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Reduced antioxidant and anti-inflammatory effects of propofol at high-dose on morbidly obese patients

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Abstract: This study was aimed to investigate differences in antioxidant and anti-inflammatory effects of propofol at two commonly used dosing schedules on morbidly obese patients. Twenty-two morbidly obese patients were randomly divided into two groups, namely, TBW (dosing based on total body weight) and LBW (dosing based on lean body weight) groups. Three biomarkers, i.e. superoxide dismutase (SOD), malondialdehyde (MDA) and nitric oxide (NO) were measured as indicators of the level of oxidation stress reaction. Pro-inflammatory cytokines including Interleukin-6 (IL-6) and Interleukin-8 (IL-8) were used to describe the degree of inflammation. Plasma levels of SOD, MDA and NO were increased and reached a peak value 0.5h after anesthesia induction, but the increase was smaller in the LBW group compared with the TBW group. Besides, plasma concentrations of IL-6 and IL-8 were also increased and attained a peak level 0.5h after anesthesia induction, but the increase was higher in the TBW group compared with the LBW group. The LBW-based dosing of propofol had more potent antioxidant and anti-inflammatory effects than the TBW-based dosing during anesthesia induction period on morbidly obese patients. This study provided a dosing recommendation of propofol for morbidly obese patients.

Keywords: Propofol, morbidly obese, antioxidant, anti-Inflammatory, lean bodyweight, total body weight.

INTRODUCTION

Propofol was extensively used for the anesthesia induction and maintenance due to its rapid sedation property (Bushuven and Heise, 2013). Because the chemical structure of propofol was semblable to phenol-based free-radical scavengers, such as vitamin E, propofol possessed antioxidant activity both in vitro and in vivo, which can inhibit cellular oxidative damage and increase glutathione levels in the tissues (Kotani *et al*., 2008). The antioxidant capacity was also increased after administration of propofol for surgery (Hans *et al*., 2008). It also has been reported that propofol had immunomodulatory activity, which might reduce the systemic inflammatory responses regarded as the main reason for organ dysfunction (Shi *et al*., 2014; Zheng *et al*., 2017). Therefore, cardio-protective and neuro-protective properties were discovered for propofol (Fan *et al*., 2014; Zhao *et al*., 2015).

Morbid obesity was a condition when one's body mass index (BMI) was more than 40kg/m^2 (Poobalan *et al*., 2009). With the continually economic growth, the number of morbidly obese (MO) patients has been raised rapidly in the recent years. It has been noted that the prevalence of adult obesity was 34.9% in the United States (Ogden *et al*., 2014). Typical symptoms associated with MO included a lack of self-esteem, high blood pressure, shortness of breath and depression (Yanovski and Yanovski, 2014). Besides, MO could result in a series of complications such as diabetes, cancer, and heart disease (Lavie *et al*., 2014). For MO, exercise, diet control, enrolling in weight-loss programs and bariatric surgery were common options of the treatment, among which bariatric surgery was the most effective way that could make 50 to 70 percent of MO patients lose at least 50 percent of the excess weight and keep it off for five years (Chen *et al*., 2007) .

There were two widely used dosing scalars of propofol during anesthesia induction period in MO patients, i.e. dosing based on lean body weight (LBW) or total body weight (TBW). However, impacts on antioxidation and anti-inflammatory properties of different dosing scalars for propofol were still unknown, puzzling the choice of dosing scalars on MO patients. Here, we aimed to investigate the difference in antioxidant and anti-Inflammatory effects of propofol at two commonly used dosing schedules. Plasma superoxide dismutase (SOD) and malondialdehyde (MDA) and nitric oxide (NO) levels were measured as indicators of antioxidant capacity. Two pro-inflammatory cytokines, namely, Interleukin-8 (IL-8) and Interleukin-6 (IL-6), were used to describe the degree of inflammation.

MATERIALS AND METHODS

Materials

WST-1 and 2-thiobarbituric acid (TBA), somogyi reagent, ethylenediamine tetraacetic acid (EDTA), 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2, 4-disulfophenyl)-2H-tetrazolium sodium salt (WST-1) and Tris base were

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Table 1: Demographic characters of patients. Data were presented as Mean ± Standard Deviation (SD)

Variables	TBW group (n = 11)	LBW group (n = 11)
Race	Chinese	Chinese
Sex ratio (M/F)	4/7	5/6
Age (years)	30.4 ± 7.52	30.4 ± 7.51
Height (cm)	1.65 ± 0.09	1.67 ± 0.08
TBW (kg)	121 ± 34.6	124 ± 28.7
LBW (kg)	61.8 ± 9.78	63.4 ± 10.5
BMI (kg/cm^2)	44.6 ± 8.04	47.8 ± 8.02

Table 2: Hemodynamic data in TBW and LBW groups. Data were presented as Mean ± Standard Deviation (SD). *P < 0.05; **P<0.01; ***P<0.001 (compared with T1 in each group)

Variables	Group	T1	30 min	60 min	90 min
SpO^2 (%)	TBW	97.6 ± 1.81	97.2 ± 0.64	96.9 ± 1.45	97.6 ± 1.72
	LBW,	98.7 ± 1.32	97.0 ± 1.12	98.2 ± 0.67	98.7 ± 1.28
HR (bpm)	TBW	80.9 ± 8.52	63.1 ± 7.95***	71.2 ± 7.07**	76.7 ± 7.76
	LBW	82.7 ± 6.83	74.8 ± 8.47*	78.6 ± 6.74	80.7 ± 5.78
CI (L/min/m^2)	TBW	4.36 ± 0.95	2.99 ± 0.53***	3.37 ± 0.68**	3.72 ± 0.77
	LBW	4.41 ± 0.67	3.64 ± 0.72*	3.95 ± 0.49	4.10 ± 1.04

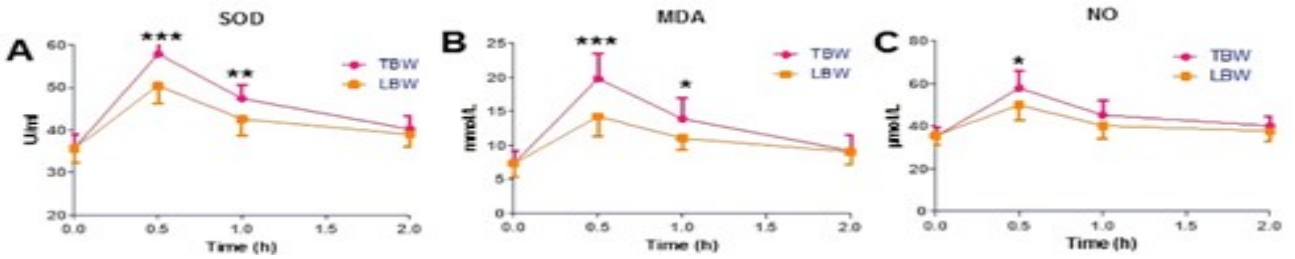

Fig. 1: Changes of antioxidant function in the TBW and LBW groups. Data were presented as mean ±SD. *P<0.05;**P< 0.01. (A) The plasma concentration of SOD; (B) the plasma concentration of MDA; (C) the plasma concentration of NO.

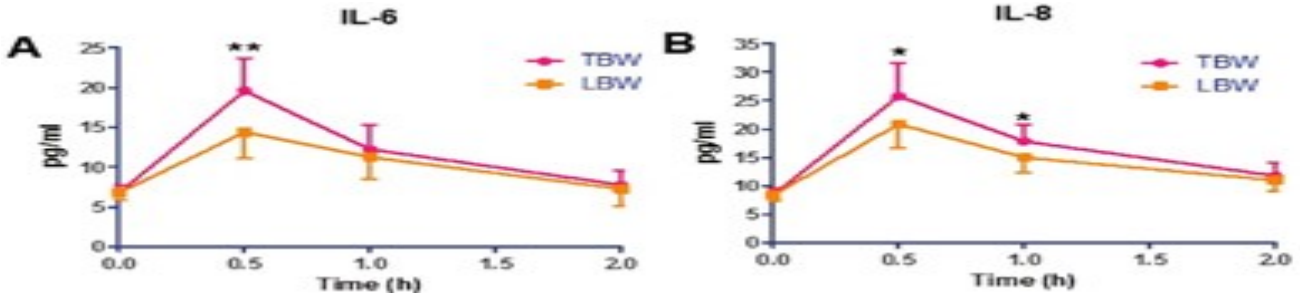

Fig. 2: Changes of plasma inflammatory cytokine concentration in the TBW and LBW groups. Data were presented as mean ± SD. *P<0.05; **P<0.01. (A) The plasma concentration of IL-6; (B) the plasma concentration of IL-8.

bought from Sigma-Aldrich (St Louis, MO). The enzyme-linked immunosorbent assay (ELISA) was obtained from Beyotime Institute of Biotech (Shanghai, China).

Subjects

This randomized controlled clinical trial was approved by the Ethics Committee of the First Affiliated Hospital of Jinan University. The clinical trial registration number for this study was ChiCTR1800015753. Each patients included in this study was given a written informed consent. Patients were included into study if they were aged between 20 and 40 years, had normal lung, liver and renal function, were American Society of Anesthesiologists physical status classification of I or II, had no cardiovascular and neural diseases. Patients were excluded if they had diabetes or the history of smoking. Patients who had administered psychotropic medicine in the recent month of the study were also excluded. Twenty-two MO patients who were scheduled to undergo laparoscopic roux-en-y gastric bypass surgery were

included into this clinical trial. All patients were administered 2 mg/kg propofol via intravenous injection for anesthesia induction. Subjects were randomly divided into two groups, namely, TBW (dosing of propofol based on TBW) and LBW (dosing of propofol based on LBW) to avoid confounding effects. The calculation of LBW was according to previous study (Janmahasatian *et al*., 2005).

In the operation room, induction of anesthesia was performed via intravenous injection of propofol (2 mg/kg), midazolam (0.05mg/kg), fentanyl (2mg/kg) and rocuronium (0.6mg/kg). Anesthesia maintenance was achieved by continuous infusion of propofol (4mg/kg per hour), remifentanil (0.2mg/kg per minute) and atracurium (8mg /kg per minute) based on LBW.

Plasma sampling

Blood samples (approximately 2ml) were collected from patients before (time 0) and at 0.5, 1, 2h after administration of propofol. Blood samples were immediately transferred to centrifuge tubes containing heparin and were centrifuged at 8000g for 4 minutes. Subsequently, the supernatant (plasma) was gathered and stored at -80°C until analysis.

Determination of nitric oxide (NO) activity

Nitrite (NO_2) and nitrate (NO_3) were served as index parameters of NO production. On the basis of Griess reaction, nitrite and nitrate levels were measured (Cortas and Waki, 1990). Somogyi reagent was firstly used for the deproteinization of plasma. After conversion of nitrate to nitrite, total nitrite was measured by spectrophotometer at 545nm. NO levels were expressed in μmol/L in plasma.

Determination of superoxide dismutase (SOD) activity

WST-1, a highly water-soluble compound, was used to calculate SOD activity. Plasma and standard substrate of SOD were transferred by a pipette into each well of a 96-well plate along with WST-1 (1mM), assay buffer, xanthine oxidase and catalase. The 96-well plate was placed in a homoiothermal environment at 37°C. The absorbance at 450nm was read via a microplate reader (SpectraMax Plus) for five minutes. Per mg of protein was set as unit for the expression of SOD activities.

Determination of malondialdehyde (MDA) activity

MDA activity was measured via the thiobarbituric acid (TBA) method. In brief, plasma was added into 1.5 ml tubes containing TBA to produce a pink product at 37°C. Subsequently, the absorbance of the liquid was measured at 530nm. MDA activity was expressed as nmol/ml.

Determination of interleukin 6 (IL-6) and interleukin 8 (IL-8) level

Plasma IL-6 and IL-8 levels were measured by ELISA with a commercially available ELISA kit (Quantikine Human Immunoassay, China) according to manufacturer's protocol. The absorbance of plasma was determined at 450nm with a microplate reader. Plasma levels of IL-6 and IL-8 were expressed in pg/mL.

STATISTICAL ANALYSIS

Data were displayed as mean ± SD (standard error). The unpaired Student's t test was applied to compare the differences in demographic and parameters of two MO groups via SPSS (version 18.0). Statistical significance was set as $p < 0.05$.

RESULTS

Demographic characters of patients were listed at table 1. Clearly, there were no significant differences with respect to demographic information between TBW and LBW groups. Intravenous injection of propofol did not affect Pulse Oxygen Saturation (SpO2) in patients, while propofol significantly decreased the level of heart rate (HR) and cardiac index (CI) compared with the base line values (table 2). HR and CI would recover normal values at 60 minutes for patients in the LBW group and at 90 minutes for patients in the TBW group. Cardiovascular inhibition effects of propofol were consistent with results of previous studies (Goodchild and Serrao, 2015; Green, 2015).

Plasma SOD, MDA and NO levels were increased after surgery and reached a peak level at 0.5 h in both two groups (fig. 1). However, the increase was less in the LBW group compared with the TBW group. In detail, compared with the LBW group, the SOD and MDA levels were significantly higher at 0.5 and 1h (fig. 1A and 1B, $p < 0.05$), and NO level was only significantly larger at 0.5 h in the TBW group (fig. 1C, $p<0.05$). There was no difference of SOD, MDA and NO levels between two groups at 2h. The concentration of two pro-inflammatory cytokines, i.e. IL-6 and IL-8 were also increased and reached a peak level at 0.5 h (fig. 2). A larger dose of propofol (i.e. dosing based on TBW) significantly caused higher pro-inflammatory cytokines levels compared with the LBW-based dosing (IL-6: 0.5 h: 19.6 VS 14.4 pg/ml; IL-8: 0.5 h: 25.8 VS 20.9, BA1 h: 17.8 VS 15.1 pg/ml).

DISCUSSION

In this study, we, for the first time, evaluated the impacts of two different dosage regimes of propofol (i.e. dosing based on TBW or LBW weight) on antioxidant and anti-inflammatory capacities on MO patients undergoing laparoscopic gastric bypass surgery. A higher dose of propofol (TBW-based dosing) during anesthesia induction period resulted in the significant increase in plasma MDA, SOD and NO levels compared with the LBW-based dosing (fig. 1). Besides, patients in the TBW group

showed a stronger inflammatory response due to higher IL-6 and IL-8 values than patients in the LBW group (fig. 2). Taken together, dosing based on LBW weight of propofol had a better antioxidant and anti-Inflammatory effects on MO patients compared with the TBW-based dosing schedules. Therefore, propofol dosing based on LBW rather than TBW was a more rational dosing regimen for MO patients according to antioxidant capacity and inflammatory responses analysis.

Plasma MDA, SOD, NO, IL-6 and IL-8 levels were related to many factors, including the history of smoking, gender, body mass index, medications and type of surgery (Haack *et al*., 1999; Kudoh *et al*., 2001) . In our study, we minimized the interference from these factors on the concentration of these biomarkers via selecting subjects with similar demographic characters (table 1). The surgery would induce inflammation and oxidative stress reaction and further result in organ injuries (Haack *et al*., 1999; Kudoh *et al*., 2001) . This was the reason why both antioxidant biomarkers and pro-inflammatory cytokines increased rapidly after anesthesia induction (fig. 1 and 2). Hence, to reduce organ injuries, it was necessary to attenuate inflammation and oxidative stress reaction during surgeries.

A number of studies demonstrated that propofol exhibited inhibition effects on oxidative stress induced by organ injuries (Khoshraftar *et al*., 2014; Ozkan *et al*., 2012; Romuk *et al*., 2016). Besides, anti-inflammatory effect of propofol could reduce the severity of organ damages during surgery (An *et al*., 2008; Jin *et al*., 2013; Tian *et al*., 2017). Ischemic brain damage in the cerebral ischemia could be attenuated by propofol via inhibiting the release of tumor necrosis factor-α and nuclear factor-kappa β (Shi *et al*., 2014). It also has been report that propofol could strengthen the antioxidant capacity against the ischemia-reperfusion injury (Ozkan *et al*., 2012). Therefore, propofol had organ-protective effect for MO patients because it can attenuate oxidative stress and inflammatory reactions. This study was firstly found that different dosing scalars (i.e. dosing based on TBW or LBW weight) had impacts on the antioxidant and anti-inflammatory capacities of propofol during anesthesia induction period.

It was an interesting finding that lower dosing of propofol (i.e. dosing based on LBW) had better antioxidant and anti-inflammatory effects on MO patients compared with higher dosing schedule (i.e. dosing based on TBW). The oxidative stress injury and expression of pro-inflammatory factors were considerably enhanced in the TBW group as compared with the LBW group (fig. 1 and 2). However, the exact reasons why the increased of propofol dosing would decrease pharmacodynamic effects (i.e. anti-inflammatory and antioxidant effects) remain unknown. Nevertheless, it was rational to speculate that intensive organ injury was associated with aggravated anesthetic effect (BIS value below 40) for the TBW-based dosing of propofol that may be harmful to patients (Dong *et al*., 2015).

CONCLUSION

This study, for the first time, evaluated the antioxidant and anti-Inflammatory effects of two propofol dosing schedules (i.e. dosing based on LBW or TBW) on MO patients undergoing laparoscopic gastric bypass surgery. Dosing based on LBW of propofol had more potent antioxidant and anti-inflammatory effects than dosing based on TBW, recommending LBW-based dosing of propofol on MO patients for *anesthesia induction.*

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