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Evaluation of Propofol Dose based on total body weight in Obese Compared to Non-Obese Patients Guided by Bispectral Index

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Abstract: ***Background:*** *Propofol may be an appropriate agent for induction and maintenance of anesthesia in obese patients. However, there is a controversy regarding the propofol dose in such patients. This study was done to evaluate propofol dose, based on total body weight (TBW), in obese compared to non-obese patients.*
Methods: *Fifty ASA I-II adult patients, who underwent different surgical procedures, were categorized into: group O; obese with body mass index (BMI) >30 kg/m2 and <40 kg/m2 and group N; non-obese with BMI ≤25 kg/m2. Propofol dose was given according to TBW guided by Bispectral index (BIS). Onset time (beginning of propofol infusion until BIS < 50), propofol infusion dose required to reach the onset time, rate and duration of infusion during maintenance, and total amount of propofol during anesthesia were recorded.*
Results: *The mean onset time was significantly longer in group O (10.0 ± 1.5 min) compared to group N (6.2 ± 2.6 min) (p < 0.0001). The mean dose of propofol (mg/kg/h) required to achieve onset time was significantly higher in group O than group N (10.2 ± 2.3 vs. 8.6 ± 2.5; respectively) (p = 0.02). The relative mean rate of infusion (mg/kg/h) during maintenance was non-significant. However, the mean total propofol consumption (mg) was significantly higher in group O (p < 0.0001) during the entire anesthesia. Mean heart rate and blood pressure values were significantly lower in group O at 6 and 9 min following induction.*
Conclusions: *From this study, with the guidance of BIS monitor, propofol dose for non-compromised obese patients can be calculated according to TBW.*

Keywords: Bispectral index (BIS), Obesity, Propofol, Total body weight.

1. Introduction

Propofol is a short-acting intravenous anesthetic drug with an excellent recovery profile having pharmacokinetic characteristics particularly suitable for continuous infusion [1], [2]. Although propofol is commonly used for induction and maintenance of anesthesia in obese patients, little is known about its tolerated and effective dose in such patients [3]. Obese individuals have larger lean body and fat masses compared to non-obese of the same age, gender, and height. The altered physiological changes that accompany obesity include an increase in blood volume, body water, muscle mass and cardiac output. These factors affect the volumes of drug distribution and total body clearance [4], [5]. Dose adjustment for these changes needs to be studied and planned. The impact of obesity on different organ systems may alter drug dose requirement, time course of drug response, and decrease the safety margin of anesthetic drugs [6]. Obesity is measured using body mass index (BMI) which is a relationship between height and weight. A BMI ≤ 25 kg/m^2 is considered as normal and BMI > 30 kg/m^2 is considered as obese [4].

Bispectral index (BIS) is a non-invasive monitor used to assess the depth of anesthesia which can be useful in guiding the anesthetic dose [7]. It also enables titration of anesthetic agents to improve anesthetic delivery, avoid adverse effects of overdose, and speed up patient recovery and discharge [8]**,** [9]. With the guidance of BIS, this prospective clinical study tested the hypothesis that propofol dose could be calculated according to total body weight in obese compared to non-obese patients. Secondary outcomes included hemodynamic side effects of propofol, recovery and discharge times.

2. Methods, Study Measurements, and Statistical Analysis

2.1 Methods

With the approval from our local ethical committee and after receiving written informed patient consent, 50 consecutive patients, who were scheduled for different elective general surgical procedures, were enrolled in the study. Inclusion criteria included adult patients between 20 and 50 years of age with American Society of Anesthesiologists (ASA) physical status I-II. Exclusion criteria included pregnancy, known allergy to propofol or its emulsion, patients on regular sedatives or narcotic medications, or patients with hepatic, renal or cardiac diseases. Patients were allocated to either group O (obese with BMI > 30 kg/m^2 and < 40 kg/m^2) (n = 25) or group N (non-obese with BMI ≤ 25 kg/m^2) (n = 25). Both groups were pre-medicated with intravenous (I.V.) midazolam 0.02 mg/kg in the preoperative holding area. Patients were then transferred to the operating room where standard physiologic monitors were connected. These included electrocardiograph leads II & V_5, heart rate, arterial oxygen saturation (SpO_2), non-invasive blood pressure, and end-tidal CO_2 ($EtCO_2$). BIS sensor was placed on patient's forehead and connected to the BIS monitor (COVIDIEN BIS LoC 2 Channel

[Dräger Medical GmbH, Lübeck, Germany]). During surgery, patients received 8 ml/kg/h Lactated Ringer's solution. All patients were pre-oxygenated with 100% O_2 and anesthesia was induced with I.V. fentanyl 1 mcg/kg and propofol 2 mg/kg, followed by IV rocuronium 0.6 mg/kg to facilitate endo-tracheal intubation. The lungs were ventilated with a fraction of inspired oxygen (FIO_2) = 0.5 using a mixture of oxygen and nitrous oxide with volume-controlled ventilation. Ventilatory parameters (V_T, RR) were adjusted to maintain $EtCO_2$ around 35 mmHg. Incremental doses of rocuronium were given to maintain 1/4 to 2/4 twitches of train-of-four (Dräger, Trident NMT monitor, Telford, PA, USA). Based on TBW, the induction dose of propofol was followed by propofol infusion at a rate of 6 mg/kg/h just before intubation and titrated to reach BIS level of 50 or less (onset time) then surgical procedure was started. Afterwards, the infusion rate was adjusted to maintain BIS values between 45 and 55 which indicate adequate level of anesthesia [9]. When BIS score went out of these limits for more than 20 s, the propofol infusion was changed up or down by increments of 0.25 mg/kg/h. All patients received paracetamol 15 mg/kg I.V. after induction of anesthesia. During the last 10 minutes of the procedure, the titration was decreased to reach BIS level between 60 and 70. Upon completion of surgery, propofol infusion and nitrous oxide were stopped; atropine and neostigmine were given I.V. (1/2.5 mg) to reverse the action of muscle relaxant which was followed by tracheal extubation. After arrival to the recovery room, tramadol 1 mg/kg was given for postoperative pain.

2.2 Study measurements

We have recorded the following parameters:

The duration of infusion (min) was defined as the time from the start of propofol infusion to its stoppage. While the onset time (min) was the time from the beginning of propofol infusion until the BIS level became less than 50. The dose of propofol infusion (mg/kg/h) required to reach the onset time. The rate of infusion during maintenance (mg/kg/h) and the total amount of propofol (mg) used during the entire anesthesia. The clinical evaluation of the recovery of anesthesia was achieved by calculating the time for spontaneous breathing (TSB) and the time for eye opening (TEO). TSB (min) was the time from the stoppage of propofol infusion to the return of spontaneous breathing. TEO (min) was the time from the stoppage of propofol infusion until patients open their eyes. The recovery time (min) was defined as the time from the stoppage of propofol infusion until the moment where BIS level was higher than 90. Time to discharge (min) was defined as the time from patient arrival to the time of patient discharge from the recovery room. For the purpose of the study, heart rate and mean blood pressure were recorded just before induction of anesthesia (T0), then every 3 minutes after induction for 15 minutes. Afterwards, these values were recorded every 10 minutes till the end of surgery.

2.3 Statistical analysis

Statistical analysis processed by using the Statistical Package for Social Science (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA). Chi-squared ($\chi 2$) or Fisher's exact test was used when appropriate. Also, paired t-test was applied as needed. Ordinal data are expressed as mean ± SD and categorical data are expressed as number of patients (n). Sample size of 18 patients per group was required to detect a 30% difference in propofol requirements ($\alpha = 0.05$ and $\beta = 0.1$). To compensate for possible dropout, we boosted the number to 25 patients in each group.

3. Results

This study enrolled 50 patients (25 obese patients with BMI> 30 kg/m^2 and < 40 kg/m^2 and 25 non-obese patients with BMI ≤ 25 kg/m^2) who underwent different surgical procedures under general anesthesia. There were no significant differences between the two groups with respect to age, gender, duration of propofol infusion, type or duration of surgery (Table 1).

Table 1. Demographic and clinical data of both study groups. Data are expressed as mean ± SD or numbers (n).

Variable	Group O (n = 25)	Group N (n = 25)
Age (years)	35 ± 11	37 ± 10
Gender (Male/Female)	8/17	10/15
ASA status: I II	7 18	19 6
Mean Duration of propofol infusion (min)	72.1 ± 5.31	69.4 ± 4.9
Mean duration of surgery (min)	60.7 ± 8.6	61.3 ± 6.2
Mean BMI (kg/m$^{2)}$	35.6 ± 4.3	22.2 ± 2.1
Mean TBW (kg)	112.8 ± 8.5 (104 -123 kg)	71.6 ± 12.3 (56 - 87 kg)
Types of surgery: Inguinal hernia Umbilical hernia Abdominal wall lipoma Breast surgeries	 5 6 8 6	 9 7 6 3

The duration of propofol infusion (min) was the mean time from start of propofol infusion to its stoppage. Duration of surgery (min) was the time from skin incision to closure. Values are expressed as mean ± SD or number. BMI: body mass index (kg/m2). TBW : total body weight (kg).

Table 2 shows the mean onset time and dose of propofol infusion to achieve the onset time which were significantly higher in group O. However, the mean rate of propofol infusion during maintenance of anesthesia was non-significant, but the total propofol consumption was significantly higher in group O during the entire anesthesia (Table 2).

Table 2. Study outcomes for both groups

Variable	Group O (n=25)	Group N (n=25)	p-value
The mean onset Time (min)	10.0 ± 1.5	6.2 ± 2.6	< 0.0001
The mean dose of Propofol to achieve target BIS (mg/kg/h)	10.2 ± 2.3	8.6 ± 2.5	0.0227
The mean rate of infusion during maintenance (mg/kg/h)	9.9 ± 2.5	9.6 ± 2.6	0.6794
The mean total propofol consumptions (mg)	1260 ± 310	820 ± 270	< 0.0001

The onset time (min) was defined as time from the beginning of propofol infusion until the BIS level was less than 50. The dose of propofol to achieve target BIS (mg/kg/h) was the dose of propofol from the beginning of propofol infusion until the BIS level was less than 50. The rate of infusion during maintenance (mg/kg/h) was the maintenance dose of propofol during the entire surgery. The total propofol consumptions (mg) was the total dose of propofol used

including the induction dose. Values are expressed as mean ± SD. P value < 0.005 was considered significant.

The recovery parameters as shown in table 3 revealed the mean 'time to eye opening' and recovery time which were significantly longer in group O. However, there were no significant differences between the two groups regarding the mean time of spontaneous breathing or time to discharge from the recovery room (Table 3).

Table 3. Tabulation of recovery parameters

Variable	Group O (n = 25)	Group N (n = 25)	p-value
The mean of TSB (min)	3.3 ± 2.4	2.6 ± 1.5	0.2222
The mean of TOE (min)	8.2 ± 2.5	5.3 ± 1.6	< 0.0001
The mean recovery time (min)	13.1 ± 3.6	8.6 ± 6.5	0.0041
The mean time to discharge (min)	82 ± 15	76 ± 13	0.1372

TSB (min) (time to spontaneous breathing) was the time from the stoppage of propofol infusion to the return of spontaneous breathing. TEO (min) (time to eyes opening) was time from the stoppage of propofol infusion until patients open eyes. Recovery time (min) was the time from the stoppage of propofol until the time which the BIS level was higher than 90. Time to discharge (min) was the time from patient arrival to the time of patient discharge from the recovery room. Values are expressed as mean ± SD. P value < 0.005 was considered significant.

Figure 1 shows no significant differences between both groups in BIS values except at 6 and 10 min after induction where there is significant difference in onset time.

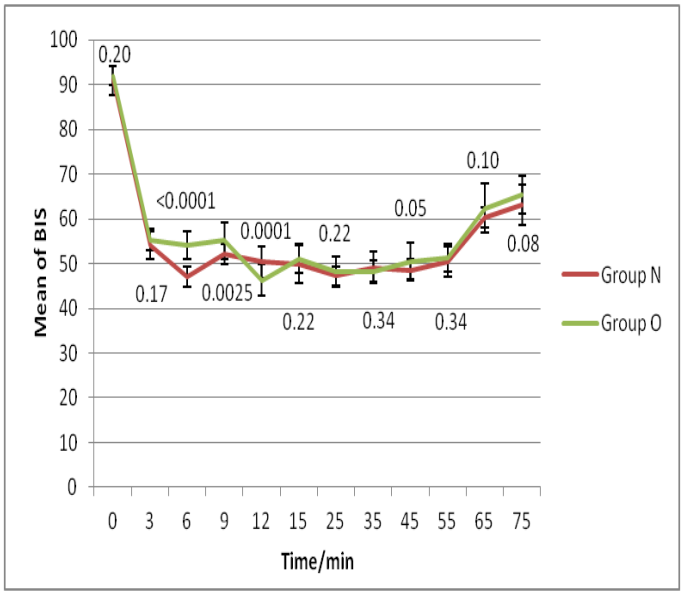

Figure 1: Bispectral index values at different time-points The mean for BIS was significantly lower at 6 min (mean of onset time) after induction of anesthesia in group N and it was significantly lower at 10 min (mean of onset time) in group O. After that, it became non-significant until the end of surgery. Time 0: just before induction of anesthesia. 3-75 min: after induction of anesthesia. Values are expressed as mean ± SD. P value <0.05 was considered significant.

The mean heart rate was significantly lower at 6 and 9 min after induction of anesthesia in group O compared to group N (Figure 2).

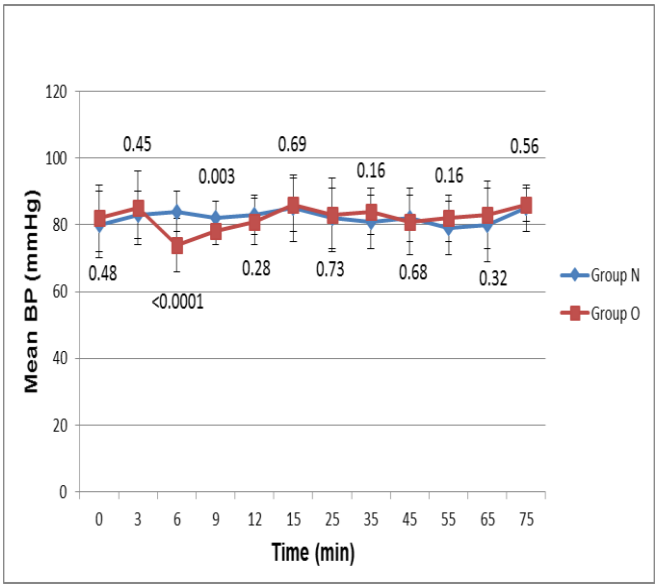

Figure 2: Intraoperative comparison of mean heart rate The mean heart rate was significantly lower at 6 and 9 min after induction of anesthesia in group O compared to group N. After that, it became non-significant until the end of surgery. Time 0: just before induction of anesthesia. 3-75 min: after induction of anesthesia. Values are expressed as mean ± SD. P value <0.05 was considered significant.

Also, the results showed that the mean arterial blood pressure was significantly lower at 6 and 9 min after induction in group O (Figure 3).

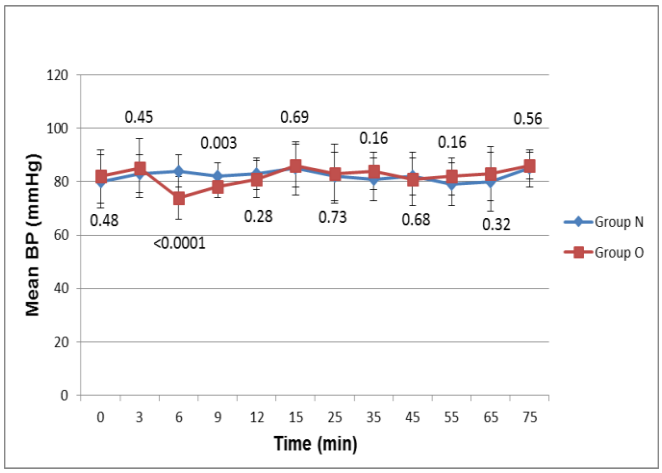

Figure 3: Intraoperative comparison of mean arterial blood pressureThe mean blood pressure was significantly lower at 6 and 9 min after induction of anesthesia in group O compared to group N. After that, it became non-significant until the end of surgery. Time 0: just before induction of anesthesia. 3-75 min: after induction of anesthesia. Values are expressed as mean ± SD. P value <0.05 was considered significant.

After that, both heart rate and blood pressure showed non-significant values until the end of the surgery. However, those changes were not clinically significant and did not necessitate any drug intervention.

4. Discussion

Obese patients carry a considerable challenge to anesthesiologists. Clinicians should know which 'weight' parameter to be used in dosage calculation: total body weight (TBW), lean body mass (LBM) or ideal body weight (IBW) in bariatric population. There is a paucity of studies that discuss such topic. In this study, obese patients received induction and maintenance propofol doses based on TBW. Propofol infusion per kg was non-significant between obese and non-obese patients. However, obese patients had consumed more total propofol and had longer recovery parameters than non-obese without effect on discharge time. Adequate anesthesia was obtained in our patients because BIS-guided administration of propofol was used as was recommended by others [2]. As nitrous oxide has no effect on BIS reading as reported by others, we have used constant percentage of nitrous oxide supplementation in our study [10].

In agreement with our study, Servin et al. [11] confirmed that the propofol dosage should be based on TBW for both obese as well as non-obese patients. They stated that the pharmacokinetics of propofol was unaltered in the obese patients, and clearance values and volumes of distribution correlated well with TBW. Similarly, Casati and Putzu [12] reported that the propofol dosage was calculated based on TBW. They explained that drug dosing is spilt into loading and maintenance where the loading dose depends on the volume of distribution, and the maintenance dose depends on the body clearance. Both volume of distribution and clearance are increased in obese patients. Moreover, Ingrande and Lemmens suggested that the volume of distribution and clearance of the highly lipophilic propofol increase linearly with TBW in obese patients. This is because there are more fatty tissues in obese patients than the lean mass in such a way affecting the volume of distribution of propofol. In addition, the higher cardiac output seen in obese subjects may increase the clearance of drugs [5]. Also, De Baerdemaeker et al. [13] recommended that the propofol dose for maintenance of anesthesia in obese patients can be given either on the basis of TBW or corrected body weight which is the ideal weight plus ± 0.4 x excess weights. Furthermore, van Kralingen et al. [14] demonstrated that the induction dose of propofol in morbidly obese patients should not be based on IBW, but based on TBW. They found that the use of 350 mg propofol dose in obese patients was safer and more appropriate at the time of intubation, compared to a dose of 200 mg which caused high and harmful systolic blood pressure to 60% of patients. In our study, the maximum dose of induction was 250 mg as the maximum weight in our obese group was 123 kg.

However, Gepts [15] has recommended that in morbidly obese patients the dose can be calculated by corrected body weight. On the other hand, others suggested that propofol dose can be used based on LBM, which was calculated from gender, weight (kg), and height (cm), instead of TBW [16], [17]. TBW could be a good approximation of LBM to scale drugs' doses [16]. Also, Albertin et al. [6] recommended that the induction dose should be based on LBM, as large doses of propofol could result in significant hemodynamic changes.

Our study showed that the mean heart rate and mean arterial blood pressure were significantly lower after induction of anesthesia in obese compared to non-obese patients during titration of propofol to reach the level of BIS to less than 50. As reported by others, low heart rate is common when propofol combines with opioids [18]. Hemodynamic changes in our study were not clinically significant and did not need any drug intervention.

5. Conclusion

With the guidance of BIS monitor, the dose of propofol can be calculated according to TBW in non-compromised obese patients. The increase in total propofol consumption in those patients, however, did not lead to clinical hemodynamic instability or prolonged discharge time.

6. Limitations

The main limitation of this study is that the pharmacokinetics of propofol was not done in order to correlate it with BIS and clinical findings. Also further studies are needed to evaluate propofol dose in obese patients with BMI > 40 kg/m^2.

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Conflict of interest

No conflict of interest to be declared.

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