.88±10.09	94.03±9.29	97.80±8.32	95.90±9.31	(2, 117)	1.660	0.195
PIX3 MAP	90.58±10.39	87.78±6.90	91.15±7.97	89.83±8.60	(2, 117)	1.783	0.173
PIX4	86.03±12.54	84.58±7.31	86.08±7.76	85.56±9.4		0.3	0.726

MAP				5	(2, 117)	21	
PIX5 MAP	84.20±11.13	83.28±9.55	81.93±14.62	83.13±11.89	(2, 117)	0.366	0.694

Mean ± SD: mean ± standard deviation; n: number of cases; df: degree of freedom;
F: ANOVA (analysis of variance ratio); P: probability of difference due to chance factors.

Fig-1Group-wise trends of mean HR and MAP at different stages

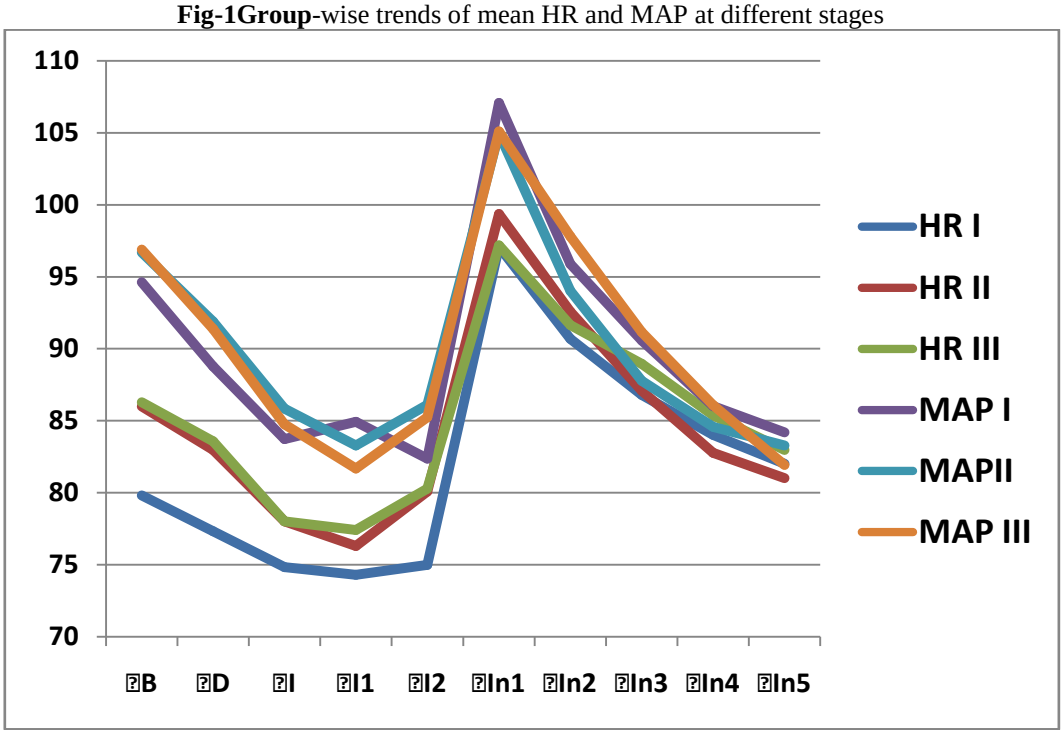

Table – 4 : Group-wise mean±SD propofol dose

Parameters	GroupI (fentanyl 2 g/kg)	GroupII (butorphanol 20 g/kg)	GroupIII (butorphanol 40 g/kg)	Total n	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	P-value
Propofol dose(in mg)	55.43±14.643	53.63±7.160	49.75±8.393	52.93±10.762	0.054
Propofol dose/weight (mg/kg)	1.01±.25	0.95±.18	0.90±.15	0.95±.20	0.062

Mean ± SD: mean ± standard deviation; n: number of cases
The propofol induction dose was comparable in all the three groups (P>0.05) as shown in table 2.

Table-5: Group-wise adverse effect

Parameters		Group I (fentanyl 2 g/kg(n=40)	Group III (butorphanol 40 g/kg(n=40)	Total (n=120)
Adverse effect	Cough	1(25.0%)	-	1(16.7%)
	Dizziness	2(50.0%)	2(100.0%)	4(66.7%)
	Nausea	1(25.0%)	-	1(16.7%)
	Total	4(100.0%)	2(100.0%)	6(100.0%)

Due to most of theoretical cell frequencies are less than 5, the test statistic especially χ^2could not be applied.

No adverse effect was noticed in group-II. In group I, one patient complained of nausea, one patient complained of cough and two patients complained of dizziness. In group III, two patients complained of dizziness.(Table 5).

IV. Discussion

In our present study, an attempt was made to assess the effect of equipotent doses of fentanyl (2µg/kg) and butorphanol (40µg/kg) in reducing propofol dose during induction of general anaesthesia.[14]The administration of propofol combined with an opioidhas become a popular anaesthetic technique. It is generally agreed that the anaesthetic effect of propofol is enhanced by the additional administration of an opioid.Our study show that the induction dose of propofol is reduced with fentanyl 2µg/kg and butorphanol at 20µg/kg and 40 µg/kg comparably. Haemodynamic parameters in all the three groups were also comparable. However, sedation was observed to a greater degree with butorphanol 40 µg/kg.The reduction in propofol dose with butorphanol 20µg/kg and fentanyl 2µg/kg in our study wascomparable with Kaur J et al[3](0.95±0.18mg/kg and 1.01±0.25mg/kg vs 1.05±0.35mg/kg and 1.1±0.50mg/kg). There was a difference in the propofol dose reduction with 40 µg/kg butorphanol in our study (0.90±0.15mg/kg) when compared with Kaur J et al[3](1.05±0.35mg/kg), which might be due to the difference in the demographic profile.The concentration of propofol required for loss of consciousness is reduced by increasing fentanyl concentration. However a ceiling effect was seen with concentrations greater than 3µg/kg.[5]

Arora V et al[15] demonstrated that the mean propofol consumption in fentanyl group (2µg/kg) was slightly higher (406.7±96.36mg) as compared to butorphanol 40µg/kg group (380.5±92.4mg). Lysakowski C et al[6]showed in their study that in the presence of analgesic concentration of fentanyl, loss of consciousness occurred at a lower effect-site concentration of propofol. Pretreatment with fentanyl also potentiated the effect of propofol and hypnotic end points are achieved at lower propofol doses and concentrations.[11]

The administration of an induction dose of propofol produces a decrease in HR, systolic and diastolic blood pressure. In our study, the hypotensive response to an induction dose of propofol is reduced by decreasing the induction dose. We observed an increase in the HR, SBP, DBP and MAP in the post intubation period in all the three groups. Our findings are comparable to those observed by Kaur J et al.[3] They found a comparable increase in HR in the post intubation period in all the three groups which returned to baseline within 5 minutes.Rao MH et al.[16] observed in their study that there was a significant fall in HR and DBP in patients who received butorphanol as premedication as compared with those who received fentanyl in which there was rise in HR and BP intraoperatively. Higher fall in DBP was seen in butorphanol group than the fentanyl group. However, the rise in HR and BP were not upto 20% of preoperative value in fentanyl premedication which is in agreement with our findings. Philip BK et al[17]found in their study that patients who received butorphanol 20 µg/kg prior to induction showed a lower heart rate before (79±14 in butorphanol group vs. 89±15 in fentanyl group) and after intubation (89±20 in butorphanol group vs. 103±20 in fentanyl group) and lower diastolic blood pressures after intubation in butorphanol group (88±18 mmHg) as compared with fentanyl 1 µg/kg (101±17 mmHg).

Pandit SK et al[14] found in his study that butorphanol 40 µg/kg gave better protection against autonomic stimulation to tracheal intubation as compared with fentanyl 2µg/kg. The only significant change occurred 2 min after tracheal intubation in the fentanyl group when both the heart rate and systolic blood pressure were significantly higher than the preoperative baseline values. However, apart from this, there was no other significant difference between butorphanol and fentanyl during either induction or maintenance of anaesthesia.

We also found that butorphanol 40µg/kg produces more sedation compared to fentanyl 2µg/kg and butorphanol 20µg/kg. Depth of sedation was assessed using modified OAA/S.[13]Our findings are in concordance with Kaur J et al[3] where higher sedation was observed with both butorphanol groups as compared with fentanyl. In our study, we observed a fall in respiratory rate and meanSpO_2 after administration of the study drugs in all the three groups. However, there was no significant difference among the three groups. Oxygen desaturation was seen in 2 patients (5%) with fentanyl, 1 patient (2.5%) with butorphanol 20µg/kg and 4 patients (10%) with butorphanol 40 µg/kg.We also found in our study that fentanyl 2µg/kg was associated with cough in 1 patient, nausea in 1 patient and dizziness in 2 patients. Butorphanol 40 µg/kg was also associated with dizziness in 2 cases.Kaur J et al[3] did not report any patient complaining of nausea or vomiting after administration of the study drug. However 3 patients (7.5%) in fentanyl group and 1 patient (2.5%) in butorphanol 20µg/kg group had mild itching.Our study has several limitations. First, no control group was studied. The incidence of cardiorespiratory depression is higher with propofol as compared to other induction agents. Induction with propofol alone will cause a significant fall in the blood pressure. Secondly, we concluded our study five minutes after intubation. A comparison of haemodynamic parameters intraoperatively would have given a better idea about the effect of the study drugs on maintaining haemodynamic stability .Third; it needs to be assessed in varied ASA status. Fourth, different dose of fentanyl needs to be evaluated.

V. Conclusion

It may be concluded that butorphanol in the twodifferent doses, reduced the induction dose of propofol comparable to fentanyl with stable hemodynamics during induction and intubation. However butorphanol 40 μg/kg was associated with more sedation.

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