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CLINICAL TRIAL REPORT

Young, Healthy, Underweight Women Require Higher Effective Doses of Propofol for Successful Gastroscope Insertion: a Dose-Finding Study Using Dixon's Up-and-Down Method

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Purpose: The number of young women undergoing painless gastroscopy is rising annually. However, the lack of studies on the effective doses of propofol sedation for young, underweight women, presents a clinical challenge. Our study aimed to determine and compare the effective doses of propofol required for successful gastroscope insertion in normal-weight and underweight young women.

Patients and Methods: Chinese women aged 18–35 years who were of normal weight (18.5 ≤ body mass index (BMI) < 25 kg/m²) or underweight (BMI < 18.5 kg/m²) and were undergoing painless gastroscopy were included. The initial induction dose of propofol was 2.0 mg/kg, and subsequent doses were adjusted using the modified Dixon's up-and-down method (step size: 0.1 mg/kg). The 50% and 95% effective dose of propofol (ED_{50} and ED_{95}), defined as the doses required for successful gastroscope insertion in 50% and 95% of patients, respectively, were determined using the modified Dixon's up-and-down method and isotonic regression analysis. All adverse events were documented.

Results: Thirty patients were included in each group. The modified Dixon's up-and-down method was used, and the ED_{50} of propofol was found to be significantly higher in patients in the underweight group (2.72 ± 0.23 mg/kg) than those in the normal-weight group (2.03 ± 0.13 mg/kg) ($P < 0.001$). The ED_{50} and ED_{95} in the normal-weight group extrapolated using isotonic regression analysis were 2.00 (83% confidence interval [CI], 1.900–2.100) mg/kg and 2.30 (83% CI, 2.300–2.400) mg/kg, respectively. In the underweight group, these values increased to 2.80 (83% CI, 2.700–2.900) mg/kg and 3.00 (83% CI, 3.000–3.100) mg/kg, respectively. The nonoverlapping CIs indicated significant differences between patients in the normal-weight and underweight groups.

Conclusion: Young, healthy, underweight women require higher effective doses of propofol for deep sedation for successful gastroscope insertion compared with young, healthy, normal-weight women.

Keywords: effective dose, propofol, gastroscope insertion, underweight women, normal-weight women

Introduction

Gastroscopy is a widely used and effective technique to diagnose and treat esophageal and gastroduodenal disorders. However, it is invasive and often causes discomfort, including retching, gagging, choking, throat pain, and fear, which can interrupt the procedure. Sedation can help alleviate patient discomfort and enhance the efficiency of gastroscopy. Among the various methods, propofol-based deep sedation has become increasingly popular in clinical practice, primarily due to its rapid onset, short recovery period, and high levels of patient satisfaction.[1–11] Propofol is considered safe for endoscopy sedation;[12–15] however, it has a narrow therapeutic window, which means that minor differences in propofol dosage can result in sedation failure and/or adverse drug reactions. Inadequate doses of propofol can lead to sedation failure or perioperative awareness, whereas excessive doses may cause hypotension, bradycardia, respiratory

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depression, airway compromise, and delayed recovery.[16] Therefore, precise dosing and prompt management of risks by trained anesthesiologists are crucial.

Propofol is a cornerstone medication for sedation during gastroscopy, but alternatives such as midazolam, ketamine, and dexmedetomidine are also used, often in combination with propofol to reduce its side effects. Propofol is a highly lipophilic sedative that is commonly used for sedation during gastroscopy owing to its quick onset (30–45 s) and short duration of action (4–8 min).[17] The choice of propofol is driven by its superior pharmacokinetic profile, though its use requires careful titration, especially in specific populations. The recommended induction dose of Propofol MCT Fresenius® for healthy adults aged 55 years or younger is 1.5–2.5 mg/kg (20–40 mg/10 s). The sedative effect of propofol is dose dependent, indicating that higher doses are required for deeper levels of sedation. Similarly, the adverse effects of propofol sedation increase with higher doses. Dosage adjustments should be made based on the patient's age, gender, body weight, and physical condition. Clinical trials have shown that women require a higher dose of propofol than men to achieve the same level of sedation.[18,19] The number of young women undergoing painless gastroscopy is increasing annually due to factors such as unhealthy lifestyle habits, fatigue, and stress. In clinical practice, young, underweight women undergoing painless gastroscopy with propofol sedation have been noted to have more body movements, requiring higher propofol doses than other adult patients, which may be attributed to differences in body composition and metabolism.

Currently, there is a lack of studies on the effective doses of propofol sedation for young, underweight women undergoing gastroscopy. We hypothesized that young, healthy, underweight women (body mass index [BMI] < 18.5 kg/m²) would require higher effective doses of propofol for successful gastroscope insertion compared to their normal-weight peers (18.5 ≤ BMI < 25 kg/m²).[20] To address this drawback, we conducted this dose-finding study using the modified Dixon's up-and-down method to determine and compare the effective doses of propofol of these two populations.

Materials and Methods

Study Design

This study was approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University (No. 2022-P2-271-01). The study protocol was registered in the Chinese Clinical Trial Registry (Registration No. ChiCTR2200063625) on September 13, 2022, before the first patient was enrolled. The trial was conducted at Beijing Friendship Hospital from September 2022 to January 2023 and the principles of the Declaration of Helsinki were followed.

Participants

All patients were fully informed before being enrolled in the study, and written informed consent was obtained from all patients. Eligible criteria included elective gastroscopy, underweight (BMI < 18.5 kg/m²) and normal-weight (18.5 ≤ BMI < 25 kg/m²) women aged 18–35 years, the American Society of Anesthesiologists (ASA) physical status classification I–II, and patients who fully understood the contents of the informed consent form and signed it before participating in the study. The exclusion criteria were allergy to propofol; the use of general anesthetics, sedatives, or analgesics within 2 weeks prior to gastroscopy; upper airway disease (eg, airway occupancy or an upper respiratory tract infection within the previous 2 weeks); pregnancy or lactation; the possibility of a difficult airway; abnormal liver and kidney function; refusal to participate in the study; and any other situation considered unsuitable by the researchers for study participation.

Study Protocol

All participants fasted for ≥ 8 hours for fatty/fried foods, ≥ 6 hours for light meals, and ≥ 2 hours for clear liquids before gastroscopy. No premedication was administered before the procedure. Pulse oxygen saturation (SpO_2), continuous electrocardiography, and noninvasive blood pressure of patients were recorded upon entering the endoscopy room. A 22-gauge intravenous cannula was inserted into the patients' right dorsal hand and sodium lactate Ringer's solution was administered. Patients were positioned on their left side with a pillow under their head and their legs slightly bent to align the head, neck, and trunk. They held a face mask with their left hand to cover their mouth and nose and took at least five deep breaths of 100%

oxygen (6 L/min) for pre-oxygenation before sedation was initiated. During the procedure, the face mask was positioned 1 cm away from the patient's nose following propofol sedation.

An anesthesiologist prepared the induction and supplemental doses of propofol (Propofol Medium and Long Chain Fat Emulsion Injection, Fresenius Kabi, Austria) covered with black paper based on patients' weight. After pre-oxygenation, this anesthesiologist administered the induction dose of propofol intravenously over 30 s and the other anesthesiologist was responsible for assessing patients' depth of sedation using the Modified Observer Assessment of Alertness/Sedation (MOAA/S) Scale (Supplementary Table 1),[12,21] 60 s after completion of the infusion. It is generally accepted that an MOAA/S score ≤ 1 implies deep sedation.[10] The second anesthesiologist recorded patients' responses, vital signs, and adverse reactions. This trial was blinded to the subjects, evaluation observers, and endoscopists.

This is a prospective dose-finding study using the modified Dixon's up-and-down method.[22,23] The induction dose of propofol was set at 2.0 mg/kg for the first patient based on pilot data and our prior experience with propofol sedation during gastroscopy.[24] An experienced endoscopist attempted endoscope insertion if the MOAA/S score was ≤ 1 after propofol induction. Patients' responses were categorized as "failure" or "success". "Failure" was chosen if coughing, gag reflexes, or body movements occurred during gastroscope insertion, whereas "success" was chosen if none of these events occurred. Body movements were defined as any physical activity that interfered with endoscopic maneuvers. If a patient's response was recorded as "failure", 0.5 mg/kg of propofol was injected repeatedly until the endoscope could be inserted successfully. If the patient did not achieve the target level of sedation (MOAA/S score > 1) after induction, the response was recorded as "failure", and supplemental 0.5 mg/kg doses of propofol were repeatedly administered until the target sedation level (MOAA/S score ≤ 1) was achieved. An experienced endoscopist then initiated gastroscopy. Sedation depth was evaluated every 90s after commencing endoscopy. If the MOAA/S score was > 1 or if coughing, gag reflexes, or limb movements occurred during the procedure, an additional 0.5 mg/kg dose of propofol was administered until the end of the procedure.

Based on the response of the previous patient to the induction dose of propofol, subsequent adjustments to the propofol dose were made for the next patient.[22] Specifically, the induction dose of propofol was increased by 0.1 mg/kg if the response of the previous patient was recorded as "failure", and it was decreased by 0.1 mg/kg if the response of the previous patient was recorded as "success". This step size of 0.1 mg/kg was determined from our pilot study and previous studies.[22,24,25] A crossover point was identified when the response changed from "failure" to "success". The primary outcomes, 50% and 95% effective dose of propofol (ED_{50} and ED_{95}), defined as the doses required for successful gastroscope insertion in 50% and 95% of patients, respectively, were determined using the modified Dixon's up-and-down method and isotonic regression analysis.

Several procedure-related data, including gastroscopy duration, the total dose of propofol, and the frequency of propofol supplementation, were documented. Vital signs, including mean arterial pressure (MAP), heart rate (HR), SpO_2, and respiratory rate (RR) were closely monitored before propofol administration (baseline, T_0), immediately after propofol administration (T_1), immediately after gastroscope insertion (T_2), 2 min after gastroscope insertion (T_3), and at the end of gastroscopy (T_4). Adverse events, including respiratory depression (SpO_2 < 90%), tachycardia (HR > 100 beats/min), bradycardia (HR < 50 beats/min), hypertension (MAP increased by ≥ 30%), hypotension (MAP < 60 mmHg), and injection pain, were recorded throughout the observation period. Immediate airway support was initiated by experienced anesthesiologists if SpO_2 decreased to < 90% for > 15s. Tachycardia, bradycardia, hypertension, and hypotension were treated using esmolol 20 mg, atropine 0.25 mg, urapidil 10 mg, and ephedrine 6 mg (or methoxamine hydrochloride 1 mg), respectively, based on the judgment of the experienced anesthesiologists.

Participants were transferred to the post-anesthesia care unit upon completion of gastroscopy, where they were closely monitored until a Modified Aldrete Score of ≥ 9 was achieved. Endoscopist satisfaction levels were surveyed (level: excellent/good/general/bad, assigned scores: 4/3/2/1). Patient satisfaction levels (level: excellent/good/tolerable/intolerable, assigned scores: 4/3/2/1) as well as intraoperative awareness, postoperative nausea and vomiting (PONV), and any adverse events were subsequently investigated 24 h after the endoscopy based on a telephonic follow-up.

Sample Size and Statistical Analysis

The modified Dixon's up-and-down method commonly requires 6 or more crossovers, and an anesthesia trial usually needs to include 20–40 patients.[22,23,26] Thirty patients were enrolled in each group in our trial to ensure reliable results.

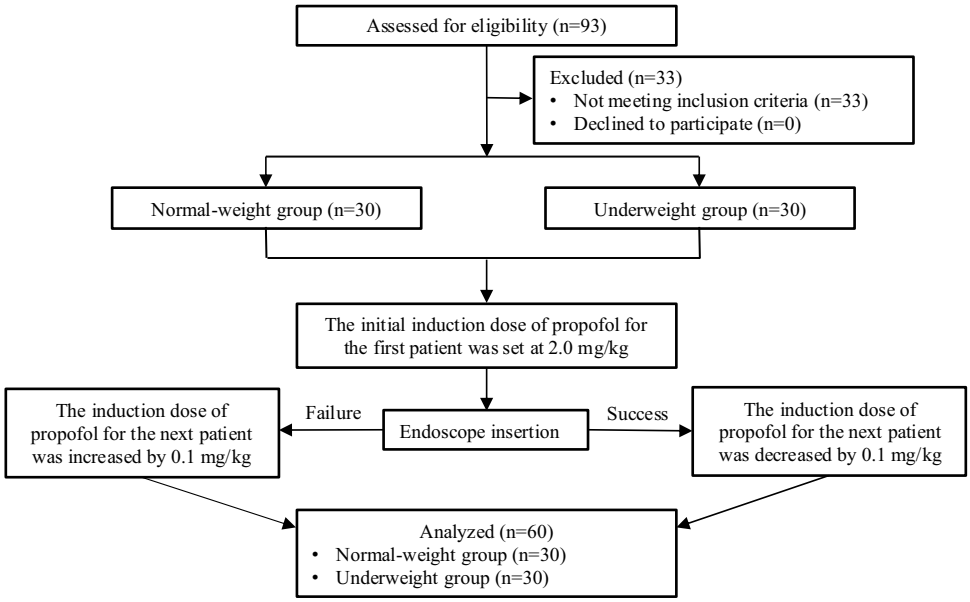

Figure 1 Flowchart of the modified Dixon's up-and-down method.

Data were analyzed using SPSS for Mac 26.0 (SPSS Inc., Chicago, IL, USA). Normality of continuous data distribution was determined using the Shapiro–Wilk test. Continuous data are expressed as mean ± standard deviation for normal distribution and as median (interquartile range) for nonnormal distributions. Independent Student's *t*-test or the Mann–Whitney *U*-test was used to compare groups depending on whether or not data were normally distributed. Changes in MAP, HR, RR, and SpO_2 over time were analyzed using one-way repeated-measures analysis of variance followed by Bonferroni's post hoc tests. Categorical data are expressed as numbers and percentages and were analyzed using Chi-squared or Fisher's exact test. $P < 0.05$ was considered statistically significant.

Based on the modified Dixon's up-and-down method, the mean of all midpoints of crossovers from "failure" to "success" were utilized to calculate the ED_{50} of propofol.[22] Next, using the "R" package (R version 4.1.3 2022–03-10), the observed responses were adjusted using the pooled-adjacent-violators algorithm (PAVA), and the ED_{50} and ED_{95} of propofol were subsequently calculated for successful gastroscope insertion based on isotonic regression analysis and the 83% confidence intervals (CIs) of ED_{50} and ED_{95} by parametric bootstrapping approaches.[23,27–29]

Results

A total of 93 patients participated in this study between September 2022 and January 2023. After applying the exclusion criteria, 60 patients were included in this study, with 30 patients in each group (Figure 1). All included subjects completed the study and achieved a sedation depth corresponding to an MOAA/S score of ≤ 1 after initial propofol induction. Patient characteristics are shown in Table 1. Both weight and BMI differed significantly between the normal-weight and underweight groups ($P < 0.001$).

Table 1 Patient Characteristics (n=30)

Parameters	Normal-Weight Group (n=30)	Underweight Group (n=30)	*P*-values
Age (years)	30.1 ± 3.2	29.0 ± 3.7	0.227
Weight (kg)	57.7 ± 5.8	47.9 ± 4.8	< 0.001*
Height (cm)	163.7 ± 4.5	165.5 ± 5.2	0.160
BMI (kg/m2)	21.6 ± 1.8	17.8 ± 0.8	< 0.001*

(*Continued*)

Table 1 (Continued).

Parameters	Normal-Weight Group (n=30)	Underweight Group (n=30)	*P*-values
ASA classifications (I/II)	30/0 (100/0)	30/0 (100/0)	-
Mallampati grades (I/II)	18/12 (60.0/40.0)	18/12 (60.0/40.0)	-
Baseline MAP (mmHg)	89.0 ± 9.7	91.6 ± 9.4	0.295
Baseline HR (beats/min)	78.7 ± 11.3	80.1 ± 11.1	0.622
Baseline RR (beats/min)	18.3 ± 2.2	18.9 ± 2.6	0.289
Baseline SpO_2 (%)	99.3 ± 1.0	99.5 ± 0.8	0.470

Notes: Results are expressed as mean ± standard deviation or number (%). *$P < 0.05$ was considered statistically significant.
Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; HR, heart rate; MAP, mean arterial pressure; RR, respiratory rate; SpO_2, pulse oxygen saturation.

Table 2 ED_{50} and ED_{95} of Propofol for Successful Gastroscope Insertion

	Normal-Weight Group (n=30)	Underweight Group (n=30)	*P*-values
ED_{50}^1 (mg/kg)	2.03 ± 0.13	2.72 ± 0.23	< 0.001*
ED_{50}^2 (mg/kg)	2.00 (83% CI, 1.900–2.100)	2.80 (83% CI, 2.700–2.900)	-
ED_{95}^2 (mg/kg)	2.30 (83% CI, 2.300–2.400)	3.00 (83% CI, 3.000–3.100)	-

Notes: Results are expressed as mean ± standard deviation or mean (83% confidence interval). *$P < 0.05$ was considered statistically significant. [1]by the modified Dixon's up-and-down method; [2]by isotonic regression analysis.
Abbreviation: CI, confidence interval.

Using the modified Dixon's up-and-down method, the ED_{50} of propofol for successful gastroscope insertion was higher in the underweight group than that in the normal-weight group ($P < 0.001$) (Table 2). The extrapolated ED_{50} and ED_{95} for successful gastroscope insertion obtained using isotonic regression analysis were shown in Table 2. The 83% CIs of the extrapolated ED_{50} and ED_{95} in the underweight group did not overlap with those in the normal-weight group, suggesting significant differences in these values between the groups.[29] Figure 2 illustrates patients' responses to different induction doses of propofol and Table 3 shows the observed and PAVA-adjusted response rates. Figure 3 depicts the dose-response curve of propofol for successful gastroscope insertion plotted based on isotonic regression analysis. The curve shifted to the right in patients who were underweight compared with that in patients who were of normal weight.

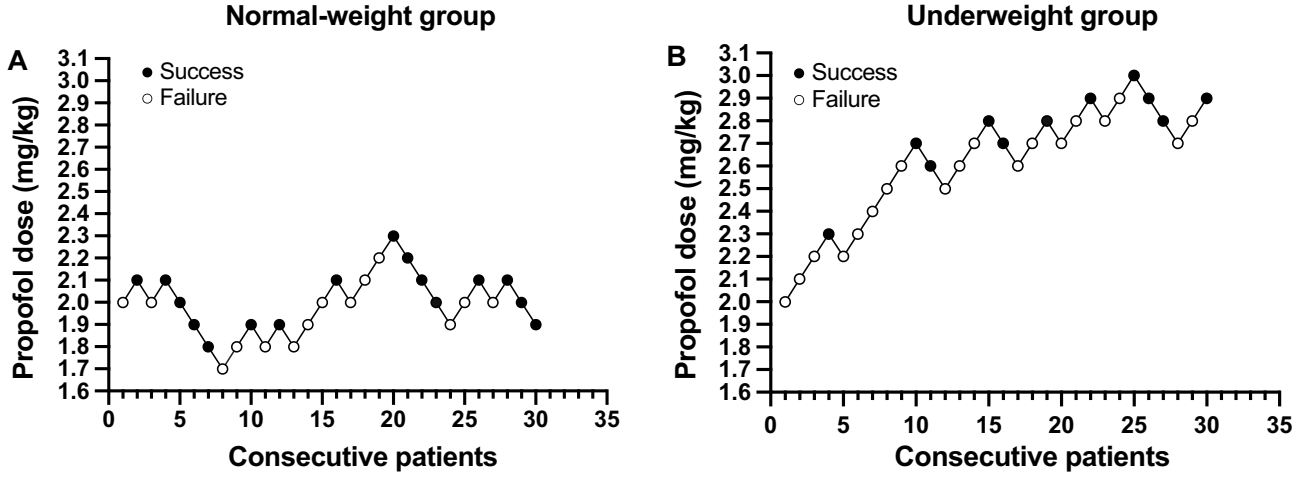

Figure 2 Responses of normal-weight (**A**) and underweight (**B**) consecutive patients to gastroscope insertion using the modified Dixon's up-and-down method.
Notes: Solid circles indicate successful insertion doses, whereas open circles indicate failed insertion doses.

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Table 3 Observed and Pool-Adjacent-Violators Algorithm (PAVA)-Adjusted Response Rates

Assigned Dose (mg/kg)	Number of Successes	Number Tested	Observed Response Rate	PAVA-Adjusted Response Rate
Normal-weight group				
1.7	0	1	0.000	0.000
1.8	1	4	0.250	0.250
1.9	4	6	0.667	0.467
2.0	3	9	0.333	0.467
2.1	6	7	0.857	0.778
2.2	1	2	0.500	0.778
2.3	1	1	1.000	1.000
Underweight group				
2.0	0	1	0.000	0.000
2.1	0	1	0.000	0.000
2.2	0	2	0.000	0.000
2.3	1	2	0.500	0.200
2.4	0	1	0.000	0.200
2.5	0	2	0.000	0.200
2.6	1	4	0.250	0.250
2.7	2	6	0.333	0.333
2.8	3	6	0.500	0.500
2.9	3	4	0.750	0.750
3.0	1	1	1.000	1.000

Changes in MAP, HR, SpO_2, and RR are illustrated in Figure 4. Patients in the underweight group had significantly higher SpO_2 and RR at T_3 and T_1, respectively, than those in the normal-weight group ($P < 0.05$). No significant differences were found in other data between these groups.

No patient in either group experienced hypotension, hypertension, or bradycardia during the procedure. Tachycardia was observed in 4 (13.3%) patients in the normal-weight group and 9 (30.0%) patients in the underweight group. However, the difference in the incidence of tachycardia among patients in the 2 groups was not statistically significant ($P = 0.117$). All 4 patients in the normal-weight group responded with "failure" to endoscope insertion. In the underweight group, 7 of the 9 patients responded with "failure", and 2 patients responded with "success". Respiratory

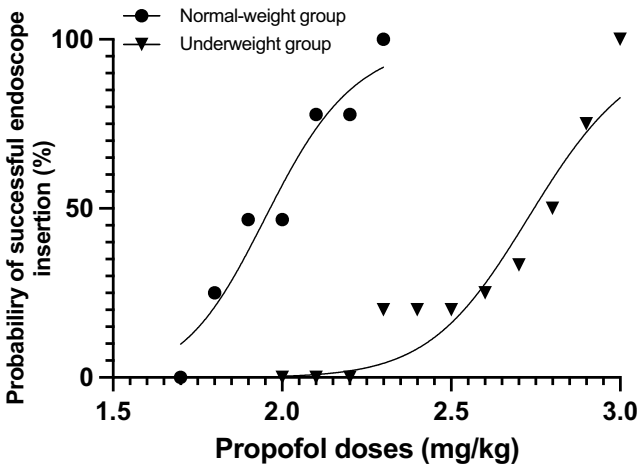

Figure 3 Dose-response curve of propofol for successful gastroscope insertion plotted based on isotonic regression analysis.

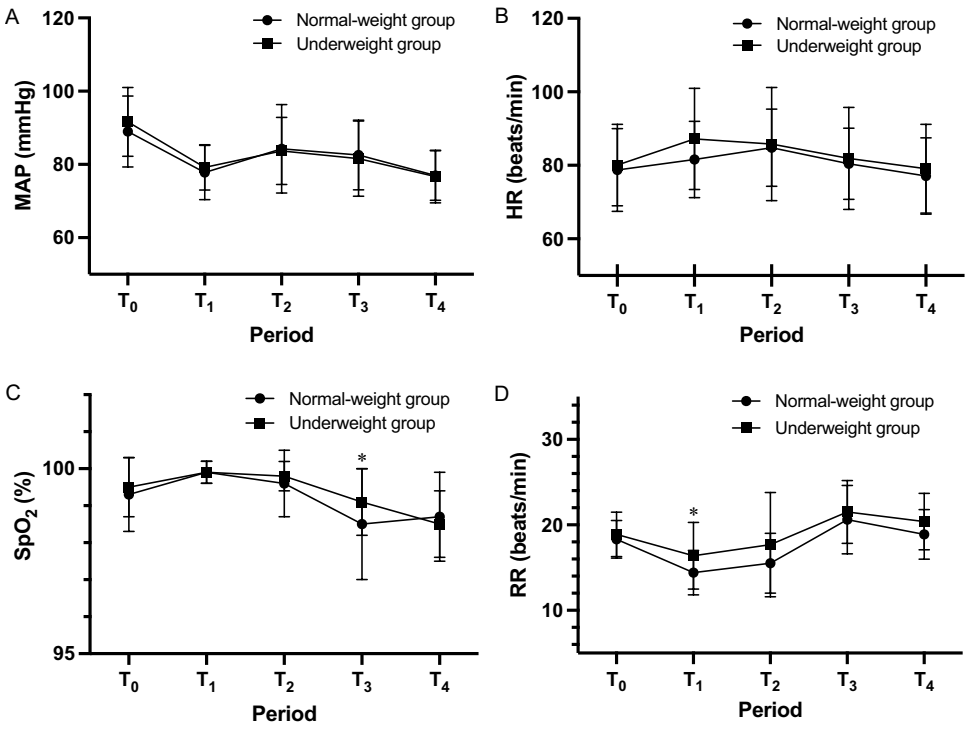

Figure 4 Changes in MAP (**A**), HR (**B**), SpO_2 (**C**), and RR (**D**) during the study period.
Notes: Data are expressed as mean ± standard deviation. *$P < 0.05$ was considered statistically significant versus the baseline.
Abbreviations: HR, heart rate; MAP, mean arterial pressure; RR, respiratory rate; SpO_2, pulse oxygen saturation; T_0, before propofol administration (baseline); T_1, immediately after propofol administration; T_2, immediately after gastroscope insertion; T_3, 2 min after gastroscope insertion; T_4, at the end of gastroscopy.

depression was observed in 1 patient from each group. Nine patients in the normal-weight group and 10 in the underweight group experienced injection pain ($P = 0.236$). No cases of intraoperative awareness and PONV were reported, and none of the adverse events required treatment.

Procedure-related characteristics are detailed in Supplementary Table 2. Patients in the underweight group required a higher frequency of propofol supplementation, with a median (interquartile range) value of 2.7 (2.5–2.8) times compared with 2.0 (1.0–4.0) times that in the normal-weight group ($P < 0.001$). No significant differences in gastroscopy duration, total dose of propofol, endoscopist satisfaction, and patient satisfaction were noted.

Discussion

A considerable number of patients in China undergo gastrointestinal endoscopy every year. A survey in 2016 reported that approximately 14 million patients underwent this procedure and showed this number to be increasing annually. Propofol has been identified as the most frequently used sedative during gastrointestinal endoscopy;[1] however, there are no studies on the effective doses of propofol for successful gastroscope insertion in young, underweight women.

Ideal sedation for gastroscopy should provide rapid and adequate anesthesia, hemodynamic stability, quick recovery, and minimal adverse events. Although propofol use is associated with excellent sedation and recovery compared with other sedatives, its clinical efficacy and pharmacokinetic characteristics are significantly influenced by variables such as age, weight, height, and gender.[11,30,31] Total body weight or some other descriptor that incorporates fat mass may be the best descriptor for size for highly lipophilic drugs like propofol.[32] Therefore, we used total body weight to calculate the propofol dose in our study. Deep sedation (MOAA/S score ≤ 1) is preferred over moderate sedation during gastroscopy as it is more comfortable for patients and effective.[10] With an improvement in economic conditions, more patients are choosing deep sedation for gastroscopy. Deep sedation with propofol is currently the most popular method in China for painless gastroscopy;[1] however, controlling the transition between deep sedation and general anesthesia with propofol

can be challenging. This transition can be rapid and unpredictable, leading to severe respiratory and cardiovascular depression that warrants anesthesiologist intervention.[15]

In this trial, underweight patients required higher effective doses of propofol than normal-weight patients for successful gastroscope insertion. The ED_{50} of propofol in the underweight group calculated using the modified Dixon's up-and-down method was significantly higher than that in the normal-weight group ($P < 0.001$). The differences between the 2 groups in the ED_{50} and ED_{95} of propofol extrapolated by isotonic regression were statistically significant based on the overlapping 83% CI method. The clinical implication of ED_{95} was that a propofol dose of 2.3 mg/kg based on the total body weight should be administered for successful gastroscope insertion in 95% of young, normal-weight women. In contrast, young, underweight women required a 30% higher dose, ie, 3.0 mg/kg of propofol. The dose-response curve for underweight patients shifted notably to the right, indicating their requirement for a higher dose of propofol per kg body weight versus normal-weight patients to achieve the same probability of successful endoscope insertion.

Our findings match those reported previously. Park et al found that the use of the modified Marsh model can lead to inadvertent underdosing of propofol in underweight patients and that BMI is a significant covariate of the rapid peripheral volume of distribution (V_d) of propofol.[33,34] Wu et al suggested BMI as one of the critical factors affecting the pharmacodynamic index of the target-controlled infusion of propofol, with the induction time decreasing with an increase in BMI.[35] These trials demonstrate that underweight patients require higher doses of propofol to achieve the same target effect–site concentration and sedation level. The term "underweight" is generally used for adults whose weight is relatively low for their height (BMI < 18.5 kg/m²) rather than using it for individuals who have a low weight.[20] As the relationship between drug clearance and total body weight is nonlinear,[36] propofol dosing based on a scale that is linearly related to the total body weight leads to underdosing of patients who are underweight.[33] Patients who are underweight have a significant reduction in both fat mass and fat-free mass compared with normal-weight patients.[37] Propofol is a highly lipophilic substance that exhibits significant decreases in apparent V_d in individuals who are underweight. Patients with lower BMI had lesser fat mass, resulting in a slower distribution of propofol and a slower onset of sedation. These factors can likely explain why patients who are underweight require a higher dose of propofol per kg of body weight versus patients with normal weight to achieve the same probability of successful endoscope insertion.

Direct comparisons of the effective doses of propofol from our study with those reported previously are challenging due to differences among subjects, infusion rates, endpoints, and statistical methods. The modified Dixon's up-and-down method is a simple approach to determine ED_{50}s, and it allows for the complete utilization of patient data to obtain relatively accurate results with fewer subjects.[23] Liu et al used this method and calculated the ED_{50} of propofol mono-sedation to be 1.89 ± 0.12 mg/kg for successful gastroscope insertion, which was 0.14 and 0.83 mg/kg lower than the values determined in our study for normal-weight and underweight patients, respectively. Using probit regression analysis, the extrapolated ED_{50} was determined to be 1.90 (95% CI, 1.78–2.10) mg/kg and the ED_{95} to be 2.15 (95% CI, 2.02–3.56) mg/kg.[24] These values for patients in the underweight group were significantly higher in our study. However, there are some differences between these 2 studies. In the study by Liu et al, the subjects were healthy, nonobese Chinese adults of both sexes aged 18 to 65 years. Moreover, propofol was administered for 20 s, and probit regression analysis was used to extrapolate the ED_{50} and ED_{95}. Previous studies indicate that slower infusion rates of propofol require smaller doses to achieve the same depth of sedation.[38] The parameter estimates of the probit regression slope may be biased due to the nonindependence of the assigned dose values.[23] Isotonic regression analysis was used in our study to extrapolate ED_{50} and ED_{95}. It is widely recognized that ED_{50} and ED_{95} obtained using isotonic regression analysis can be less biased and provide more accurate targeted doses.[23,39] As the effect of a drug does not always increase proportionally with an increase in its dose, the first step should be adjusting the observed response probability using PAVA. ED_{50} and ED_{95} can be subsequently determined using isotonic regression analysis, and CIs can be calculated using parametric bootstrapping approaches.[28,40]

Hao et al used the modified Dixon's up-and-down method and demonstrated that the ED_{50} of propofol was 1.44 ± 0.11 mg/kg for successful gastroscope insertion in males, which is significantly lower than that determined in our study.[25] Isotonic regression analysis revealed the ED_{50} of propofol to be 1.40 (95% CI, 1.40–1.63; 83% CI, 1.31–1.53) mg/kg and the ED_{95} to be 1.60 (95% CI, 1.56–1.65) mg/kg, which were also significantly lower than those determined in our study. Differences in sex, age, and sedation scales may account for these variations. Hao

et al recruited males aged 35 to 65 years, whereas females aged 18 to 35 years were recruited in our study. Females require higher propofol doses to achieve the same sedative effect as males, possibly due to the larger peripheral V_d and higher metabolic clearance.[31,41] Our patients were younger and had higher metabolic rates, thereby requiring higher doses of propofol for deep sedation. Furthermore, the study by Hao et al used Ramsay's score of 5, which differs from the MOAA/S score of 1 used in our study. Different sedation scales undoubtedly affect propofol doses. Differences between the results of these 2 studies further suggest that patients' age, height, gender, and physical condition should be considered in addition to patients' weight when using propofol sedation. Therefore, optimizing propofol doses for different populations in various clinical situations is crucial.

The incidence of tachycardia in our study was high, and it occurred in 4 patients in the normal-weight group and 9 patients in the underweight group with incidence rates of 13.3% and 30.0%, respectively ($P = 0.117$). All 4 cases of tachycardia in the normal-weight group and 7 of the 9 cases in the underweight group were observed in patients with higher baseline HR and responded with "failure". It is worth noting that other studies have not reported instances of tachycardia.[24,25,42] This difference may be due to varying definitions of tachycardia, differences in the types of patients included in the study, and variations in drug doses used in these studies. It is important to highlight that the drug doses used in the modified Dixon's up-and-down method are not fixed and are constantly adjusted between failing and successful doses. One patient (3.3%) in each group experienced respiratory depression. Hao et al reported a similar result, with 1 of the 29 patients (3.4%) experiencing oxygen desaturation (SpO_2 = 75% to 89% for < 60s).[25] However, hypoxemia (SpO_2 < 90%) was not observed in the study by Liu et al, likely due to better pre-oxygenation of patients in their study.[24] Ye et al reported a higher incidence of hypoxia (SpO_2 < 90% for > 1 min) at 16.9%,[42] which might be attributed to the inclusion of elderly patients aged > 65 years and the use of a combination of 0.2 μg/kg remifentanil in their study. The incidence of injection pain with propofol was high in our study. Nine patients (30.0%) in the normal-weight group and 10 (33.3%) in the underweight group experienced injection pain ($P = 0.236$). In contrast, Liu et al and Ye et al have reported corresponding values of 11.5% and 12.3%, respectively.[24,42] Although a minor problem, injection pain is a factor that can impact patients' mood and overall satisfaction levels. Injection pain can be reduced by a rapid propofol injection administered through a larger vein.[43] In the current study, propofol was administered at slower rates. The participants in this study were young women, and veins in this younger population are typically smaller. Patients in the underweight group had a higher frequency of propofol supplementation; however, the total dose of propofol was not significantly different.

Our study has some limitations that warrant attention. First, objective measures of sedation level, such as bispectral index (BIS) monitoring, were not used in this study, and we relied solely on the MOAA/S scale, which may have led to subjective bias when assessing sedation depth. However, multiple studies have reported a significant association between BIS and the MOAA/S scale during sedation with propofol.[44–48] Moreover, the state of consciousness of subjects changes rapidly because of the rapidly changing pharmacokinetics of propofol. BIS values on the monitor depict averages over a period of time and lag behind the pharmacodynamic effect, thereby limiting their reliability in rapidly changing situations that occur during propofol sedation. Accordingly, the easy-to-use and cost-effective MOAA/S scale was chosen as an indicator of sedation level as opposed to BIS monitoring, which is an objective indicator. Second, the effect of the menstrual cycle on propofol doses was not accounted for in our study. Variations in progesterone levels among menstrual phases can result in differences in anesthesia. Sex hormones have anesthetic and sedative effects;[49–51] for example, increased progesterone synthesis decreases the requirement for anesthesia through the luteal phase of the menstrual cycle.[52] Fu et al have demonstrated that the EC_{50}s of propofol for the loss of consciousness and the emergence time were significantly influenced by different phases of the menstrual cycle.[53] Thus, further research is needed to determine the impact of the menstrual cycle on the sedative effect of propofol. Third, this study only covered the period from induction to the end of endoscopy. Further evaluation of recovery-related parameters is therefore necessary. Lastly, this study focused on determining the effective doses of propofol for a specific population and a specific condition. Therefore, the results of this trial cannot be generalized to patients of different ages, genders, races, and physical states. Furthermore, the estimated ED_{50} and ED_{95} should be interpreted with caution due to possible precision-related limitations. Future studies using more precise methods to determine the effective doses of drugs is

a viable approach. Improvements in methodology and statistics as well as further research are therefore warranted to address and overcome these existing issues.

Conclusion

The ED_{50} of propofol was 2.72 ± 0.23 mg/kg in the young, healthy, underweight women and 2.03 ± 0.13 mg/kg in the normal-weight peers. The findings of our study demonstrated that young, healthy, underweight women required higher effective doses of propofol for successful gastroscope insertion compared with young, healthy, normal-weight women.

Data Sharing Statement

The data generated during the study are available from the corresponding author, Yun Wang, upon reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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