EFFECT OF PROPOFOL TITRATION V/S BOLUS DURING INDUCTION OF ANESTHESIA ON HEMODYNAMICS AND BISPECTRAL INDEX

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Abstract

Background: Propofol when given as 2 mg/kg I.V bolus for induction of anesthesia is known to cause hypotension requiring vasopressors. The objective of our study was to compare Propofol 2 mg/kg single IV bolus (Precalculated group, PG) with the titration of Propofol (Titration group, TG) to clinical parameters as10 mg IV increments every 3 seconds on hemodynamic Parameters and Bispectral Index (BIS), during induction. The effect of titration on dose requirement for induction was also evaluated.

Methods: Effects on Hemodynamic parameters [Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP)], and vasopressors use were recorded at baseline and every 2 minute intervals for 10 minutes. The percent difference in HR, SBP, DBP, and MAP from baseline at 2, 4, 6, 8 and 10 minutes were calculated, to determine the effect on hemodynamic parameters. BIS was recorded at baseline, after injection of Propofol, at intubation and at 10 minutes. Dose requirement of Propofol in TG was also recorded.

Results: At 2 and 4 minutes, SBP decreased in PG by 21% and 18% vs. 11% and 9% in TG (p = .00 & .02); DBP decreased by 17% and 15% in PG vs. 5% and 4% in TG (p = .02 & .03); MAP decreased by 19% and 17% in PG vs. 5% and 4% in TG (p = .00 & .01). Vasopressors were required in 14/43 patients in PG vs. 5/41 in TG (p = .03). Titration resulted in 30% reduction in dose.

Conclusion: Titration of Propofol reduces hemodynamic changes, dose requirement and is able to achieve same level of BIS as in bolus.

Introduction

The properties like faster recovery and minimal postoperative complications has made propofol very popular intravenous anesthetic agent. It is the most commonly used intravenous agent for induction of general anaesthesia and is frequently administered in a dose of 2 mg/kg as a single I.V bolus. However, one of the

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known side effects of Propofol is to cause arterial hypotension with systolic blood pressure decreasing by as much as 30% or more[1-4]. The mechanism of hypotension is attributed to a decrease in sympathetic activity[5], myocardial depression[2,6,7], and direct vasodilation[1,2,6]. Hypotensive effects of Propofol are generally proportional to the dose and rate of administration[2,3,8]. Several studies have tried to address this by either reducing dose requirement[9-13] or changing the method of administration of propofol. Later studies involved slower infusion or titration of propofol and many of these studies employed Target controlled infusion system or infusion pumps. One such method is to incrementally increase the propofol dose till the loss of verbal response and eyelid reflex. It is very simple, used in day to day practice and does not require additional equipment. Despite, it is still a very common practice to administer propofol as a single I.V bolus. We undertook this study to compare the two clinically adopted conventional methods of administering propofol; the standard method as 2 mg/kg single IV bolus with titration of propofol, given in 10 mg IV increments every 3 seconds, to clinical parameters. We evaluated the effect of these two methods on hemodynamic parameters, vasopressors use, and dose requirement of Propofol. In the later part of the study we also investigated the effect of these two methods on Bispectral index (BIS) to objectively assess the level of consciousness; and on hemodynamic changes occurring during intubation.

Materials and Methods

The study design is a prospective, single-blind, randomized-controlled trial. We learned through literature review of Propofol use during induction of anesthesia that all the studies had utilized 60-100 patients for comparison between 2 or 3 groups[14-17]. They all had achieved statistical significance of < 0.05. Hence in our study we chose to compare the effect of Propofol administration as bolus or titration on hemodynamic parameters and BIS in 2 groups of 50 each for a total of 100 patients. After Institutional review board approval and written consent, 100 adult patients with a median age of 60 years (23-85 years) and ASA physical status 1-4 were studied.

They were scheduled for elective surgery under general anaesthesia requiring tracheal intubation. Patients who had a documented allergy to eggs and/or propofol were excluded from the study. Patient's age, body weight, baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial blood pressure (MAP) were recorded before induction. Patients were allocated randomly by envelope method to group 1 (precalculated group, PG) or group 2 (titration group, TG). All patients were given Versed 2 mg, 2 minutes before propofol. They also received fentanyl, 100 µg for patients weighing 70 kg or more, and 50 µg for patients weighing less than 70 kg, and lidocaine 50 mg during induction. These drugs are given 1 minute before propofol. PG received propofol 2 mg/kg as a single IV bolus over 10 seconds. TG received propofol 10 mg every 3 seconds at the rate of 100 mg/30s until loss of verbal response and eyelid reflex. Subsequent neuromuscular blockade and tracheal intubation was achieved with succinylcholine or rocuronium as per anaesthesia providers and further anaesthesia was maintained with inhalational anesthetics. Hemodynamic parameters including HR, SBP, DBP and MAP were recorded every 2 minutes after induction until the 10 minute mark. Percentage difference in HR, SBP, DBP and MAP from the baseline at 2, 4, 8, 10 minutes were calculated. If vasopressors were required, ephedrine and/or Phenylephrine were used for hemodynamic stability. Criterion for using vasopressors was >20% decrease in SBP from baseline &/or decrease of SBP to <90 mmHg. The choice of drug was at the discretion of the anaesthesia provider.

Total propofol dose used and the number of patients requiring vasopressor was recorded until the 10

minute mark.

In titration method we required less amount of Propofol and there is a possibility that patient may not be asleep/unconscious. To answer that question we monitored our last 31 patients with BIS monitor to assess the level of consciousness.BIS was continuously monitored using BIS monitor (Aspect Medical System, Model A-2000, Natick, MA, USA) and the values were recorded at baseline, during induction, before & after intubation and at 10 minutes. In these patients we also aimed to investigate effect of PG and TG on hemodynamic changes occurring during intubation. The percentage difference in hemodynamic parameters (HR, SBP, DBP and MAP) from before intubation to immediately after intubation was compared between the two groups.

For Statistical analysis of hemodynamic parameters and propofol dose, Shapiro-Wilk test and Levene's test was performed to determine normality assumption and to check for equality of variances. The samples with the normal distribution were analyzed by the independent sample T-test to determine the differences between groups. For Non-Normal Variables, Kruskal-Wallis Test was performed. Fisher exact test was used to compare the use of vasopressors in both groups. The software used is SPSS 17.0. P value <0.05 was considered significant.

Results

Patients with difficult tracheal intubations requiring multiple direct laryngoscopies, re- dosing of the propofol were not included for the analysis. Therefore, out of 100 patients enrolled in the study, 84 patients were analyzed (43 in PG; 41 in TG) for hemodynamic parameters, and 31 patients (16 in PG; 15 in TG) for BIS and for hemodynamic changes during intubation.

Demographic data (Table 1) were comparable for age, body weight and sex among both the groups. Baseline hemodynamic parameters-HR, SBP,DBP and MAP did not differ significantly among both the groups.

Table 1

Patient Characteristics (Age, Gender, ASA Status, Body Weight) and baseline hemodynamic parameters (Heart Rate, Systolic Blood Pressure, Diastolic Blood Pressure, Mean Arterial Pressure): Values are mean +/-SD or a number

	Age (yr)	**Gender (M / F)**	**ASA Status 1/2/3/4**	**BW (kg)**	**HR (beat/min)**	**SBP (mmHg)**	**DBP (mmHg)**	**MAP (mmHg)**
PG	58.1 ± 11.5	42 / 1	2/14/27/0	90.3 ± 16.4	68.9 ± 10.7	147.1 ± 21.6	82.3 ± 13.8	103.9± 13.5
TG	52.5 ± 15.2	35 / 6	5/10/25/1	87.4 ± 18.4	69.6± 11.8	139.7 ± 19.0	78.9 ± 14.5	99.2 ± 13.3
P Value	Not Significant	Not Significant	Not Significant	Not Significant	Not Significant	Not Significant	Not Significant	Not Significant

BW (body weight), HR (heart rate), SBP (systolic blood pressure), DBP(diastolic blood pressure), MAP (mean arterial pressure), PG (Precalculated group), TG (titration group).

Increase in HR (Table 2) was seen in both groups after propofol injection. A maximum increase occurred at the 6 minute mark in the PG and 8 minute mark in the TG. However, these changes were not statistically significant. SBP, DBP and MAP decreased in both groups after propofol injection. This decrease was greatest at 2 minutes in the PG and 10 minutes in the TG. Decrease in SBP, DBP and MAP were more in PG compared to TG. This decrease was statistically significant at 2, 4 and 8 minutes for SBP and 2 and 4 minutes for DBP and MAP. The total number of patients who required vasopressors (ephedrine and/or Phenylephrine) was 14/43 PG and 5/41 in TG. This difference was statistically significant.

Table 2

Percentage change in Hemodynamic Parameters (Heart Rate, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Arterial Pressure) in precalculated v/s Titration Group

Hemodynamics		**PG**	**TG**	**P Value**
HR	2 minutes	5.9+/-15.6	5.4+/-19.4	0.64
	4 minutes	12.9+/-21.3	8.2+/-20.3	0.54
	6 minutes	13.8+/-25.6	11.1+/-28.0	0.92
	8 minutes	12.4+/-28.3	13.9+/-20.2	0.24
	10 minutes	6.6+/-20.4	7.8+/-18.2	0.79
SBP	2 minutes	-21.2+/-13.8	-11.1+/-13.4*	0.00
	4 minutes	-18.2+/-27.6	-9.1+/-17.9*	0.02
	6 minutes	-13.1+/-25.4	-6.6+/-26.3	0.26
	8 minutes	-16.9 +/- 24.8	-6.81+/-21.6*	0.05
	10 minutes	-19.6+/-22.1	-11.9+/-17.5	0.08
DBP	2 minutes	-16.5+/-22.07	-5.5+/-23.1*	0.02
	4 minutes	-14.9+/-24.9	-3.9+/- 21.3*	0.03
	6 minutes	-7.0+/-27.9	-2.63+/-32.3	0.51
	8 minutes	-11.01+/-24.6	-4.7+/- 29.8	0.37
	10 minutes	-15.2 +/-23.3	-9.0+/-25.8	0.25
MAP	2 minutes	-19.1+/-16.0	-8.4+/-17.2*	0.00
	4 minutes	-16.9+/-24.1	-6.7+/-18.0*	0.01
	6 minutes	-10.5+/-24.5	-5.0+/-26.9	0.34

	8 minutes	-14.3+/-22.7	-6.3+/-23.3	0.11
	10 minutes	-17.7+/-21.7	-10.9+/-20.2	0.14

* p ≤0.05 v/s PG.

HR (heart rate), SBP (systolic blood pressure), DBP (diastolic blood pressure), MAP (mean arterial pressure), PG (Precalculated group), TG (titration group).

When the percentage difference in hemodynamic parameters (HR, SBP, DBP and MAP) from before intubation to immediately after intubation was compared between the two groups, PG showed increase in HR and decrease in SBP, DBP and MAP. TG had similar increase in HR, however, SBP, DBP and MAP also increased in them. Only the difference in DBP and MAP were statistically significant (Table 3).

Table 3

Percentage Changes in Hemodynamic parameters (Heart Rate, Systolic Blood Pressure, Diastolic Blood Pressure, Mean Arterial Pressure) of Precalculated v/s Titration Group before and after Intubation. Values are mean+/-SD:

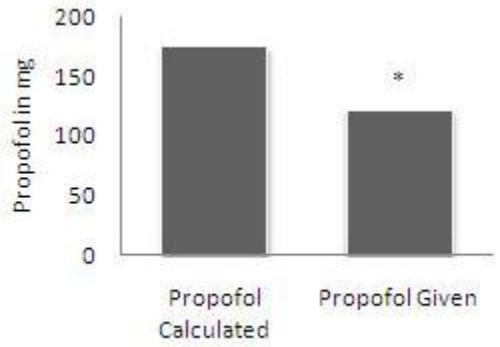
	PG	TG	P Value
Changes in Heart Rate Before &After Intubation	14.1 +/- 18.8	14.1 +/- 22.7	0.80
Changes in SBP Before &After Intubation	-19.0 +/- 28.3	1.3 +/- 21.8	0.07
Changes in DBP Before &After Intubation	-12.3+/- 32.5	11.9* +/- 24.0	0.04
Changes in MAP Before &After Intubation	-15.6 +/- 30.2	6.4* +/- 19.9	0.02

* p ≤0.05 v/s PG.

HR (heart rate), SBP (systolic blood pressure), DBP (diastolic blood pressure), MAP (mean arterial pressure), PG (Precalculated group), TG (titration group).

Mean induction dose of propofol (Fig. 1) in the TG was 122.4 mg. It was significantly lower ($p < 0.05$) than the mean calculated propofol amount 174.9 mg if propofol was given in them based on bodyweight as 2 mg/kg similar to PG.

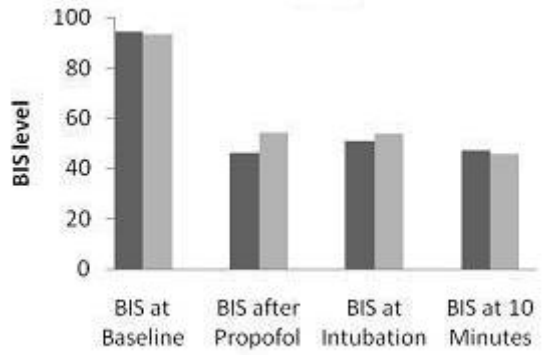
Fig. 1
Propofol Dose in Titration Group



* p ≤0.05 vs. Propofol Calculated as 2 mg/kg.

BIS decreased in both the groups immediately after injecting propofol. It had reduced from 94.2 at baseline to 46.2 after induction in PG and from 93.4 at baseline to 54.3 after induction in TG. In both the groups BIS remained around 50 at the time of intubation and at 10 minute mark. There was no significant difference in BIS at baseline, after propofol induction, at intubation, and at 10 minutes between two groups (Fig. 2).

Fig. 2
Bispectral Index in Precalculated v/s Titration Group.



PG (Precalculated group), TG (titration group), BIS (Bispectral Index).
* p = Not significant.

Discussion

Induction with propofol is known to cause decrease in blood pressure. Studies have demonstrated up to a

28% decrease in SBP, an 11% decrease in MAP, and a 19% decrease in DBP[2,18]. In our study, when propofol was administered as a 2 mg/kg IV bolus (PG), SBP decreased by 20%. There was also a decrease in DBP and MAP by 16% and 19%. In a recent study, cheng et al has proposed a molecular pathway that may contribute to vasodilatory effect of Propofol[19]. Due to the inhibitory effect of propofol on baroreflexes and sympathetic activity, the effect of propofol on heart rate is variable with many studies showing decrease in heart rate[20,21]. In our study, we found an increase in heart rate following induction with propofol similar to a study by Robinson et al[22].

Several studies with varied methods of delivery have demonstrated reduced hemodynamic effects and a decrease in dose requirements of Propofol. Studies have also shown that a slower injection of Propofol decreases cardiovascular effects[23,24]. However, slow injection may also result in longer induction times[25]. In a recent study using a target controlled infusion, Liu et al demonstrated that the decrease in SBP was significantly less when propofol was given in a step wise technique with an initial plasma concentration of 2.0 mg/ml and then raised to a target plasma concentration of 4.0 mg/ml[26]. In a study evaluating a priming principle for Propofol, there was a decrease in dose requirement, and fewer hemodynamic side effects. Priming was accomplished by first giving 20% of the total calculated dose and then the remaining dose until loss of eyelid reflex[27].

In our study, we titrated propofol to clinical parameters with incremental doses of 10 mg every 3 seconds until loss of eyelid reflex and/or verbal response. We found that titration reduced the hemodynamic effects of propofol. All through 10 minutes SBP, DBP and MAP decreased in PG more compared to TG. Titration also resulted in a 30 % reduction in dose requirement.

Laryngoscopy and tracheal intubation is known to increase sympathetic response and therefore result in hypertension. Following intubation, increase of MAP from 35 mmHg to 60 mmHg compared to preintubation values have been reported[28,29]. One of the important factors which could contribute to increased sympathetic response is intubation provider himself. We wanted our study to be clinically oriented; hence tracheal intubation providers were different at different point of the study. This could have affected the hemodynamic response to intubation. To overcome this, we excluded from analysis all the patients who had difficult tracheal intubation requiring either multiple laryngoscopies &/or re dosing of propofol. Earlier studies had shown that propofol even in high bolus doses up to 3.5 mg/kg or different rate of infusion did not modify hypertensive response to intubation[30,31]. In our study, we found increase in blood pressure in TG, However in PG there was further decrease in SBP, DBP and MAP after intubation compared to preintubation values. Administration of fentanyl and lidocaine might have attenuated the hypertensive response to intubation[32,33] and thus decreasing the effect of intubation on hemodynamic changes.

Studies have confirmed the use of BIS monitoring as an objective marker for assessing level of consciousness[34]. BIS index correlates with the magnitude of sedation & loss of consciousness[35]. BIS value of 40-60 is preferred for surgical patients[36]. When we compared BIS in both PG and TG, we found no significant difference between the groups and TG was able to achieve same BIS in spite of low induction dose.

Our study was basically designed to mimic clinical practice as close as possible. Hence it is limited by many factors as we included most patients who presented to our clinic without exercising stringent inclusion criteria like ASA status or history of hypertension/ cardiac disease etc. Tracheal Intubation providers were different for different patients and no changes were made with the clinical protocol of the patients like administration of other agents like Versed, fentanyl or lidocaine as all of these agents are routinely used for induction of anesthesia. In our study, all the patients in both the groups received these drugs.

Titration to clinical parameters is common among anaesthesia practitioners as nearly all drugs are titrated to an objective or subjective end point. Propofol titration is also a conventional method. However, it is our experience that it is very common practice to inject propofol as a bolus dose for induction. Our method of titrating propofol to clinical parameters with incremental dose is very simple, negates the need for extra equipment like an infusion pump and, is easy to clinically adapt.

In conclusion, titration of propofol with incremental increases reduces changes in blood pressure, induction dose requirement and is able to achieve same level of BIS as in bolus.

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