Comparison of Hemodynamic Effects of Dose Response vs. Conventional Dosing of Propofol for Anesthesia Induction Under Bispectral Index Monitoring: A Clinical Trial

Zahra Khazaeipour[1], Niloufar Khoshnam-Rad[2], Khalil Pestei[3,4], Shahram Samadi[4,5]

[1] *Brain and Spinal Cord Injury Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran*

[2] *Thoracic Research Center, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran*

[3] *Department of Anesthesiology, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran*

[4] *Anesthesia, Critical Care and Pain Management Research Center, Tehran University of Medical Sciences, Tehran, Iran*

[5] *Sleep Breathing Disorders Research Center (SBDRC), Tehran University of Medical Sciences, Tehran, Iran*

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Abstract- Propofol is an advantageous agent for anesthesia induction. It can cause dose-related hemodynamic adverse effects. The bispectral index (BIS) is a brain function monitor utilized to assess the depth of anesthesia. This study aimed to compare the adverse hemodynamic effects of BIS-guided response dosing with conventional weight-based dosing of Propofol. In this clinical trial, patients were anesthetized with propofol in two different orthopedic operating rooms. In one operating room, patients received propofol with dose-response method (group A), and the other received weight-based dosing (group B). For both groups, BIS was used as an index of anesthesia depth. Hemodynamic parameters were recorded at baseline, during induction, and at different time points. A total of 73 patients were included in the final analysis. The mean dose of propofol for induction was higher in the control group than in the response-guided group (1.94±1.65 vs. 1.09±0.32, respectively, P=0.006). There were no reported significant adverse hemodynamic effects in patients of the two groups. Response-guided propofol dosing can be used to decrease propofol dose during anesthesia induction. Further studies are needed to investigate the clinical benefit of this dosing strategy.

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Introduction

Propofol is the most commonly used intravenous (IV) induction agent in general anesthesia, with rapid onset of action and recovery. Propofol possesses antiemetic, antipruritic, bronchodilator, muscle relaxant, and anticonvulsive properties that make it a good option in many situations and is being increasingly used in the management of traumatic head injury, status epilepticus, delirium tremens, status asthmaticus, and sepsis (1,2). This drug is also a suitable choice for patients with renal or hepatic dysfunction (3). The disadvantages of propofol include dose-dependent effects of hemodynamic parameters (hypotension and respiratory depression), injection site pain, contamination risk, and rare allergic reactions (3-5).

The induction dose of propofol for general anesthesia is 1 to 2.5 mg for every kilogram of body weight (6). Dose-dependent hemodynamic adverse effects can be avoided by reducing the initial dose and titrating propofol in increments, particularly when it is concomitantly administrated with one or more adjuvant anesthetic agents and in elderly or hypovolemic patients (7-9).

In medically paralyzed patients, monitoring is challenging as scoring systems cannot determine the

Corresponding Author: Kh. Pestei
Department of Anesthesiology, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 2166581560, E-mail address: khalilpesteh@yahoo.com

level of pain, sedation depth, or presence of delirium. Heart rate (HR) and blood pressure (BP) have historically been utilized as indicators of distress, but these vital signs are neither sensitive nor specific (10). The bispectral index (BIS) is a brain function monitor utilized to assess the depth of anesthesia based on the information from raw electroencephalogram (EEG) waveforms. It provides a numerical value between 0 and 100 that corresponds to the level of sedation (11). Gürses *et al.*, reported a 43% reduction in propofol induction dose using BIS analysis compared to traditional weight-based dosing (12).

Propofol dose optimization is beneficial for reducing hemodynamic instability (13). The present study aimed to compare the hemodynamic effects of propofol dosing guided by response and weight-based dosing. We also compared the amount of required propofol to achieve anesthetic effects, by using BIS in both groups to avoid awareness during induction period.

Materials and Methods

This study was prospective, non-randomized clinical trial conducted at a tertiary hospital affiliated to Tehran University of Medical Sciences, Tehran, Iran. The Ethical Committee had approved the study (IR.TUMS.IKHC.REC.1399.281).

Consenting adult patients undergoing elective surgeries under general anesthesia with ASA physical status I and II were included in this study. Patients with cardiovascular diseases, severe anemia (hemoglobin <10 mg/dL), kidney or liver failure, pregnancy or any serious medical condition that would interfere with Cardiovascular System (CVS) response, history of allergy to any general anesthesia agents, morbid obese patients, and those undergoing surgeries lasting less than 30 minutes were excluded.

Sample size was calculated based on Shangne *et al.*, study (13). With the power of 90 % and α=0.01, the sample size was calculated 25 in each group.

Patients were anesthetized, non-randomly, in two different clinics by two specialists in orthopedic operating rooms. One expert calculated the amount of anesthetic using the dose-response method (group A) and the other calculated the weight-based dosing (group B). For both groups, BIS was used as an index of anesthesia depth.

I.V normal saline (5 mL/hr) was administrated for all patients during the procedure. Standard hemodynamic monitors and pulse oximeters were used to monitor heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and oxygen saturation. The BIS electrodes were attached and connected to a BIS monitor in both groups. All patients were pre-medicated with 2 mg midazolam and 100 mcg fentanyl with pre-oxygenation using 100% O_2 for three minutes based on the institutional protocol.

For anesthesia induction, group A received propofol slowly to achieve apnea and loss of eyelash reflex, with a BIS value of less than 60 for 30 seconds, while group B received weight-based dosing (1-2 mg/kg) of propofol with BIS monitoring. Hemodynamic parameters including, HR, SBP, DBP, and MAP, were recorded at baseline, during induction, and at different time points (15, 30, 45, and 60 minutes after intubation).

Categorical parameters were reported with frequencies or percentages as appropriate. Quantitative variables were presented as either mean±standard deviation (SD) or frequencies. The Kolmogorov-Smirnov test was to assess the normality of quantitative variables. Comparison between categorical variables was performed using the Chi-square or Fisher's Exact test for qualitative variables when appropriate. Student t-test was used for comparison between continuous variables in 2 categorical variables. Repeated-measurements analysis was used to compare the trend of BIS, and other continuous variables changes at different times in both groups.

The data analysis was processed using SPSS (version 25.0, Chicago, IL, USA) with a per-protocol analysis.

Results

Seventy-six patients (33 in group A and 43 in group B) were included in the final analysis. There was no significant difference between the baseline characteristic of the two groups (Table 1).

The mean dose of propofol for induction was higher in the control group than in the BIS-guided group (1.94±1.65 vs. 1.09±0.32, respectively, P=0.006).

As represented in table 2, figure 1, the trend of BIS changes at different times in both groups was significantly decreasing (P<0.001), but these changes were not significantly different between the two groups (P=0.099).

As summarized in table 2, the trend of MAP and pulse rate, and changes at different times in both groups was significantly decreasing (P<0.001), but these changes were not significantly different between the two groups (P=0.199, P=0.95, respectively). The trend of oxygen saturation changes after the second measurement in both groups increased significantly and then remained

constant (*P*=0.005). These changes were significantly different between the two groups (*P*=0.003), although this difference was different from the beginning.

Table 1. Baseline characteristics of the patients examined, grouped based on randomized treatment

Parameter	Group A (n=33) (BIS- guided dosing)	Group B (n=43) (Weight-based dosing)	*P*
Age (years), (mean±SD)	44.95 ± 16.08	45.03 ± 11.9	0.9[a]
Gender (Female %)	48.5	48.8	0.9[b]
Weight (Kg), (mean±SD)	75.90 ± 13.46	78.78 ± 10.8	0.3[a]
Smokers (%)	31.3	13.3	0.4[c]
Baseline Systolic Blood Pressure	131.3 ± 16.2	137.8 ± 20.4	0.1[a]
Baseline Diastolic Blood Pressure	83.2 ± 10.1	86.3 ± 11.1	0.2[a]
Baseline Heart rate	81.2 ± 16.9	81.0 ± 16.8	0.9[a]
Oxygen saturation	98.7 ± 1.5	97.8 ± 1.8	0.1[a]
Bispectral index	88.7 ± 12.8	89.6 ± 7.5	0.7[a]

a: t-test, b: Chi-Square Tests, c: Fisher's Exact Test

Table 2. Trends of hemodynamic outcomes

Group	Before induction	After premedication	After induction	After 15 minutes	After 30 minutes	After 45 minutes	After 60 minutes
BIS							
Control	89.6 ± 7.5	79.6 ± 8.3	46.9 ± 21.7	43.7 ± 9.6	45.8 ± 6.6	46.2 ± 7.4	44.4 ± 6.1
BIS guided	88.7 ± 12.8	76.7 ± 11.0	46.9 ± 9.2	50.2 ± 8.1	48.5 ± 7.6	47.7 ± 7.2	45.8 ± 7.5
Heart Rate (Beats/minutes)							
Control	81.0 ± 16.8	80.2 ± 15.9	80.6 ± 19.2	78.4 ± 17.4	73.2 ± 14.7	72.1 ± 14.4	70.6 ± 13.1
BIS guided	81.2 ± 16.9	79.9 ± 14.3	74.0 ± 13.2	76.1 ± 15.2	75.6 ± 14.7	73.7 ± 15.1	72.7 ± 11.6
Mean arterial pressure							
Control	104.8 ± 12.9	95.4 ± 11.8	82.5 ± 18.4	79.2 ± 8.8	79.0 ± 5.3	80.4 ± 8.8	82.0 ± 9.9
BIS guided	98.7 ± 8.8	90.9 ± 7.6		81.9 ± 5.9	79.2 ± 8.6	77.5 ± 8.7	78.7 ± 11.1
Oxygen saturation (%)							
Control	97.8 ± 1.7	98.1 ± 1.8	98.6 ± 2.2	99.1 ± 1.0	99.2 ± 1.0	99.1 ± 1.3	99.1 ± 1.0
BIS guided	98.7 ± 1.5	99.0 ± 0.9	-	99.3 ± 0.4	99.3 ± 0.5	99.0 ± 0.6	99.2 ± 0.4

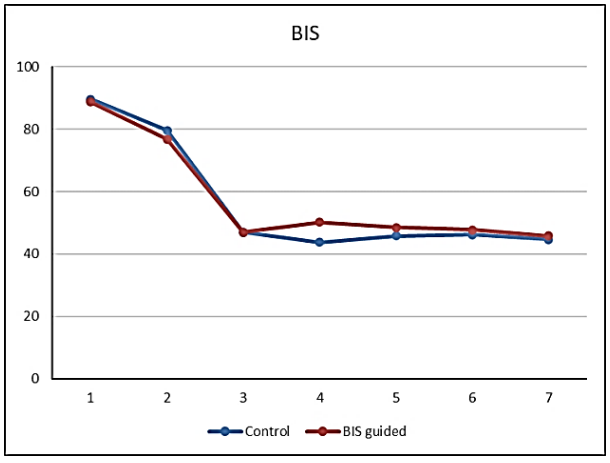

Figure 1. Trends of change of BIS conventional dosing (Blue) and BIS guided dosing (Red) based on the study time points

Discussion

To the best of our knowledge, this is the first study in Iran that compared conventional anesthetic agent dosing with BIS-guided dosing. We observed a significant difference between the propofol dose in the BIS-guided group compared to conventional dosing (1.09±0.32 vs. 1.94±1.65, respectively, *P*=0.006). The dose reduction of propofol when BIS-guided monitoring was used to guide induction and maintenance dose of propofol has been reported in several studies (13-16). Gan TJ *et al*.,

concluded that propofol titration based on BIS monitoring during balanced anesthesia significantly decreased propofol use and improved recovery compared to conventional dosing (17). Our study is in accordance with these studies; thus, applying BIS guided dosing for propofol dosing could be beneficial in clinical practice.

We also compared hemodynamic adverse effects, as propofol can result in diverse hemodynamic unfavorable outcomes (18). It can induce hypotension via decreasing systemic vascular resistance. This effect is more evident in hypovolemic patients or those with underlying cardiovascular problems (19,20). Cardiac output can be reduced following propofol administration by decreasing myocardial contractility and preload. Additionally, propofol can improve venous capacitance by relaxing the vascular system walls, which can lead to a transient decrease in venous return and cardiac output (21). It also can cause bradycardia by suppressing the activity of the sinoatrial node (22). Respiratory depression by depressing the central respiratory drive and reducing the responsiveness of the respiratory muscles to carbon dioxide is another possible adverse effect of propofol (23). Overall, these adverse effects of propofol are dose-dependent and may be more pronounced in patients with pre-existing cardiovascular disease or hypovolemia. Consequently, careful tracking of hemodynamic parameters is essential during propofol administration (14). Regarding the significantly lower required doses of propofol in BIS-guided dosing group, we expected lower hemodynamic adverse effects in these patients; however, due to small sample size of our study we did not detect hemodynamic adverse effects in our study. None of the patients experienced hypoxemia; hence, interoperation of changes in O_2 saturation might not be reliable.

The present study has many limitations, and the results of this study should be interpreted by considering these limitations: This is a non-randomized trial, and it is possible that different surgeries with different anesthesia time were performed. The sample size is not enough to accurately detect hemodynamic complications. Further randomized controlled studies with appropriate sample size, considering these points, can be helpful in determining the benefits of using BIS-guided dosing in reducing hemodynamic complications in clinical practice.

Our study showed that BIS monitoring is helpful for monitoring sedation and reducing the dose of propofol and possibly it's adverse events at a very low price. Studies with a larger sample size may help with the systematic implementation of this form of anesthesia monitoring and drug dosing Iran sedation protocols.

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