DOI: 10.7860/JCDR/2022/55756.16330

Original Article

Anaesthesia Section

Comparison between Haemodynamic Responses of Propofol Induction between BIS Guided Dose and Sleep Dose: A Randomised Control Trial

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ABSTRACT

Introduction: Propofol contributes largely in the rapid evolution of day care surgery due to its superior recovery characteristics. However, it is associated with dose-dependent systemic arterial hypotension which increases morbidity and mortality. Bispectral index (BIS) is an Electroencephalographic (EEG) derived parameter used to assess the depth of anaesthesia. Titrating drugs to a specific BIS value during general anaesthesia allows to adjust the dose of anaesthetic needed by the patient thereby, reducing the dose related side-effects.

Aim: To determine whether the dose of propofol guided BIS values causes less arterial hypotension than the commonly used sleep dose method.

Materials and Methods: The present study was a randomised control trial conducted on 92 patients of American Society of Anesthesiologists (ASA) I and II physical status, aged 18-60 years, of both genders, scheduled for elective surgeries under general anaesthesia and were randomly divided into group A and B (46 in each). For induction of anaesthesia, group A received propofol till the BIS values reached 50±1 for 30 seconds, while group B received sleep dose of propofol without BIS monitoring. Haemodynamic effects Heart Rate (HR), Diastolic Blood Pressure (DBP), Systolic Blood Pressure (SBP) and Mean Arterial Pressure (MAP) were recorded at baseline, during induction and at 1,5, 10 and 15 minutes after intubation. Total propofol consumption and secondarily, level of sedation after extubation using Ramsay Sedation Scale were also measured in both the groups.

Results: The total dose requirement of propofol was reduced significantly in group A compared to group B ($p<0.005$). Blood pressure decreased from the baseline in both the groups following induction with propofol but was insignificant. The HR increased by 2.2% in group A while it decreased by 8.5% in group B but was insignificant ($p>0.005$). On arrival to Post Anaesthesia Care Unit (PACU), group A were more co-operative, oriented patients compared to group B (67.4% vs 32.6, respectively.

Conclusion: The BIS monitoring significantly reduces the consumption of propofol for induction of anaesthesia while the incidence of hypotension was similar in both the groups. Lower sedation level with comparatively better extubation score with the use of BIS helps in fast tracking.

Keywords: Bispectral index, Day care surgery, Extubation, General anaesthesia, Sedation

INTRODUCTION

Ambulatory or day-care surgery has gained wide popularity throughout the globe. The fast pace of life, need of early return to work and the potential benefits of shorter hospital stay, lower procedural cost, shorter surgical waiting list has led to its widespread acceptance [1]. Rapid and satisfactory procedural outcome owing to advancements in anaesthesia technique, availability of newer drugs like propofol and sophisticated monitors like BIS monitors have contributed immensely to the progress of day-care surgeries. Studies have shown that ambulatory surgery provides better respiratory and cardiovascular outcomes, facilitating early post-operative recovery with fewer complications [2,3].

Propofol, a hypnotic inducing agent contributes largely in the rapid evolution of day-care surgery due to its rapid onset, adequate depth of anaesthesia and rapid recovery [4,5]. However, it causes dose dependent systemic arterial hypotension and bradycardia due to reduced systemic vascular resistance.

The BIS is an EEG derived parameter which is used to assess the depth of anaesthesia/sedation. It can be used to reflect propofol concentration in the blood. Titrating drugs to a specific BIS value during general anaesthesia allows to adjust the dose required by the patient, thereby reducing the dose related side-effects of the drug [6,7]. It is known that propofol, when used as an induction agent during general anaesthesia, causes intraoperative hypotension. This can be prevented by targeting a clinical end point during induction either with BIS guided or sleep dose. This may in addition provide a favourable outcome during extubation and postoperative period. Therefore, it was hypothesised that BIS guided dose adjustment of intravenous propofol provide a stable haemodynamic profile, smooth extubation and alertness during postoperative period.

As one of the most commonly used induction agents in general anaesthesia, propofol dose optimisation is required to avoid haemodynamic instability. The present study aimed to determine whether the dose of propofol guided by BIS values causes less arterial hypotension than the commonly used sleep dose method. The primary outcome was to compare the haemodynamic responses of propofol during induction in terms of SBP, DBP, MAP and HR between BIS guided dose and sleep dose method. The secondary outcome was to compare the extubation score and sedation after extubation using Ramsay Sedation Scale [8].

MATERIALS AND METHODS

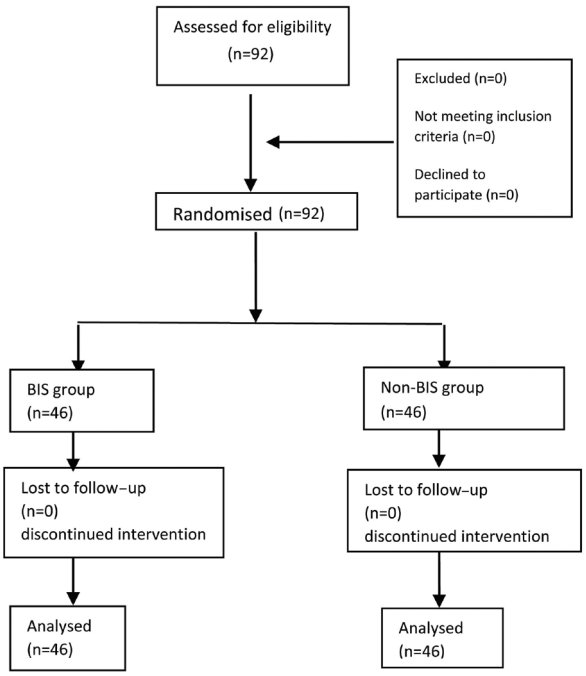
This randomised control trial was conducted from September 2020-January 2022 at Jawaharlal Nehru Institute of Medical Sciences, Imphal, Manipur, India. The Institutional Ethical Committee (IEC) had approved the study (vide protocol no.183/6/PGT-2019).

Inclusion criteria: Consenting male and female patients, between 18-60 years, with ASA physical status I and II undergoing elective surgeries under general anaesthesia.

Exclusion criteria: Patients with history of cardiac diseases, pregnancy or any serious medical condition that would interfere with Cardio Vascular System (CVS) response, history of allergy to any general anaesthesia drugs and cases lasting less than 30 minutes.

Sample size calculation: Sample size of 92 with 46 in each group was calculated with proportion of occurrence of a hypothesis among manually guided at 47% and among BIS guided at 17% with α=5%, β=10%, 90% power and 95% confidence limit [9].

The patients were randomised into two groups, group A (BIS group) and group B (non-BIS group), based on computer generated random number tables [Table/Fig-1].



[Table/Fig-1]: CONSORT flowchart.

Study Procedure

All patients received Tab. ranitidine 150 mg and Tab. alprazolam 0.25 mg the night before surgery. After shifting to operating room, intravenous drip was started with Ringer's lactate (5 mL/hr) after intravenous access. Standard monitors were attached and the baseline HR, SBP, DBP and MAP were recorded. The BIS electrodes were attached and connected to a BIS monitor in group A. As per protocol, all patients were pre-medicated with Inj. ondasetron 4 mg i.v, Inj. fentanyl 2 mg/kg prior to induction along with pre-oxygenation using 100% O_2 for three minutes.

For induction of anaesthesia, group A received propofol till BIS value reached 50±1 for 30 seconds while group B received sleep dose of propofol without BIS monitoring. Both the groups were intubated using succinylcholine 1.5 mg/kg. Sevoflurane, N_2O and vecuronium were used for maintenance of anaesthesia. HR, SBP, DBP and MAP were recorded at baseline, during induction, and at 1,5,10,15 minutes after intubation. All intraoperative complications were treated appropriately. Patients were extubated using reversal agent after extubation criteria were met. Total propofol consumption, haemodynamic changes and level of sedation after extubation using Ramsay Sedation Scale [8] were compared in both the groups.

STATISTICAL ANALYSIS

Data was analysed using Statistical Package for the Social Sciences (SPSS) software (21.0 version) and presented as mean±Standard Deviation (SD). Chi-square test and Fischer's exact test were used to find out association between categorical variables. All the test were considered significant at p<0.05.

RESULTS

Demographic data like age, sex, weight, duration of surgery and anaesthesia were comparable in both the groups (p>0.05) [Table/Fig-2].

Group	Age (years)	Gender Male/ Female (%)	ASA status I/II (%)	Body weight (kg)	Duration of surgery (minutes)	Duration of anaesthesia (minutes)
A	38.37± 9.48	45.7/54.3	45.7/ 4.3	62± 7.83	58.04± 12.04	78.04±12.04
B	37.50± 8.19	54.3/45.7	46.7/ 3.3	63.78± 8.5	61.74± 12.16	81.74±12.16
p-value	0.144*	0.404**	1.000**	0.71*	0.816*	0.816*

[Table/Fig-2]: Demographic variables.
**Fischer's exact test, *Student's t-test

Total dose requirement of propofol: The mean dose of propofol for induction was more in group B compared to group A and was statistically significant (1.94 vs 1.64 mg/kg respectively, p=0.017). Females required lower dose of propofol for induction as compared to males in both the groups but was insignificant (p>0.05). On comparing among males of the two groups, lower doses of propofol was observed in group A compared to group B and was statistically significant (p=0.001) [Table/Fig-3].

Group	Mean dose of propofol (Male)	Mean dose of propofol (Female)	Mean dose of propofol
A	1.66±0.33	1.61±0.22	1.64±0.28
B	2.05±0.09	1.82±0.16	1.94±0.17
p-value	0.001	0.225	0.017

[Table/Fig-3]: Dosage (mg/kg) of propofol between two groups.
(Student's t-test)

Mean HR: The baseline mean HR were comparable in both the groups (p=0.060). Immediately after induction, HR decreased by 8.5% in G group B while it increased by 2.2% in group A from the baseline (p>0.05). At one min, five mins, 10 mins and 15 mins interval after intubation, mean HR was comparable in both the groups. Maximum increase in HR was seen in both the groups after extubation but was insignificant.

MAP, SBP, DBP: Baseline MAP, SBP, and DBP between group A and B were comparable. More fall in MAP from the baseline immediately after induction was seen in group B compared to group A but was insignificant (13.47% vs 11.05%. 1 min after intubation, rise in MAP from the baseline was more in group A compared to group B but was statistically insignificant (5.7% vs 2.08%). SBP, DBP and MAP at five mins, 10 mins and 15 mins after intubation and five mins after extubation were comparable between the two groups. In group A 67.4% were cooperative, oriented and tranquil post extubation compared to 32.6% in group B. There was no cough/strain in 63% of patients in group A during extubation compared to 34.8% in group B [Table/Fig-6].

Haemodynamics		Group A	Group B	p-value (Student's t-test)
HR	Baseline	79.02±9.89	79.15±7.65	0.060
	Induction	80.72±10.28	72.43±11.23	0.285
	1 min after intubation	78.61±11.72	74.20±10.94	0.983
	5 mins	75.43±10.78	73.39±10.27	0.882
	10 mins	78.43±10.55	74.43±9.92	0.885
	15 mins	76.09±12.19	74.93±11.56	0.694
	5 mins after extubation	83.89±10.22	84.30±10.09	0.933
SBP	Baseline	130.48±11.11	129.70±11.03	0.826
	Induction	115.48±12.13	115.22±10.78	0.285
	1 min after intubation	140.28±15.06	137.61±12.53	0.576
	5 mins	115.17±15.91	118.89±14.31	0.668
	10 mins	118.13±15.05	118.59±15.03	0.835
	15 mins	124.65±15.77	122.04±14.35	0.584
	5 mins after extubation	138.80± 11.81	133.09±10.11	0.306

DBP	Baseline	80.22±11.45	77.39±10.99	0.664
	Induction	71.63±9.75	70.67±9.06	0.394
	1 min after intubation	83.67±14.76	82.54±12.19	0.169
	5 mins	72.33±12.58	74.22±10.55	0.432
	10 mins	73.61±13.59	72.22±12.66	0.655
	15 mins	80.46±13.13	78.98±12.16	0.345
	5 mins after extubation	88.57±7.79	86.59±7.04	0.908
MAP	Baseline	96.97±10.51	94.82±9.29	0.765
	Induction	86.24±9.84	85.52±8.63	0.231
	1 min after intubation	102.54±12.83	100.89±10.10	0.190
	5 mins	87.60±12.05	89.10±10.44	0.988
	10 mins	88.44±13.48	87.67±12.78	0.619
	15 mins	95.18±13.29	93.33±11.89	0.217
	5 mins after extubation	105.3±1 8.55	102.08±6.49	0.224

[Table/Fig-4]: Haemodynamic parameters.
HR: Heart rate; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; MAP: Mean arterial pressure

Petrun A and Kamenik M showed that propofol caused significant hypotension even when doses were given with BIS guided protocol for induction [13]. Haemodynamic instability caused by propofol even with the use of BIS was demonstrated by Lui N et al., [7]. In contrast, some studies found that BIS cannot predict haemodynamic responses to intubation during anaesthesia induction with propofol and fentanyl [4,14].

In this study, there was an increase in HR from the baseline by 2.2% in group A while in group B, it decreased by 8.5% during induction with propofol but was insignificant. This reduction in HR may be due to the dose dependent inhibition of baroreflexes and sympathetic activity by propofol [2]. Some studies found increase in HR following propofol induction [3]. Increase in HR is due to reflex increase in the sympathetic activity due to hypotension induced by propofol [12].

Previous studies were conducted in the dose requirement and side-effects of propofol using clinical end points such as loss of eyelash reflex [7,15-17]. However, this method can cause underdosing or overdosing of propofol. BIS monitoring is increasingly preferred in

Group	Induction	1 min after intubation	5 mins after intubation	10 mins after intubation	15 mins after intubation	5 mins after extubation
HR						
A	2.2%	-0.5%	-4.5%	-0.7%	-3.7%	6.2%
B	-8.5%	-6.3%	-7.3%	-5.9%	-5.3%	6.5%
SBP						
A	-11.5%	7.5%	-9.4%	-9.5%	-4.5%	6.4%
B	-11.2%	6.1%	-8.3%	-8.6%	-5.9%	2.6%
DBP						
A	-10.7%	4.3%	-9.8%	-8.2%	0.3%	10.4%
B	-8.7%	6.7%	-4.1%	-6.7%	2.1%	11.9%
MAP						
A	-11.05%	5.7%	-9.65%	-8.79%	-1.84%	8.60%
B	-13.47%	2.08%	-9.84%	-11.29%	5.57%	3.29%

[Table/Fig-5]: Haemodynamic changes expressed as percent difference from baseline value.

Groups	Ramsay sedation scale n (%)				Extubation score n (%)		
	Anxious , agitated, restless	Cooperative, oriented, tranquil	Responds to command only	Brisk response to light glabellar tap	No cough/strain	Moderate cough	High degree of coughing
Groups A	2 (4.3)	31 (67.4)	13 (28.3)	0	29 (63)	17 (37)	0
Groups B	8 (17.4)	15 (32.6)	20 (43.5)	3 (6.5)	16 (034.8)	27 (58.7)	3 (6.5)
p-value (Fisher's exact test)	0.002				0.007		

[Table/Fig-6]: Ramsay sedation scale and extubation score.

DISCUSSION

Propofol reduces systemic vascular resistance, cardiac contractility and preload. Several studies have shown reduction in SBP, DBP and MAP when propofol was given as i.v bolus [10]. In this study, there was a decreased SBP (11.2%), DBP (8.7%) and MAP (13.47%) from the baseline during induction in group B compared to group A i.e. SBP (11.5%), DBP (10.7%) and MAP (11.05%) respectively but was insignificant. This was similar to a study by Riisch D et al., where they demonstrated that the maximal drop in MAP from the baseline between the BIS guided, manually-administered propofol and the dose based on weight were comparable (33% vs 30%, respectively) [9]. Puri GD et al., demonstrated that BIS had no co-relation with MAP and that decrease in MAP were comparable even when the BIS value was significantly different between the group manually guided by BIS and BIS guided by closed-loop administration of propofol during induction [11]. However, another study by Shah NK et al., demonstrated a decrease in SBP by 20%, DBP by 16% and MAP by 19%, two minutes following induction of propofol at 2 mg/kg i.v bolus using BIS [12]. Another study by Möller

routine clinical practice for achieving adequate anaesthesia and reducing the dose of propofol by titration of the drug to a desired hypnotic level. Accordingly, it was assumed that the incidence of unintended side-effects such as arterial hypotension would be minimised with the decrease in propofol consumption. Many studies have demonstrated that propofol target concentration correlates with BIS values and predicts the level of sedation and loss of consciousness accurately [18-20].

In this study, there was significant reduction in the dose of propofol in group A compared to group B (1.64 mg/kg vs 1.94 mg/kg, respectively, p=0.017). The dose reduction of propofol when BIS guided monitoring was used to guide induction and maintenance of manually controlled administration as well as closed loop delivery have been demonstrated in several studies [7,12,21]. Gan TJ et al., concluded that titrating propofol with BIS monitoring during balanced anaesthesia reduced propofol use significantly and improved recovery compared to the standard practice group (116 mcg/kg/hr vs 134 mcg/kg/hr respectively, p<0.001) [22]. However, a study by Arya S et al., showed that use of BIS was associated with

insignificant reduction of propofol dosage (p>0.05) [23]. Another study by Struys MM et al., found similar induction doses of propofol when compared between closed-loop controlled administration of propofol using BIS and standard practice controlled administration with BIS [24]. A significant decrease in propofol dosage was observed in males guided by BIS compared to those guided by sleep dose (1.66±0.33 vs 2.05±0.09 respectively, p=0.0001). This dose reduction of propofol was consistent with the findings of several studies [14,25].

Alertness and sedation: On arrival to the PACU, group A had more co-operative, oriented patients compared to group B. Similarly, Krupali et al., found that the BIS monitored group receiving propofol i.v had less sedation compared to midazolam group post-operatively upto 45 minutes [26].

Limitation(s)

The study was conducted in elective patients adequately optimised for surgery among younger age group (18-60 years). A wider range of age would have given the idea of variations in haemodynamic parameters with propofol induction. The use of BIS over the routinely practiced sleep guided dose of propofol in terms of haemodynamics needs further trials with inclusion of geriatric age group, more study sample size and those subjects with existing co-morbidities. The dose reduction of propofol with comparatively better extubation score and lower sedation level as measured by Ramsay Sedation Scale helps in fast-tracking (although this could not be demonstrated in detail in present study).

CONCLUSION(S)

The BIS monitoring significantly reduces the consumption of propofol for induction of anaesthesia. Incidence of hypotension was similar in both the BIS guided group as well as sleep guided, non-BIS group. Patients with BIS monitoring were more cooperative and oriented on arrival to PACU than those without BIS monitoring.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Feb 25, 2022
- Manual Googling: Mar 12, 2022
- iThenticate Software: Mar 24, 2022 (9%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Feb 22, 2022**
Date of Peer Review: **Mar 12, 2022**
Date of Acceptance: **Mar 31, 2022**
Date of Publishing: **May 01, 2022**