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Original Research Article

Application of 'Priming Principle' on the induction dose requirements of propofol - A Randomized Clinical Trial

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Abstract

Background: To assess the worth of 'Priming Principle 'applied for the induction dose of Propofol would perturb the total induction dose requirement of Propofol and the concerned hemodynamic changes.
Methodology: 100 patients were registered in this prospective, randomized double blind study. In group B (Bolus Group) patients received Inj. fentanyl µg kg^{-1} i.v. administered over a period of 30 seconds followed by i.v. Propofol till loss of eyelash reflex (LOER). In group P (Priming Group) patients received 25% of the total calculated dose of Inj. Propofol 2 mL kg^{-1} 30 seconds later Inj. fentanyl µg kg-1was administered over 30 seconds which was again followed by the administration of i.v. Propofol till LOER. Various hemodynamic parameters were measured just before induction, just after intubation, one minute after induction and five minutes after intubation.
Results: 28.92% dose reduction was seen in group P as compared to group B. Heart rate was significantly higher in group B (8.2%) at one minute after induction. The systolic blood pressure was significantly lower in group B (11.82%) at one minute after induction, immediately after intubation (11.36%) and 5 minutes after induction (6.91%) than in group P. Similarly the diastolic blood pressure and mean arterial pressure values were significantly lower in group B at one minute after induction (5.35%, 8.2%), immediately after intubation (3.99%, 7.23%) and 5 minutes after induction (2.2%, 4.27%) than in group P.
Conclusion; By applying 'Priming Principle' a significant reduction in total induction dose and better hemodynamic parameters were observed with priming dose of Propofol.
Keywords: Hemodynamics; Priming; Propofol.

1. Introduction

Propofol provides faster onset of action, potent attenuation of airway reflexes, adequate depth of anaesthesia during intubation, anti-emesis and rapid recovery. These properties make Propofol the most commonly used induction agent worldwide. However, a major pitfall of rapid induction with Propofol inappreciable decrement in the systemic arterial blood pressure secondary to the decrease in systemic vascular resistance. Various methods have been used to reduce the induction dose of Propofol with variable success rate. These include nitrous oxide [1-3], opioid [4, 5], barbiturates [6], benzodiazepines [7], alpha 2 agonists [8], local anaesthetics [9], and magnesium sulphate [8]. Propofol auto co-induction or 'Priming Principle' to reduce Propofol requirements has also been proposed [10,11]. However, lack of substantial evidence makes this technique an uncommon practice amongst anaesthesiologists.

Application of Priming Principle' is well reported in relation to the use of non-depolarizing muscle relaxants, wherein priming diminish the onset of neuromuscular blockade, yield better intubating conditions and reduces the total consumption of the drug [12,13].

Extrapolation of this phenomenon to the domain of Propofol forms the basis of our study. The aim of our study was to evaluate the effect of similar 'Priming Principle 'on the induction dose requirement of Propofol and thereby its hemodynamic effects.

2. Materials and Methods

After Institutional Ethical Committee approval, 100 patients of American Society of Anaesthesiologists (ASA) physical status I or II of either sex between 20-55 years of age plan for elective surgery were enrolled into this randomized, double-blind study.

Patients allergic to study drugs, ischemic heart disease, hypertension, diabetes mellitus, psychiatric disorder and pregnant women were excluded from the study. All patients were given Tab. Ranitidine hydrochloride 150mg in the previous night and on the morning of surgery. After shifting the patient to the operating room, standard monitors were attached and baseline values of heart rate (HR), blood pressure (BP) and oxygen saturation (SpO_2) were noted. The BIS (Bispectral index) electrodes (BIS Quatro Leads) were applied on forehead and connected to a BIS monitor (COVIDIEN).An average of two different readings of HR, BP and BIS taken at least 5 minutes apart before induction. A suitable intravenous line was secured and a slow I'VE drip was started in all patients with ringers lactate. All patients were pre-medicated Inj. Midazolam 0.03 mL kg^{-1} IV 5 minutes prior to induction. The patients were assigned to one of the two treatment groups according to a computer-generated randomization chart. In group B (Bolus group) patients received Inj. fentanyl µg kg-1I.V. administered over a period of 30 seconds followed by I.V. Propofol titrated to the loss of eyelash reflex (LOER). In group P (Priming Group) patients received 25% of the total calculated dose of Inj. Propofol 2mL kg^{-1} followed by 30 Inj. Fentanyl µg kg-1was administered over 30 seconds, which was followed by the administration of I.V. Propofol till LOER. Total dose of Propofol required for induction in both the group was recorded. BIS value was noted at the time of LOER in both the groups. Rate of Propofol injection was limited to 30 mg per10 seconds in both groups. Subsequent relaxation and intubation was achieved with Inj. Rocuronium 1mL kg^{-1} I.V. and anaesthesia was sustained with O_2+N_2O (1:2) + Isoflurane 1%. Inj. Vecuronium was utilised as a muscle relaxant intra-operatively in both groups. No stimulus was applied for the first 5 minutes. The base line BIS values prior to induction and during the time of LOER were taken into consideration. Total dose of Propofol, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) by non-invasive blood pressure monitoring method were measured just before induction, one minute after induction, just after intubation and five minutes after intubation. Calculation of dose reduction was done by a formula as below.

$$\% \text{ Dose reduction} = \frac{\text{Mean induction dose (Group B – Group P)}}{\text{mean induction dose in Group B}} \times 100$$

The statistical significance of categorical variables between two groups was determined by Chi Square test/ Fischer exact test. Because of the rapid change in each patient's hemodynamic parameters each episode was treated as a single observation for statistical analysis. Results are expressed as mean ± SD. Two ways repeated measure ANOVA was performed to find out the association between and within the groups. Statistical significance was set at less than 0.05 levels.

3. Observation and Results

A total of 50 patients in each group were included in this study. The patients' demographic profile including age, weight and gender were comparable in both the groups [Table 1]. The mean induction dose of Propofol in group B and group P were 95.84±12.34 mg and 68.12±9.45 mg (p=0.00) respectively [Table 1]. The mean induction dose was 1.88mL kg^{-1} and 1.28 mL kg^{-1} in the group B and group P respectively. We found 28.92 % reduction in dose in Group P as compared to group B. Before administration of the test drugs, baseline hemodynamic (HR, SBP, DBP, MAP) parameters were normal and comparable in both the groups [Table 2]. 1 minute after induction the HR was 80.1±9.78 /min in group B and 74.62±8.2 beats/min in group P which was statistically significant (p =0.003). There was no statistically significant difference in the mean HR immediately after intubation and 5 minutes after induction. Similarly before induction, SBP was 121.32±6.90 mm Hg in group Band 121.28±8.13mm Hg in group P (p=0.979). 1 minute after induction the SBP was 106.98±9.20 mm Hg in group B and 110.72±6.66mm Hg in the group P which was statistically significant (p=0.022). Immediately after intubation the mean SBP was 107.54±9.77mm Hg in group B and 113.32±5.60mm Hg in group P which was statistically significant (p=0.001). And 5 minutes after induction the mean SBP was 112.94±8.30mm Hg in group B and 117±5.67mm Hg in group P which was statistically significant (p =0.005). Similarly DBP and MAP was statistically significant 1 minute after induction, after intubation and 5 minutes after induction. BIS values at baseline and at the time of LOER were comparable in both the groups (p=0.117) [Table 3].

Apnoea for more than 30 seconds was found in 28% of the patients of Group B and only 6% of patients of the Group P (p= 0.003). Similarly hypotension i.e. fall in MAP by more than 20% from baseline after induction was found in 18%of case of the Group B and in 4% of patients of Group P (p= 0.025).

HR was significantly higher in group B (8.2%) at one minute after induction. The SBP was significantly lower in group B (11.82%) at one minute after induction, immediately after intubation (11.36%) and 5 minutes after induction (6.91%) than in group P. Similarly the DBP and MAP values were significantly lower in group B at one minute after induction (5.35%, 8.2%), immediately after intubation (3.99%, 7.23%) and 5 minutes after induction (2.2%, 4.27%) than in group P [Table 4].

Table 1: Demographic data and induction dose of Propofol (mg) [MEAN ± 2SD]

Parameter	Groups		p-value
	B	P	
Age(Yrs)	33.87±10.58	33.42 ±10.13	0.83
Weight(Kg)	50.9±9.52	53.16±8.09	0.20
Gender (M/F)	30/20	27/23	0.54
Mean induction dose (mg)	95.84±12.34	68.12±9.45	0.00

M= Male, **F**= female

Table 2: Haemodynamic parameter at different interval of time [MEAN ± 2SD]

Parameter	Group	Base line	Before induction	1 min after induction	Immediately after intubation	5 mins after induction
HR	Group B	76.2±6.9	74.04±6.8	80.1±9.78	77.34±6.8	76.68±6.63
	Group P	75.94±7.34	73.94±7.34	74.62±8.2	76.9±7.27	76.3±6.97
	P value	0.856	0.944	0.003	0.751	0.781
SBP	Group B	122.74±9.24	121.32±6.90	106.98±9.20	107.54±9.77	112.94±8.30
	Group P	122.66±7.94	121.28±8.13	110.72±6.66	113.32±5.60	117±5.67
	P value	0.963	0.979	0.022	0.001	0.005
DBP	Group B	79.54±6.05	77.32±5.12	73.18±7.01	74.24±6.95	75.62±3.64
	Group P	80.06±5.87	78.22±6.18	77.12±6.78	77.28±6.63	77.82±5.47
	P value	0.664	0.430	0.005	0.027	0.020
MAP	Group B	93.93±4.95	91.99±4.01	84.45±7.15	85.34±6.92	88.06±3.90
	Group P	94.26±3.90	92.51±4.32	88.25±5.12	89.29±5.23	90.88±4.65
	P value	0.715	0.536	0.003	0.002	0.001

HR= Heart rate, SBP= Systolic Blood Pressure, DBP= Diastolic Blood Pressure, MAP=Mean Arterial Pressure

Table 3: BIS Value (Mean±2SD)

Time	Group P	Group B	Range	P value
Baseline (before induction)	96.3 ± 1.27	96.52 ± 1.4 7	90-100	0.425
At loss of eye lash reflex	50.52± 3.53	51.6 ± 3.45	40-60	0.117

Table 4: Hemodynamic changes in both the groups

Groups	Change in mean heart rate		
	OAI	IAI	5AI
B	6.06 (+8.2%)	3.3 (+4.45%)	2.64 (+3.56%)
P	0.68 (+0.92%)	2.96 (+4%)	2.36 (+3.2%)
	Change in mean systolic blood pressure		
B	14.34 (-11.82%)	13.78 (-11.36%)	8.38 (-6.91%)
P	10.56 (-8.7%)	7.96 (-6.56%)	4.28 (-3.53%)
	Change in mean diastolic blood pressure		
B	4.14 (-5.35%)	3.08 (-3.99%)	1.7 (-2.2%)
P	1.1(-1.4%)	0.94 (-1.2%)	0.4 (-0.51%)
	Change in mean arterial pressure		
B	7.54 (-8.2%)	6.65 (-7.23%)	3.93 (-4.27%)
P	4.26 (-4.6%)	3.22 (-3.48%)	1.63 (-1.76%)

OAI = One minute after induction, IAI = Immediately after intubation, 5AI = Five minutes after induction.

4. Discussion

Rapid induction with Propofol is associated with fall in BP, which is dose dependent [14, 15]. Induction of anesthesia with 2mL kg-1of Propofol produces a fall of 11% of MAP, 26-28% of SBP and 19% of DBP without any change in cardiac output and stroke volume [14, 15].

'Priming Principle' used in the past refers to injecting a small dose (priming dose) of a nondepolarising relaxant followed by injecting a remaining higher dose which produces a suitable scenario for rapid and easy intubation of trachea [12, 13].

We noticed a 28.92% decrease in the induction dose requirement of Propofol by using 'Priming Principle' which is similar as observed by A Kumar *et al* (27.48%), Maroof *et al* (21.4%) and Naphade *et al* (35%) [5-7]. Significant diminution of induction dose of Propofol in our study could be due to the use of midazolam (0.03 mL kg-1) as a pre-medicant 5 minutes prior to induction, compared to the use of i.m. Meperidine 1mL kg^{-1} and Promethazine 0.025 mL kg^{-1} by Maroof *et al*. Use of midazolam as premedication is known to decrease the induction dose need of Propofol as analysed by Cressy *et al* [8]. This reduction

in dose requirement can be due to GABA agonist effect of Propofol at low doses resulting in hypnosis and sedation. Similar results were noticed by Anderson *et al* [9] wherein 30 mg of Propofol was administered few seconds prior to induction and Djaiani *et al* [10] who had administered 0.4mL kg^{-1} (20%) of induction dose prior to induction with Propofol. Prior application of sub hypnotic doses of Propofol produced anxiolytic thereby diminished the associated sympathetic drive and the induction dose to produce hypnosis. We also assess, whether applying 'Priming Principle' would affect the associated haemodynamic parameters. Increase in the HR (table 2and 4) at one minute after induction in group B, in our study was similar to the increase in the HR observed in other studies as conducted by Maroof *et al*, A. Kumar *et al* and Fairfield *et al* [6,11]. Propofol cause hypotension by diminish vascular smooth muscle tone and total peripheral resistance and by reducing sympathetic activity causes reflex increase in the sympathetic activity which lead to increase in the HR [16]. Our findings does not correlate with the results by Pensado *et al*[14] and Caleys *et al* [15] wherein there was no significant change in the HR with the use of 2mL kg^{-1} of Propofol, however both these studies used nitrous oxide during induction with Propofol. In our study no N_2O was used during induction, which perhaps could explain tachycardia.

The mean SBP was significantly higher in group P at one minute after induction, immediately after intubation and five minutes after induction in comparison to group B [Table 2] confirming that haemodynamic side effects were dose dependent as stated by Pauline *et al* [17] and Major *et al* [9]. With an increase in the induction dose of propofol from 1.5mL kg^{-1} to 2.5mL kg^{-1} the MAP was lowest when 2.5mL kg^{-1} of Propofol was used in the study by Major *et al*. The fall in the SBP at one minute after induction compared to values just before induction was 11.82 % in group B compared to 8.7 % fall in group P [Table 4]. Lower SBP values (28%) were observed at 2 minutes after induction with Propofol in studies conducted by Caleys *et al*.

At five minutes after induction, compared to values just before induction the fall in the SBP was 6.91 % in group B and only 3.53 % in group P [Table 4]. Similar results were noticed by Caleys *et al* (36%) at 6 minutes after induction and Kumar *et al* 5 minute after induction. The decrease in the SBP in group B compared to group P could be attributed to the higher dose for induction in group B.

We observed less haemodynamic changes in group P. Similar results were observed by Kumar *et al* and Maroof *et al*. We had used LOER as end point for induction and BIS were used only to detect the depth of anaesthesia at the time of LOER as studies done by Arya *et al* [18] have shown that both clinical method and BIS guided method for induction are comparable. From our study we found that the depth of anaesthesia were comparable in both the groups at time of LOER unlike the study done by Kumar *et al*, where he showed that fasciculation's from succinyl-choline could be attributed to lower depth of anaesthesia in Priming group due to lower dose of Propofol used for induction.

A limitation of this study was that Inj. Midazolam 0.03 mL kg^{-1} IV was used 5 minutes prior to induction. Dose of Propofol used as 2mL kg^{-1} is slightly on the higher ranges. It would be prudent to plan further studies with no use of benzodiazepine or use of Propofol in range of 1-1.5mL kg^{-1}. Another likely weakness is that this study was performed in elective patients who were adequately optimized prior to surgery.

However, more studies with larger samples are required before considering these observations. More studies with variable priming doses of Propofol can be done to see haemodynamic instability. It would also be a field of curiosity to implement 'Priming Principle' in hemodynamically unstable patients for rapid sequence induction.

5. Conclusion

It is observed that 28.92% reduction in the induction dose requirement of Propofol and better haemodynamic parameters obtained by applying 'Priming Principle'. The depth of anaesthesia compared by BIS during LOER, gave comparable results suggesting similar depths of anaesthesia. Hemodynamic instability is more in bolus group as compared to priming group.

Financial Disclosure

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Ethics Committee Approval

Ethics committee approval was received for this study from the ethics committee of S.C.B. Medical College, Cuttack, India

Informed Consent

This study performed in humans was approved by the Institutional Review Board and written informed consent was obtained from all patients or parents of minors.

Conflict of Interest

No conflict of interest was declared by the authors.

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