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Characterization of cardiovascular depression effect for propofol during anesthesia induction period on morbidly obese patients

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ABSTRACT

This study aims to determine the pharmacodynamics (PD) effect (measured by cardiovascular depression) of propofol during anesthesia induction period on morbidly obese (MO) patients. Four hemodynamics indexes [i.e., three indexes about blood pressure and cardiac output (CO)] representing cardiovascular function were measured.

Pharmacokinetic/pharmacodynamic (PK/PD) modeling was performed by population analysis to obtain PD parameters. Two propofol dosing scalars, namely, dosing based on total body weight (TBW) or lean body weight (LBW), were used for MO subjects. The PD data were well described by a PK/PD model. Blood pressure and CO were rapidly decreased within one minute after intravenous injection of propofol (2 mg/kg). TBW group showed significantly lower blood pressure and CO values at and 1 min after propofol administration compared with the control group, whereas the control and LBW groups had similar PD profiles. In addition, the propofol EC_{50} value was significantly decreased in MO patients, whereas all other PD parameters were similar between control and MO subjects. This change indicated that propofol potency and/or sensitivity was increased in MO subjects. For MO patients, dosing of propofol based on LBW rather than TBW would be a safer choice due to a less cardiovascular depression effect.

1. Introduction

Propofol was a widely used hypnotic anesthetic for the induction and maintenance of general anesthesia [1]. Though it was commonly used in the clinical, much undesirable side effects had been reported for the propofol, including pain on injection, mild itching, difficult breathing and cardiovascular depression [2]. Among which, cardiovascular depression, one of the most common side effects for propofol, was likely to occur at higher blood concentrations as a result of rapid increase in infusion rates or bolus dosing [3]. Cardiovascular depression could result in the change of hemodynamic properties, such as arterial hypotension and decrease in cardiac output (CO) [3].

Morbid obesity was a serious health condition that can result in some complications, such as diabetes, sleep apnea, depression and heart disease [4,5]. Besides, the rate of morbid obesity has been rising continually over the past twenty years [6]. There were three primary types of treatment for morbid obesity, namely, lifestyle change, weight loss drugs and surgery [7–9]. Surgical intervention was an effective and safe methods compared with other two ways [8]. This was because surgery could provide a long-term solution to morbid obesity [8].

Abbreviations: MO, morbid obesity; MAP, mean arterial blood pressure; SAP, systolic arterial blood pressure; DAP, diastolic arterial blood pressure; CO, cardiac output; PK, pharmacokinetic; PD, pharmacodynamics; TBW, total body weight; LBW, lean body weigh; k_{e0}, the transfer rate constant of drug molecules from the central compartment to the effect compartment; C_e, the effect-site concentration; E_{max}, the maximum effect from the baseline value; EC_{50}, the concentration required to produce half of the maximum effect; S_0, the baseline value; γ, the hill exponent describing steepness of the response curve

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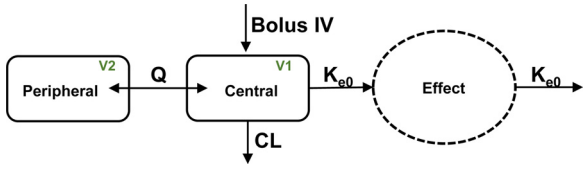

Fig. 1. Schematic diagram of PK/PD model. Q, the distribution clearance; CL, the elimination clearance; k_{e0}, the transfer rate constant from the central to effect compartment.

Table 1
Demographic information of patients in the three groups. Data were presented at mean (standard error).

Parameter Race	Control (n = 6) Chinese	LBW (n = 11) Chinese	TBW(n = 12) Chinese
Age (years)	28.8 (10.8)	30.4(7.51)	30.4(7.52)
Total Body Weight (kg)	55.2(6.04)	124 (28.7)***	121 (34.6)***
Height (m)	1.66(0.05)	1.67(0.08)	1.65(0.09)
BMI (kg/m^2)	23.8(0.41)	47.8(8.02)***	44.6(8.04)***
Sex ratio(M/F)	3/3	5/6	4/8
Comorbid disease	No	No	No

*** $P <$ 0.001 compared with control group.

Propofol has been frequently used for anesthesia induction during weight loss or other surgery in morbidly obese (MO) patients [10,11]. However, the PD parameters of propofol-caused cardiovascular depression have not been determined in MO patients. A correct dosing regimen of propofol was essential for the safety of anesthesia induction. The objectives of this study were to determine cardiovascular depression effect of different propofol doses in MO patients, and to provide a recommendation for the dosing schedule for MO subjects. All patients included in this clinical trial were administrated propofol by intravenous injection (2 mg/kg) based on total body weight (TBW) or lean body weight (LBW). Four hemodynamics indexes including mean arterial blood pressure (MAP), systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP) and CO were monitored. PK/PD modeling was performed by population analysis to get PD parameters.

2. Methods

2.1. Study design

This clinical trial was approved by the Ethic Committee of the First Affiliated Hospital of Jinan University and was performed at the First Affiliated Hospital of Jinan University (Guangzhou, China). The registration number was ChiCTR1800015753. Written informed consent was given by the patients before the clinical trial. A total of 29 patients were divided into one control (n = 6) and two MO groups [i.e., LBW (n = 11) and TBW (n = 12) groups]. Patients with BMI > 35 kg/m^2 were selected into MO groups. The study groups (LBW and TBW) involved MO patients undergoing elective laparoscopic gastrectomy while the control group underwent "semi-"elective laparoscopic assisted gastrectomy due to a diagnosis of stomach cancer or gastric bleeding. All subjects had normal liver and renal function and were free of clinically significant neurologic, psychiatric, neuromuscular, or blood diseases. Propofol was administrated by intravenous injection (2 mg/kg). Subjects in the control and TBW groups were given propofol based on total body weight, whereas subjects in the LBW group were received propofol based on lean body weight. The quantification of LBW was performed by following formulas [12]:

$$LBW\,(male) = \frac{9.27 \times 10^3 \times TBW}{6.68 \times 10^3 + 216 \times BMI}$$

$$LBW\,(female) = \frac{9.27 \times 10^3 \times TBW}{8.78 \times 10^3 + 244 \times BMI}$$

2.2. Arterial blood pressure monitoring

An intra-arterial catheter (Leader Cath 20 G, Vygon, Germany) was inserted into the right radial artery and was connected to a transducer.

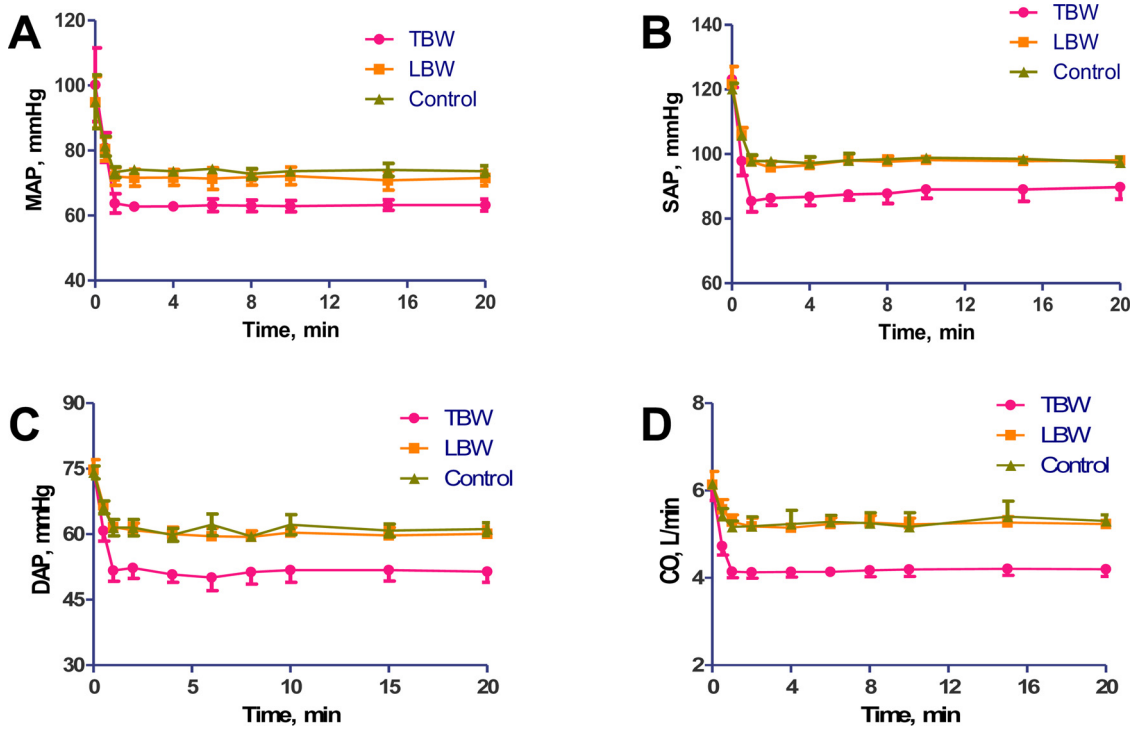

Fig. 2. Comparisons of mean MAP (A), SAP (B), DAP (C) and CO (D) values versus time curves between control group and MO groups. The control and LBW groups had similar PD profiles, while PD values were significantly lower at and after one minute in TBW group than control group.