

# A Prospective Randomized Control Trial to Study Effect of Priming Principle on the Induction Dose Requirements of Propofol

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## ABSTRACT

**Introduction:** Priming refers to administration of a subanaesthetic dose (priming dose) of an agent prior to its actual anaesthetic dose. The “priming principle” is a method to reduce the total dose requirements of a drug. This study was undertaken to study the effect of priming principle on induction dose requirements of propofol.

**Material and Methods:** Sixty (60) patients with American Society of Anaesthesiologists (ASA) I and ASA II grades, of both sexes, aged 18-55 years, and undergoing elective surgical procedures under general anaesthesia were randomly allocated into two equal groups with 30 patients each. Group I (control) received calculated induction dose of injection (inj.) propofol 2mg/kg. Group II (study) received 20% of total calculated induction dose of propofol 2 mg/kg as a priming dose and remaining dose after 60 seconds titrated till loss of the eyelash reflex.

**Results:** The control group consumed a higher dose of inj. propofol (2 mg/kg) as compared with the study group ( $1.34 \pm 0.28$  mg/kg), i.e., there was 33% reduction of the total dose in the study group. The hemodynamic changes in HR, SBP, DBP, MAP and RPP at 30 minutes before induction, just before induction, immediately after intubation and 5 minutes after induction were similar in both groups ( $P > 0.05$ ). The hemodynamic changes in HR, SBP, DBP, MAP and RPP at one minute after induction were statistically significant in both the groups ( $P < 0.05$ ). Incidence of pain and apnea was comparable in both groups but hypotension was seen in 4 patients in control group and none in study group.

**Conclusion:** The priming technique effectively reduced the total induction dose requirements of propofol and favourably reduced extent of hypotension following induction with propofol.

**Keywords:** Priming Principle, Propofol, Induction Dose

## INTRODUCTION

Priming principle refers to administration of a small subanaesthetic dose of an agent prior to its actual full anaesthetic dose. Schwartz et al<sup>1</sup> by trial and error proposed that 15-20% of the customary intubation dose can be used for priming and was referred as ‘priming dose’. The sum of priming and intubation doses is smaller than the conventional intubating dose. Priming principle carries this advantage and also additional property of decreasing the frequency and severity of dose related side effects, reveals undiagnosed, pathologic or idiopathic increased sensitivity to the anaesthetic agent.<sup>1</sup> This technique had been widely practiced in relation to the non-depolarizing type of muscle relaxants to hasten their onset of action.<sup>2,3</sup>

Propofol is the most recent intravenous anaesthetic agent

released for general use in 1989. Propofol is the most frequently used intravenous agent for induction and maintenance of anaesthesia as well as for sedation during regional anaesthesia or intensive care unit. Use of propofol has advantages like fast induction, short duration of action, fast and clear-headed recovery, inactive metabolites, no post-operative nausea, vomiting and patient rapidly becoming roadworthy. The main disadvantages are pain on injection, hypotension, bradycardia, anaphylaxis reactions and high cost. A decrease of 26-28% of systolic blood pressure, 19% of diastolic blood pressure and 11% of mean arterial pressure, without any change in systemic vascular resistance and cardiac output were observed when patients are induced with 2mg/kg of propofol.<sup>4,5</sup> Most of these hemodynamic side effects of propofol are dose related. A search of the literature reveals that many methods were used to reduce the induction dose requirements of propofol, like use of nitrous oxide, opioids, barbiturates like thiopentone, benzodiazepines like midazolam, use of local anaesthetics, magnesium sulphate and use of ‘Priming Principle’.<sup>6,7,8</sup>

As priming causes reduction in dose requirement, we hypothesized that its application for propofol induction would reduce its dose related side effects. Hence this study was undertaken to study the effect of priming principle on induction dose requirements of propofol and its effect on the peri intubation hemodynamic changes like heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, rate-pressure product and the associated side effects of propofol like pain on injection, apnea during induction and hypotension on induction of general anaesthesia.

## MATERIAL AND METHODS

After the Institutional Ethics Committee approval and

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written valid informed consent, 60 patients of age group 18-55 years, ASA Grade I & II, scheduled for elective surgery under general anesthesia were randomly divided into two groups of 30 patients each. Sealed envelopes containing chits were used for randomization of patients into two groups. Patients with history of allergy to study medication, anticipated difficult intubation, obese patients and pregnant and lactating women were excluded from study.

In both the groups on the day of surgery 30 min before induction HR, SBP, DBP, MAP, RPP were noted. Patients were taken inside the operation theatre and cardioscope, pulse oximeter, noninvasive blood pressure cuff were attached. Peripheral line was taken with 18/20-gauge angiocath over large forearm vein. Patients were premedicated with Inj. Glycopyrrolate 0.004 mg/kg IV, Inj. Ranitidine 2 mg/kg IV, Inj. Midazolam 0.03 mg/kg IV and Inj. Fentanyl 2 µg/kg IV. Patients were preoxygenated with 100% O<sub>2</sub> for 5min.

In Group I (control group) patients were induced with precalculated dose of Inj. Propofol 2 mg / kg IV till loss of eye lash reflex at the rate of 30 mg / 10sec. Inj. Vecuronium 0.10-0.15 mg / kg IV was used as muscle relaxant for facilitation of endotracheal intubation after induction. After administration of vecuronium patients were given intermittent positive pressure ventilation for 2 min using 50% O<sub>2</sub> +50%N<sub>2</sub>O. Direct laryngoscopy and endotracheal intubation was performed with appropriate size cuffed polyvinyl chloride endotracheal tube. Auscultation for confirming tracheal placement of endotracheal tube by bilateral equal air entry was done, cuff inflated. Patients was connected to anesthesia breathing circuit.

In Group II (study group) patients were induced with priming dose of propofol which was 20% of calculated dose of 2 mg/kg followed by remaining dose of propofol till loss of eyelash reflex at the rate of 30 mg/ 10 sec. After that rest of the steps were as mentioned in control group. No stimulus was given to the patient for first 5 minutes after induction. Any complaint of pain by the patient while injecting propofol was noted. Patients with clinically noticeable apnea >30 seconds were given intermittent positive pressure ventilation with bag and mask.

In both the groups patients were maintained on O<sub>2</sub> + N<sub>2</sub>O

(50: 50) with IV propofol infusion 3-4 mg / kg / hour with inj. Vecuronium 1 mg top up as a relaxant with controlled ventilation with Modified Magill's circuit. Patients were reversed from neuromuscular blockade at end of surgery after confirmation of return of spontaneous breathing with IV neostigmine 0.05 mg / kg and IV atropine 0.02 mg /kg. Patients were extubated after confirming adequate tone, power, respiratory rate, SpO<sub>2</sub> and obeying verbal commands. Patients were shifted to postoperative recovery room for observation. Following parameters were recorded in both the groups:

1. Total induction dose of propofol required
2. Heart rate, Systolic blood pressure, diastolic blood pressure was noted and from that mean arterial pressure and rate pressure product was calculated at
  - I. Baseline i.e. 30 min before induction
  - II. Just before induction
  - III. 1 min after induction
  - IV. Immediately after intubation
  - V. 5 min after induction
3. Side effects like pain on propofol injection, apnea (clinically noticeable >30 seconds), hypotension (systolic blood pressure <90 mm of Hg)

## STATISTICAL ANALYSIS

Statistical analysis of the demographic data was done using unpaired 't' test and Pearson chi-square test. Comparison between the groups for induction dose and hemodynamic parameters were done using Student "t" test. A p-value less than 0.05 were considered statistically significant.

## RESULTS

The demographic data were comparable [Table 1]. The type of surgical procedures performed were as shown in Table 2. Total induction dose of propofol in study group was  $1.34 \pm 0.28$  mg/kg as compared to 2 mg/kg in control group [ Table 3]. There was approximately 33% reduction in the induction dose requirement of propofol which was statistically significant [p value 0.000]. The data in [Table 4,5,6,7,8 and Graph 1,2,3,4,5] shows the descriptive analysis of mean heart rate, mean systolic blood pressure, mean

Parameters	Control Group		Study Group		p-Value	Association
	Mean	S.D.	Mean	S.D.		
Age (years)	34.63	8.27	32.47	10.61	0.382	Not Significant
Weight (kg)	54.86	7.52	56.16	8.74	0.540	Not Significant
Sex (F/M)	10/20		10/20		1	Not Significant

Table-1: Demographic Data

Sr. No.	Type of Surgery	Control Group	Study Group	Total
1.	Open Cholecystectomy	11	10	21
2.	Fibroadenoma Excision	4	5	9
3.	Modified Radical Mastoidectomy	8	9	17
4.	Functional Endoscopic Sinus Surgery	6	5	11
5.	Incisional Hernioplasty	1	1	2
Total		30	30	60

Table-2: Type of Surgeries

	Control Group		Study Group		p-Value	Association
	Mean	S.D.	Mean	S.D.		
Total Induction Dose (mg/kg)	2	0.00	1.34	0.281	.000	Significant

**Table 3:** Comparison of Total Induction Dose of Propofol (mg/kg)

Heart rate	Control Group		Study Group		p-Value	Association
	Mean	S.D.	Mean	S.D.		
30 min before induction	81.27	5.907	80.50	4.470	.573	Not Significant
Just before induction	78.60	5.203	78.47	4.539	.916	Not Significant
One min after induction	76.67	4.498	79.63	4.089	.010	Significant
Immediately after intubation	90.77	6.140	89.80	3.881	.469	Not Significant
5 min after induction	84.93	5.825	82.93	3.016	.100	Not Significant

**Table 4:** Comparison of Heart rate (Beats per min)

Systolic blood pressure (mm Hg)	Control Group		Study Group		p-Value	Association
	Mean	S.D.	Mean	S.D.		
30 min before induction	122.47	6.404	121.27	5.789	.450	Not Significant
Just before induction	120.60	5.512	119.00	6.097	.291	Not Significant
One min after induction	100.33	7.522	114.33	4.671	.000	Significant
Immediately after intubation	117.20	7.676	119.20	4.656	.227	Not Significant
5 min after induction	109.00	5.626	110.80	3.134	.131	Not Significant

**Table 5:** Comparison of Systolic Blood Pressure (mm Hg)

Diastolic Blood pressure (mm Hg)	Control Group		Study Group		p-Value	Association
	Mean	S.D.	Mean	S.D.		
30 min before induction	76.53	5.303	78.37	4.367	.149	Not Significant
Just before induction	75.47	5.277	75.20	4.597	.835	Not Significant
One min after induction	64.07	5.212	73.87	3.893	.000	Significant
Immediately after intubation	74.80	4.972	75.27	5.105	.721	Not Significant
5 min after induction	72.87	4.747	74.47	3.471	.142	Not Significant

**Table 6:** Comparison of Diastolic Blood Pressure (mm Hg)

Mean Arterial Pressure (mm Hg)	Control Group		Study Group		p-Value	Association
	Mean	S.D.	Mean	S.D.		
30 min before induction	91.87	5.342	92.67	3.736	.504	Not Significant
Just before induction	90.50	5.118	88.90	3.881	.178	Not Significant
One min after induction	76.17	5.509	86.27	2.864	.000	Significant
Immediately after intubation	88.93	5.369	89.50	4.516	.660	Not Significant
5 min after induction	84.87	4.200	85.33	2.746	.612	Not Significant

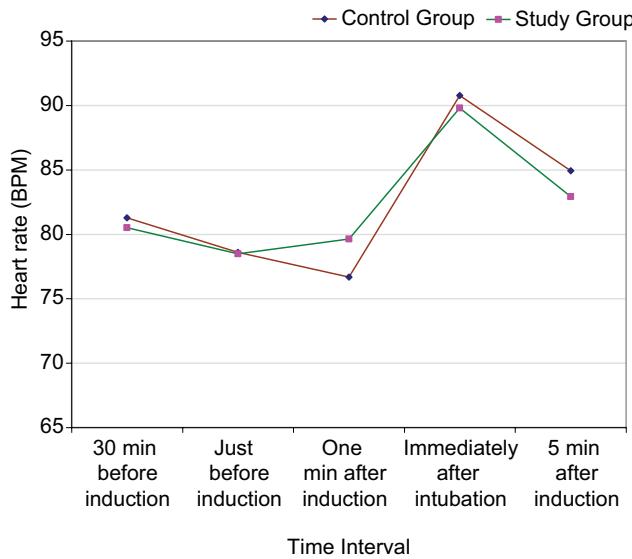
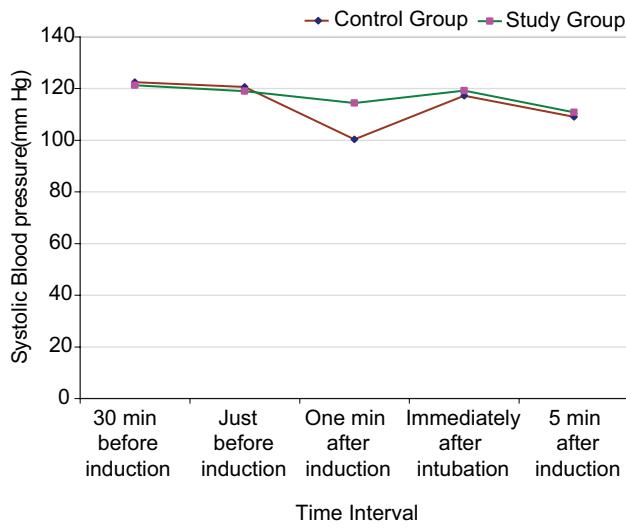
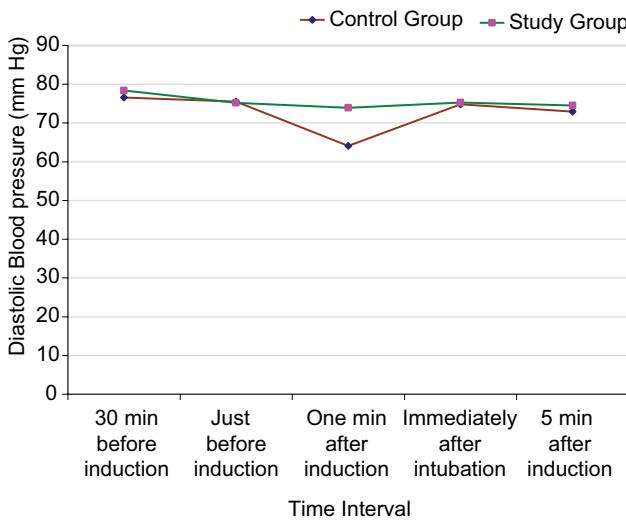
**Table 7:** Comparison of Mean Arterial Pressure (mm Hg)

R.P.P.	Control Group		Study Group		p-Value	Association
	Mean	S.D.	Mean	S.D.		
30 min before induction	9962.67	1001.366	9764.20	736.815	.386	Not Significant
Just before induction	9481.87	801.007	9339.07	740.443	.476	Not Significant
One min after induction	7701.47	824.265	9109.27	658.480	.000	Significant
Immediately after intubation	10664.73	1247.201	10706.47	656.367	.872	Not Significant
5 min after induction	9276.07	980.673	9189.73	441.176	.662	Not Significant

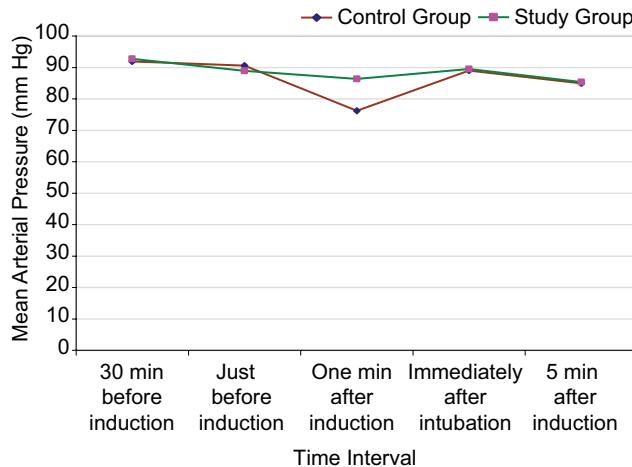
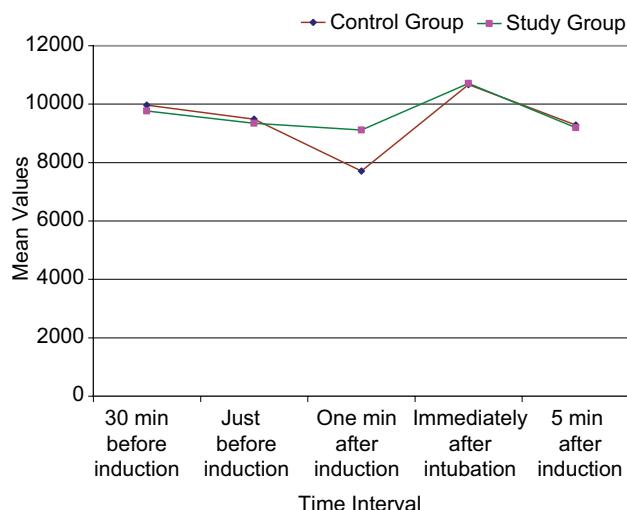
**Table 8:** Comparison of Rate Pressure Product

Parameters	Control Group		Study Group		p-Value	Association
	No. of Patients	% within Group	No. of Patients	% within Group		
Pain	5	16.7%	4	13.3%	0.718	Not Significant
Apnea	11	36.7%	5	16.7%	0.080	Not Significant
Hypotension	4	13.3%	0	0%	0.030	Significant

**Table 9:** Comparison of Incidence of Pain, Apnea and Hypotension

**Graph-1:** Comparison of Heart rate (Beats per min)**Graph-2:** Comparison of Systolic Blood Pressure (mm Hg)**Graph-3:** Comparison of Diastolic Blood Pressure (mm Hg)

diastolic blood pressure, mean arterial blood pressure and mean rate pressure product in the control (Group I) and study group (Group II) at various time intervals respectively.

**Graph-4:** Comparison of Mean Arterial Pressure (mm Hg)**Graph-5:** Comparison of Rate Pressure Product

There was reduction in the mean heart rate, mean systolic blood pressure, mean diastolic blood pressure, mean arterial blood pressure and mean rate pressure product at 1 min after induction which was statistically significant [ $p$  value 0.000]. There was no statistically significant difference in the mean heart rate, mean systolic blood pressure, mean diastolic blood pressure, mean arterial blood pressure and mean rate pressure product variations at other time intervals of 30 minute before induction, just before induction, immediately after intubation and 5 minutes after induction [ $p$  value  $> 0.05$ ]. There was statistically significant difference in the incidence of hypotension between the control and study group [ $p$  value 0.038]. There was no statistically significant difference in the incidence of pain and apnea between the control and study group [ $p$  value 0.718 and 0.08 respectively] [Table 9].

## DISCUSSION

Propofol is the most recent intravenous anaesthetic agent used for induction and maintenance of general anaesthesia. Propofol has advantages like fast induction, short duration of action, fast and clear-headed recovery, inactive metabolites, no post-operative nausea, vomiting and patient rapidly becoming roadworthy. The main disadvantages are pain on injection, hypotension, bradycardia, anaphylaxis reactions

and high cost. Most of these hemodynamic side effects of propofol are dose related. A search through the literature reveals that various methods were used to reduce the induction dose requirements of propofol. Application of 'Priming Principle' with use of non-depolarizing muscle relaxants shortens the onset of neuromuscular blockade and provides better intubating conditions. How "Priming" causes reduction in dose was studied by Miller R.D<sup>9</sup> and Prys – Roberts C.<sup>10</sup> Miller R.D describes the classic receptor theory of interaction between ligand (drug molecule) and receptor. At molecular level this interaction causes binding of agonist to receptor to initiate a change in receptor conformation changing the receptor from an inactive to an activated state. Priming dose being considered as agonist who increases the probability of activated receptor that then rapidly occupy the ligand in the principal dose thus reducing the total dose. Similarly, Prys – Roberts C in his textbook "International practice of Anaesthesia" explain the Concept of positive co – operativity and state that 'Occupancy of receptors at low concentrations increases the apparent receptor affinity at higher concentrations'.

A similar 'Priming Principle' was applied to the induction dose of propofol to study reduction in dose thereby reduction in hemodynamic adverse effects in our study.

The demographic profile and types of surgical procedures of both the groups were comparable [Table no 1, 2]. Total induction dose of propofol in study group was  $1.34 \pm 0.28$  mg/kg as compared to 2 mg/kg in control group [ Table 3]. There was approximately 33% reduction in the induction dose requirement of propofol which was statistically significant [p value 0.000].

This reduction in the induction dose was more than that observed by Maroof et al<sup>6</sup> (21.4%) and Anilkumar et al<sup>8</sup> (27.48%), but lower than that observed by Naphade et al<sup>7</sup> (35%). Significant reduction of induction dose of propofol in our study could be due to the use of midazolam (0.03mg/kg) and fentanyl 2 ug/kg as a premedication just before induction, compared to the use of intramuscular meperidine 1mg/kg and promethazine 0.025 mg/kg by Maroof et al. Pre-treatment with midazolam also reduces the induction dose requirements of propofol as studied by Cressy et al.<sup>11</sup>

After giving injection propofol there was decrease in heart rate which was more in control group as compared to study group because of more dose of propofol being used in control group. In addition, there was an increase in heart rate in both the group immediately after intubation in response to laryngoscopy and intubation. The p value at 1 min after induction was significant while heart rate at 30 min before induction, just before induction, immediately after intubation and 5 min after induction P values were insignificant statistically. [Table 4 and Graph1]

Propofol is known to have a biphasic effect on the cardiovascular system. Firstly, immediately after injection, decrease in the systemic vascular resistance and mean arterial pressure predominate leading to reflex increase in the sympathetic activity, which is mediated by the baroreceptors present in the carotid sinus and aortic arch, thereby causing an increase in

the heart rate. Secondly, from 2 minutes after injection, despite less than normal systemic vascular resistance, the heart rate and stroke volume are decreased to less than baseline due to 'resetting' of the baroreceptor reflex.<sup>12</sup>

In our study we observed statistically significant decrease in heart rate at 1 minute after induction which can be attributed to simultaneous administration of midazolam and fentanyl as a premedication. Propofol is also known to cause bradycardia occasionally which is responsive to atropine. In combination with other centrally vagotonic drugs, such as opioids, resetting of the baroreflex set point may result in a slower heart rate.<sup>13</sup>

We observed the values of systolic blood pressure, diastolic blood pressure and mean arterial pressure and found that changes were significant 1min after induction, while they were insignificant at 30 min before induction, just before induction, immediately after intubation and 5 min after induction [Table no 5,6,7 and Graph 2,3,4 respectively]. There was a fall in value of the mean systolic blood pressure, mean diastolic blood pressure and mean arterial pressure in both the groups but there was more fall in the control group than the study group.

These changes are confirming that hemodynamic side effects were dose dependent as stated by Pauline et al and Major R et al<sup>14</sup> with an increase in the induction dose of propofol from 1.5mg/kg to 2.5mg/kg the mean arterial pressure was lowest when 2.5mg/kg of propofol was used. Gerald Edelist<sup>15</sup> showed that propofol cause decrease in heart rate, systolic blood pressure, diastolic blood pressure that was significantly greater than thiopentone. Prys – Roberts et al<sup>16</sup> states that when propofol was used for induction systolic and diastolic blood pressure decreased rapidly during first 2 min to average 79% and 84% respectively from baseline value without any ECG changes. Caleys et al<sup>17</sup> in their study of hemodynamic changes induced and maintained with propofol concluded that hypotension was due to decrease in afterload reduction without compensatory increase in heart rate and cardiac output.

The rate pressure product was introduced as an index of myocardial oxygen consumption by Gerola and associates<sup>18</sup> in 1957. In the study of Sonntag et al<sup>19</sup>, poor correlation between myocardial oxygen consumption ( $mVo_2$ ) and rate pressure product was found during halothane anaesthesia in man. This finding merit special attention, since rate pressure product was recommended as a guide to the prevention of intraoperative ischemic injury. For the patient with coronary artery disease, a proposed goal is not to exceed a rate pressure product level 12000. Angina threshold of rate pressure product ranges from 15,000 to 20,000 mm of Hg per minute. A high rate pressure product is a potential danger of myocardial ischemia, but a normal or low value of rate pressure product does not rule out ischemia. Patients with tachycardia and hypotension may have a normal rate pressure product, but both tachycardia (increasing oxygen demand, decreasing oxygen supply) and hypotension (decreasing oxygen supply) may cause myocardial ischemia. The rate pressure product has been shown to be a useful measure of

myocardial oxygen demand in awake patients, but direct comparisons of myocardial oxygen demand in anaesthetized patients have shown an unreliable correlation.

In our study rate pressure product value was always maintained below the recommended level of 12000 in both the groups at all time intervals. The highest values of mean rate pressure product for control and study group are 10664.73 and 10706.47 and lowest values of mean rate pressure product (RPP) for both groups are 7701.47 and 9109.27 respectively [Table no 8 and Graph no 5]. This shows greater variations in mean rate pressure product in control group than study group.

In our study, in control group 5 patients and in the study group 4 patients complained of pain on injection of propofol. Thus, the incidence of pain in control group is 16.7% while the incidence of pain in study group is 13.3%. The overall incidence of pain in our study is 15%. The lower incidence of pain (15%) on injection of propofol in our study compared to the higher incidence of pain (28%-90%) on injection in other studies, could be attributed to injecting propofol in the large vein on the forearm and prior administration of 2 ug/kg of fentanyl. In our study, in control group 11 patients and in the study group 5 patients observed to have apnea for >30 seconds on injection of propofol. Thus, the incidence of apnea in control group is 36.7% while the incidence of apnea in study group is 16.7%. The overall incidence of apnea in our study is 26.7%. In our study, in control group 4 patients had hypotension while no patient in the study group observed to have hypotension on injection of propofol. The higher incidence of apnea and hypotension on injection of propofol in control group as compared to study group could be attributed to the cardiorespiratory depressant effects of propofol, which are dose dependent.<sup>14</sup> All the patients with clinically observed apnea (>30 sec) were given intermittent positive pressure ventilation with 100% O<sub>2</sub> and hypotension was treated with crystalloids. The fall in the blood pressure was transient and rarely required any drug therapy. All patients in both the groups recorded good intubation conditions. Priming with propofol showed that the induction dose reduced by approximately 33% causing lesser degree of hypotension and bradycardia. There was significant change in the heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and rate pressure product at 1 minute after induction with propofol because of large total dose of propofol being used in the control group as compared to small and divided dose of propofol being used in the study group. The incidence of pain and apnea had not shown statistically significant decrease on priming.

## CONCLUSION

To conclude, priming with propofol significantly reduces the induction dose of propofol and favorably reduces the extent of hypotension and bradycardia following induction with propofol. Propofol produces smooth, rapid, pleasant and safe anaesthesia. Priming with propofol can be practiced owing to its cost effectiveness and better hemodynamic profile and safety.

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