Drug Design, Development and Therapy

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CLINICAL TRIAL REPORT

Determination of ED50 and ED95 for Ciprofol in Morbidly Obese Patients During Induction of General Anesthesia: A Single-Center, Up-and-Down Study Based on Lean Body Weight

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Background: Obesity alters the pharmacokinetics and pharmacodynamics of hypnotic agents; however, dose-finding data for ciprofol during the induction of general anesthesia in morbidly obese adults remain limited. We estimated the lean body weight (LBW)-scaled 50% effective dose (ED50) and 95% effective dose (ED95) of ciprofol for loss of consciousness by using an up-and-down sequential design.

Methods: This prospective single-center trial enrolled adults aged 18–65 years with morbid obesity who underwent elective surgery. Ciprofol was administered as a slow intravenous bolus at an initial dose of 0.76 mg kg^{-1} (LBW), followed by an up-and-down algorithm with an adjacent dose ratio of 1.1. Primary outcome: LBW-scaled ED50 and ED95 of ciprofol for loss of consciousness. ED50 and ED95 values were estimated using probit analysis. Hemodynamics and adverse events were collected as pre-specified secondary endpoints.

Results: Thirty-six patients were included in the study. The sequence yielded either successful or failed crossovers. The LBW-scaled ED50 and ED95 of ciprofol for loss of consciousness were 0.492 mg kg^{-1} (95% CI 0.453–0.531) and 0.634 mg kg^{-1} (95% CI 0.524–0.744), respectively. The mean arterial pressure and heart rate decreased after induction, reaching a nadir approximately 5 min after tracheal intubation, and generally remained ≥70% of baseline for most patients. In exploratory, post hoc comparisons of response-defined groups, the incidence of hypotension (37% vs 41%, p=0.79), bradycardia (5% vs 6%, p=0.94), and tachycardia (26% vs 35%, p=0.27) was similar. No other adverse events were reported.

Conclusion: The LBW-scaled ED50 and ED95 of ciprofol for loss of consciousness during the induction of general anesthesia in morbidly obese adults were 0.492 and 0.634 mg kg^{-1}, respectively. Hemodynamics were generally well controlled and adverse events were infrequent.

Keywords: ciprofol, morbidly obese, anesthesia induction, 50% effective dose, 95% effective dose

Introduction

Obesity has become a significant global public health concern and its prevalence continues to increase. Approximately 16% of the adult population worldwide is estimated to be affected by obesity.[1] Morbid Obesity (MO)—also referred to as class III obesity—is typically defined as a body mass index (BMI) ≥ 40 kg/m^2, or BMI ≥ 35 kg/m^2 in the presence of at least one obesity-related comorbidity (eg, type 2 diabetes, cardiovascular disease, or obstructive sleep apnea),[2] and is associated with severe health risks.[3] Compared with normal-weight individuals, obese patients exhibit unique pathophysiological characteristics—such as increased cardiovascular and pulmonary burdens, augmented adipose tissue, and abnormal hemodynamics—that substantially affect anesthetic requirements.[4] The increased proportion of adipose tissue

https://doi.org/10.2147/DDDT.S568472
Received: 18 September 2025
Accepted: 19 January 2026
Published: 24 January 2026

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also changes metabolic status and distribution volumes, thereby influencing pharmacokinetics (PK) and pharmacodynamics (PD).[5] These characteristics make obese patients more susceptible to either drug overdose or underdose during anesthesia and increase the risk of complications such as accidental awareness, hypotension, hypoxemia, and pulmonary complications.[3,6] Therefore, it is particularly important to develop precise and individualized anesthetic dosing regimens for obese populations.

Propofol is commonly used to induce general anesthesia, but its marked circulatory inhibitory effects can cause significant hemodynamic fluctuations.[7–10] Multiple weight scalars have been proposed for dosing in obesity, including total body weight (TBW), ideal body weight (IBW), lean body weight (LBW).[2,11,12] In general, TBW-based bolus dosing may overestimate central compartment size and increase hypotension risk, whereas IBW may underdose and delay loss of consciousness. LBW correlates better with metabolically active tissue and clearance and is frequently recommended for induction boluses to balance efficacy and safety.

Ciprofol is a 2,6-disubstituted phenol and a structural analog of propofol that acts as a positive allosteric modulator of the GABA_A receptor.[13] In the general population, ciprofol provides effective hypnosis with rapid onset of action, favorable clearance characteristics, and a lower incidence of injection pain and may cause milder circulatory suppression compared with propofol.[14] However, obese-specific dosing evidence remains limited. Small studies in obese patients—predominantly in procedural sedation or short general anesthesia—have largely used TBW-based dosing (for example, fixed mg/kg boluses) and suggested hemodynamic advantages relative to propofol, but they have not established the optimal weight scalar for MO, nor are their findings directly generalizable to induction for surgery.[15,16] Given the mechanistic parallels between propofol and ciprofol and the consistent performance of LBW for propofol induction in obesity, LBW is a physiologically defensible starting point for ciprofol dose calculation in MO.

Given the unique pharmacokinetic and pharmacodynamic challenges in MO patients and the potential advantages of ciprofol over propofol, this study aimed to use a sequential up-and-down method to determine the ED50 and ED95 of ciprofol in MO patients undergoing general anesthesia-induced loss of consciousness(LOC). Our specific objective was to estimate effective doses based on LBW,[17,18] which is considered a more reliable scalar than the total or ideal body weight in MO owing to its correlation with metabolically active tissue mass and drug clearance.[19]

Materials and Methods

Study Design

This prospective, single-center study was approved by the Ethics Committee of Lishui People's Hospital (approval number: 2024-023-01) and registered with the Chinese Clinical Trial Registry (ChiCTR2400094305). Written informed consent was obtained from all participants. The study adhered to the Declaration of Helsinki and relevant national regulations.

Participants

The inclusion criteria were as follows: (1) age 18–65 years, (2) American Society of Anesthesiologists (ASA) grade II–III, (3) BMI≥ 35 kg/m^2 with other obesity-related comorbidities (4) scheduled for elective surgery under general anesthesia, and (5) ability to provide informed consent.

The exclusion criteria were as follows: (1) pre-existing neurological or psychiatric disease affecting assessment; (2) allergy to the drugs used in this study; (3) long-term preoperative use of benzodiazepines and opioids; (4) severe arrhythmia, such as second- or third-degree atrioventricular block or significant bradycardia (HR<50 beats/min); and (5) participation in another clinical trial within 30 days.

Weight Scalars and Monitoring

Height and TBW were measured on the day of surgery. LBW was calculated using the Janmahasatian formula:[20]

Male: LBW = 9270 × TBW / (6680 + 216 × BMI)

Female: LBW = 9270 × TBW / (8780 + 244 × BMI)

Intervention

All patients fasted for 8 h and abstained from fluid for 2 h preoperatively. All patients underwent standardized surgical and anesthetic care without preoperative medication. Upon arrival in the operating room, intravenous access was established for the infusion of sodium chloride, and oxygen was administered via a facemask at 5 L/min. Continuous monitoring was maintained for pulse oximetry (SpO_2), electrocardiography (ECG), heart rate (HR), noninvasive blood pressure(NIBP), and bispectral index (BIS). HR and NIBP were measured three times consecutively after the patient entered the operating theatre for a 10-minute rest and averaged as baseline values. The BIS was chosen as the processed EEG metric because of its wide clinical adoption[21] and prior evidence that BIS values track clinical sedation with ciprofol and are comparable to propofol at equivalent hypnotic depths.[22,23] Anesthesia was induced with slow intravenous injection of ciprofol. The initial dose of ciprofol was set at 0.76 mg kg^{-1} LBW for the first patient,[24] subsequent doses were adjusted according to the success or failure of induction using an up-and-down approach. From the start of the ciprofol bolus, no other sedatives, opioids, or anesthetics were administered until the prespecified 90-second assessment. Modified Observer's Assessment of Alertness/Sedation scale (MOAA/S) and BIS were recorded every 30 seconds. Successful induction was defined as MOAA/S ≤ 1 and BIS < 60 at the fixed 90-second time point without any rescue medication; otherwise, induction was classified as failed.[23,25,26] According to the adjacent dose ratio (1:1.1), the ciprofol dose was increased by 10% for the subsequent patient if the prior patient experienced "failed sedation"; otherwise, it was decreased by 10%.[25] If MOAA/S remained >1 at the 90-second assessment (induction failure), additional ciprofol (0.1–0.2 mg.kg^{-1}) was administered as rescue. After successful induction, sufentanil 0.3–0.5ug.kg^{-1} and cisatracurium 0.2 mg.kg^{-1} were administered intravenously. Following muscle relaxation, tracheal intubation was using a video laryngoscope and a single-use endotracheal tube of size 7.0–7.5. Mechanical ventilation was then initiated. Immediately afterward, sevoflurane and propofol were used to maintain the depth of anesthesia throughout the surgery, with intermittent boluses of sufentanil and cisatracurium to maintain analgesia and muscle relaxation. After surgery, the endotracheal tube was removed and the patient was transferred to the Post-Anesthesia Care Unit(PACU), where their HR, SpO_2, NIBP, and MOAA/S were monitored. The modified Aldrete score was used to assess recovery. Patients were only allowed to leave the recovery room if they achieved an Aldrete score ≥ 9.

Dose Allocation

We used Dixon's up-and-down sequential allocation to guide dosing and determine the stopping rule. The initial LBW-scaled dose was 0.76 mg/kg; the dose step factor was 1.1. After a success, the next dose decreased one step; after a failure, it increased one step. Enrollment stopped after eight crossovers.[27]

Study Outcomes

The primary endpoint of this study was the LBW-scaled ED50 of ciprofol for LOC. The study's stopping rule was calibrated to ensure a predetermined level of precision for the ED50 estimate, defined by the width of its 95% CI. Secondary outcomes: ED95 was pre-specified only as a exploratory endpoint derived from the fitted dose–response mo Hemodynamic responses: HR and MAP measured at pre-specified time points: baseline (T1), 1 min after induction (T2), 3 min after induction (T3), immediately after tracheal intubation (T4), 5 min after tracheal intubation (T5), immediately after extubation (T6), 5 min after extubation (T7), and at PACU discharge (T8); adverse events, including hypotension (MAP $\leq$ 70% baseline or MAP < 65 mmHg), hypertension ($\geq$130% baseline), bradycardia (HR ≤ 45 beats/min), tachycardia (HR $\geq$ 120% baseline), hypoxemia ($SpO_2 < 90\%$), injection pain, intraoperative awareness, and postoperative nausea and vomiting (PONV). All outcomes were assessed throughout the observation period after induction (T2–T8). Hemodynamic management followed a standardized target-based protocol: the attending anesthesiologist adjusted anesthetic dosing and vasoactive medications to maintain MAP within ±30% of baseline and HR between 50 and 100 beats/min. The timing and agents/doses of all interventions relative to each assessment time point were recorded.

Demographic and baseline characteristics were collected for descriptive purposes and are reported separately.

Sample Size and Statistical Analysis

The sample size and stopping rule were based on the up-and-down design (trial ended after eight crossovers). ED50 was estimated using probit regression on LBW-scaled dose and binary outcome (success/failure). ED95 was obtained as the 95th percentile of the same fitted curve and is presented as an exploratory, model-based estimate with wider uncertainty. The 95% CI for ED50 and ED95 were calculated using the Wald (delta) method, based on the asymptotic variance–covariance matrix of the GLM coefficients.To assess the robustness of the primary ED50 estimate,the ED50 was also calculated using the Dixon-Mood method, with its 95% CI generated via a nonparametric bootstrap procedure (B=2000 replicates).

Continuous data were expressed as mean ± standard deviation, while categorical data were expressed as number (percentage) or median (Q1,Q3), as appropriate. Independent sample *t*-tests were used to compare continuous variables with a normal distribution between the groups, whereas the Mann–Whitney *U*-test was used for variables with a non-normal distribution. The chi-square test or Fisher's exact test was used to compare categorical variables between the groups. The normality of the distribution was analyzed using the Shapiro–Wilk test. Two-sided $P < 0.05$ was considered statistically significant. Because the up-and-down design yields response-defined strata (successful vs failed induction) rather than randomized groups, all comparisons between these groups (hemodynamics, adverse events, and baseline features) were conducted as exploratory/descriptive post hoc analyses. Data were analyzed using the R software (version 4.3.1; R Foundation, Vienna, Austria).

Results

A flowchart of the study is presented in Figure 1. We assessed the eligibility of 39 patients. Three patients were excluded: two cancelled surgeries and one patient with severe heart failure. Ultimately, 36 patients were enrolled and completed the experiment, with with 19 successful inductions and 17 failed inductions. The demographic characteristics of the patients are presented in Table 1. As expected with response-defined stratification, patients in the successful induction group were older than those in the failed induction group (40.4 ± 14.9 vs 29.8 ± 11.0 years; $p = 0.02$).

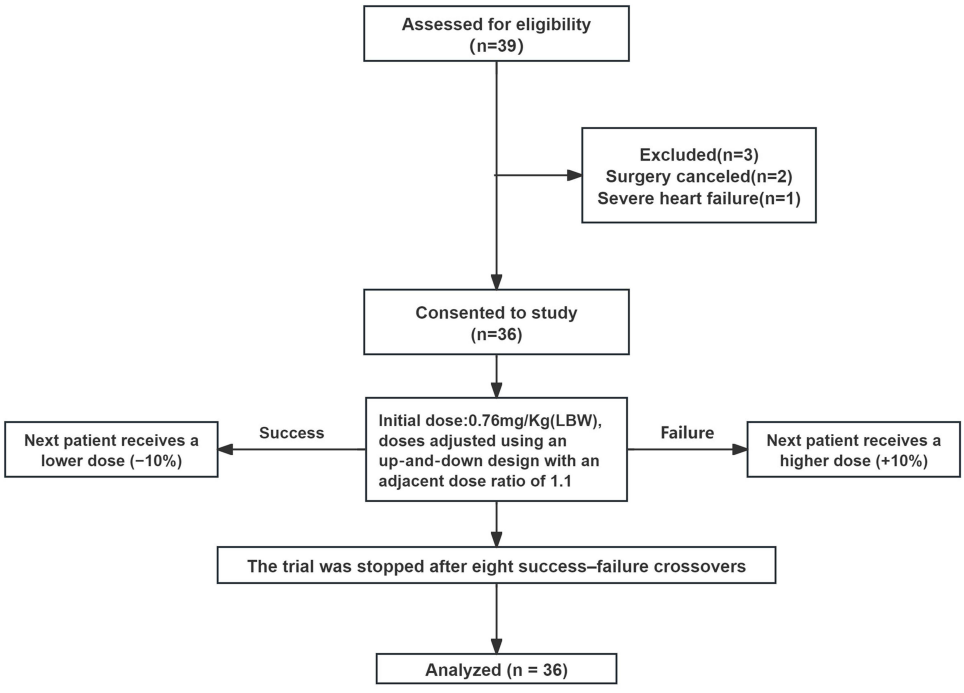

Figure 1 Participant flow and up-and-down dose allocation for ciprofol induction. Successful induction was defined as MOAA/S ≤ 1 and BIS < 60 at the fixed 90-s assessment without any rescue medication or additional ciprofol. Failed induction was defined as any other outcome, including use of additional ciprofol/rescue medication before 90s or not meeting both criteria.

Table 1 Characteristics of Patients

	Successful Induction (n=19)	Failed Induction (n=17)
Gender		
Male, n (%)	12(63)	8(47)
Female, n (%)	7(37)	9(53)
Age(years)	40.4±14.9	29.8±11.0
Weight(Kg)	103.8±10.9	106.7±13.7
BMI(Kg/m^2)	36.6±1.8	39.4±5.4
LBW(Kg)	59.6±8.5	62.0±10.0
ASA		
II, n (%)	13(68)	9(53)
III, n (%)	6(32)	8(47)
Comorbidities		
Hypertension, n (%)	6(32)	4(24)
Diabetes, n (%)	1(5)	3(18)
OSAS, n (%)	6(32)	6(35)
Other comorbidities, n (%)	19(100)	17(100)

Notes: Data are shown as the mean ± standard deviation or number (percentage). Other Comorbidities include dyslipidemia caused by obesity, joint disease, and heart disease. Groups are defined post hoc by induction response; values are descriptive.
Abbreviations: BMI, body mass index; LBW, lean body weight; ASA, American Society of Anesthesiologists; OSAS, obstructive sleep apnea syndrome.

Primary Outcome

Figure 2 depicts the patient-by-patient dose allocation according to Dixon's up-and-down design. The trial reached the pre-specified stopping rule after eight success–failure crossovers. The probit analysis yielded an estimate for the primary endpoint, with an ED50 of 0.492 mg/kg (95% CI: 0.453–0.531) (Figure 3). The estimate for the exploratory endpoint of

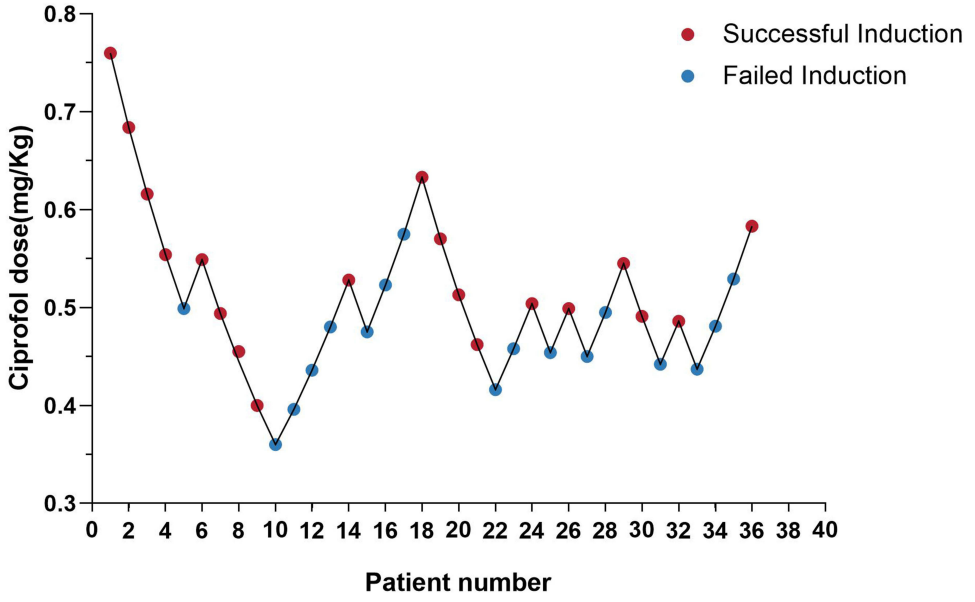

Figure 2 Up-and-down allocation sequence of ciprofol doses for induction of loss of consciousness in morbidly obese patients. The trial used Dixon's up-and-down design with an initial dose was 0.76 mg/kg and a step ratio of 1.1. Enrollment stopped after eight crossovers. Red dots indicate "successful induction" and blue dots indicate "failed induction". This figure depicts the allocation design only; ED50/ED95 were estimated subsequently by probit regression (see Figure 3).

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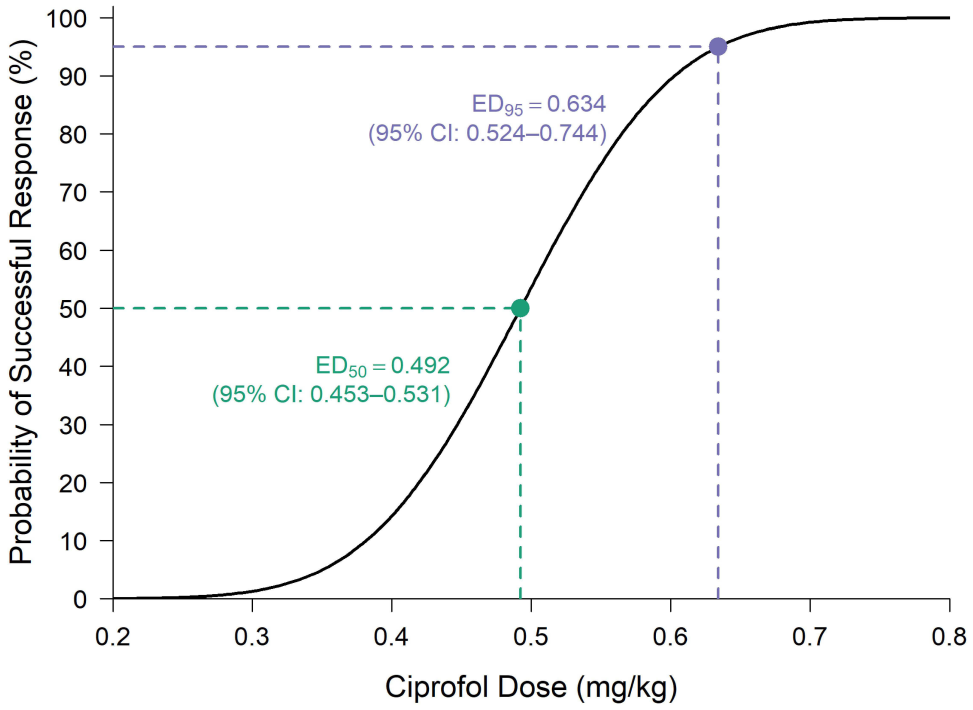

Figure 3 Probit dose-response curve for ciprofol-induced loss of consciousness. The curve was fitted using probit regression on LBW-scaled doses and binary responses from all enrolled patients. The dashed lines show ED50 (0.492 mg/kg; 95% CI 0.453–0.531) and ED95 (0.634 mg/kg; 95% CI 0.524–0.744).
Abbreviations: ED50, 50% effective dose; ED95, 95% effective dose.

ED95 was 0.634 mg/kg (95% CI: 0.524–0.744). A sensitivity analysis using the Dixon-Mood method, which is specifically suited for up-and-down study designs, yielded a consistent ED50 of 0.487 mg/kg (95% bootstrap CI: 0.455–0.521). The strong agreement between the two methods confirms the robustness of the ED50 estimate.

Secondary Outcomes

Hemodynamic Parameters

Figure 4 shows the MAP and HR trajectories for the successful and failed induction groups. Group mean MAP reached its nadir 5 min after intubation (T5) and generally remained near or above 70% of baseline across the recorded time points. HR changes were broadly similar between groups, with the failed induction group showing greater stability, whereas the successful induction group exhibited greater variability (lowest at T5 and peaking immediately after extubation at T6 before declining). Despite these mean patterns, 14/36 (39%) patients met the prespecified hypotension criterion at least once. Hypotension was adjudicated at the patient level across the study observation period after induction (T2–T8) using the prespecified threshold (MAP ≤70% of baseline or MAP <65 mmHg). Because qualifying nadirs were often transient and could occur between the plotted time points, they may not be apparent in the group mean curves.

Adverse Events

Table 2 shows the incidence of adverse observed in this study. In exploratory post hoc comparisons, the incidences of hypotension (37% vs 41%; p=0.79), bradycardia (5% vs 6%; p=0.94), and tachycardia (26% vs 35%; p=0.27) were similar. Other adverse events, such as hypoxemia, intraoperative awareness, injection pain, and PONV, were not observed in either group.

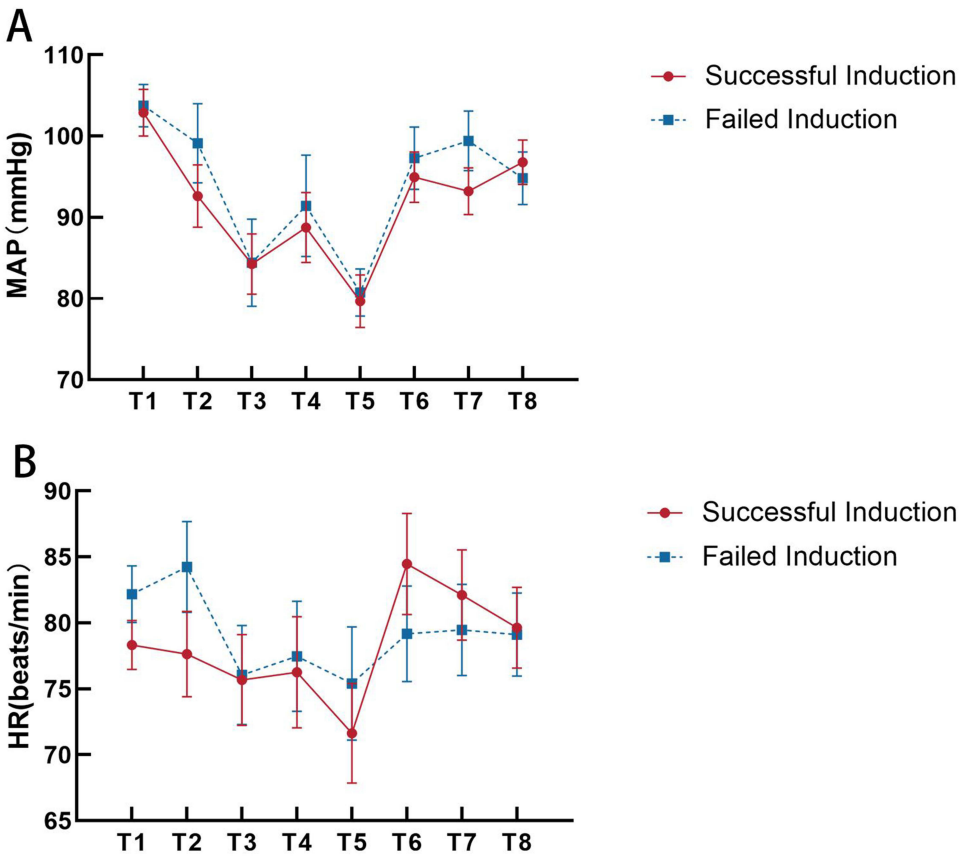

Figure 4 Hemodynamic data for MAP and HR. (**A**) Mean arterial pressure (MAP) at predefined time points. (**B**) Heart rate (HR) at the same time points. Red circles indicate the successful induction group; blue squares indicate the failed induction group. T1, baseline; T2, 1 min after induction; T3, 3 min after induction; T4, immediately after tracheal intubation; T5, 5 min after tracheal intubation; T6, immediately after extubation; T7, 5 min after extubation; T8, after leaving the PACU. MAP, mean arterial pressure; HR, heart rate. Note: Curves display group means at discrete, prespecified time points (T1–T8). Hypotension incidence reflects patient-level events meeting the prespecified threshold (MAP ≤70% of baseline or MAP <65 mmHg) at any time during the observation period after induction (T2–T8); brief nadirs occurring between time points may therefore not be visible in the mean trajectories.

Discussion

In this prospective dose-finding study using a sequential up-and-down design, we determined the LBW-scaled ED50 and ED95 of ciprofol for LOC during induction of general anesthesia in patients with MO. The point estimates obtained by the probit analysis were 0.492 $mg.kg^{-1}$ (95% CI, 0.453–0.531) and 0.634 $mg.kg^{-1}$ (95% CI, 0.524–0.744), respectively.

Table 2 Incidence of Adverse Events

	Successful Induction (n=19)	**Failed Induction (n=17)**	***P***
Hypertension, n (%)	0(0)	0(0)	–
Hypotension, n (%)	7(37%)	7(41%)	0.79
Bradycardia, n (%)	1(5%)	1(6%)	0.94
Tachycardia, n (%)	5(26%)	6(35%)	0.27
Hypoxemia, n (%)	0(0)	0(0)	–
Intraoperative awareness, n (%)	0(0)	0(0)	–
Injection pain, n (%)	0(0)	0(0)	–
PONV, n (%)	0(0)	0(0)	–

Notes: Data are presented as numbers (percentages). Unadjusted p-values are reported for exploratory/descriptive purposes only.
Abbreviation: PONV, postoperative nausea and vomiting.

https://doi.org/10.2147/DDDT.S568472

Hemodynamic trajectories were broadly comparable between patients with successful and failed induction at the assigned dose, and the incidences of hypotension, bradycardia, and tachycardia were not statistically different between the groups. No episodes of hypoxemia, injection pain, intraoperative awareness, or PONV were recorded. Taken together, these findings indicate that LBW-based dosing can deliver predictable hypnosis with an acceptable safety margin in the morbidly obese population while highlighting that dose requirements are higher than those reported for non-obese or elderly cohorts.

Our estimates were higher than those reported for nonobese patient populations. Zhao et al definitively established ED50 and ED95 of 0.318 and 0.496 mg.kg^{-1}, respectively, to suppress the tracheal intubation response in female adults receiving sufentanil.[28] Yuan et al reported ED50 values around 0.26–0.27 mg.kg^{-1} for LOC in elderly patients, irrespective of frailty status, with ED95 values close to 0.30 mg kg^{-}1.[25] Our study clearly showed that morbidly obese patients required higher LBW-scaled doses.

First, the pharmacokinetic context was different. Ciprofol, similar to propofol, is a highly lipophilic drug that quickly enters tissues with high blood flow, such as the brain, to induce anesthesia before gradually moving into fat stores.[29] In morbidly obese individuals, the body has more blood volume and higher cardiac output, which expands the initial "central compartment" where the drug is first distributed after injection.[5,30–32] Additionally, the drug moved out of this central compartment and into other tissues more rapidly in the early minutes after administration.[11] As a result, for a given dose based on LBW, the concentration of ciprofol reaching the brain, where it must act to cause unconsciousness, may be reduced or "diluted." Therefore, a higher dose might be needed to ensure that enough drug reaches the brain to achieve the desired depth of anesthesia within the short time frame required for induction. Second, the pharmacodynamic endpoints were not identical across studies. One study focused on the suppression of the intubation response in female patients pretreated with sufentanil, where the co-administration of an opioid likely reduced the required dose of hypnotic agents by mitigating nociceptive stimulation during laryngoscopy.[28] Another study evaluated LOC within three minutes among elderly patients in the absence of surgical stimulation,[25] reporting lower ED50 values that aligned with the recognized age-related increase in sensitivity to GABA ergicagents.[33,34] In contrast, our patients were younger, morbidly obese adults scheduled for general anesthesia. Although opioids were only given after successful induction, the forthcoming airway instrumentation, higher sympathetic tone, and obesity-associated respiratory loading may have favored more robust hypnosis at induction.

Third, dose-scaling strategies influence the apparent requirements. Dosing lipophilic hypnotics to TBW in MO risks overshoot, whereas using IBW may result in underdose due to the expansion of the lean compartment and cardiac output. LBW is considered a more appropriate scalar for many anesthetic drugs in the obese because it better reflects metabolically active tissue mass and correlates with drug clearance.[17,31,35–37] Recent studies on obese patients undergoing gastroscopy have investigated the effective dose of ciprofol, including its combination with sufentanil, to inhibit responses to scope insertion, revealing that optimal dosing scalars (eg,TBW, IBW, or LBW) and median effective doses vary significantly compared to non-obese cohorts, underscoring the complexity of achieving adequate sedation in this population;[15,16] However, such procedures typically involve minimal noxious stimulation and brief sedation compared with the deeper hypnosis required for induction under general anesthesia. Our results using LBW during the induction of general anesthesia, with airway management via endotracheal intubation or laryngeal mask airway, support LBW as a rational compromise, but they also show that, even on this scale, morbidly obese patients demand higher doses than elderly or non-obese cohorts. Moreover, obesity is associated with chronic low-grade inflammation and neurohumoral activation, which can shift the arousal threshold and sympathetic tone upward, potentially opposing the hypnotic effects.[38]

Separately, an internal study design factor may also have influenced the observed responses. Although elderly patients were excluded, age has a continuous influence on sensitivity to hypnotic propofol-like GABAergic agents across adulthood. Population PK/PD studies treat age as a covariate and demonstrate that the effect-site concentration and dose required for loss of consciousness decrease progressively with increasing age.[39,40] In our cohort, the successful induction group was older on average than the failed induction group, which plausibly increased the probability of successful induction at the assigned dose. As the up-and-down design forms groups based on response rather than

randomization, baseline balance is not expected, and between-group comparisons should be interpreted as exploratory. Future dose-finding work will stratify by age or incorporate age as a covariate in the dose–response model.

We intentionally withheld opioids before endpoint assessment to isolate the hypnotic doseresponse to ciprofol in morbidly obese adults, which is a common design choice in up-and-down dose-finding studies.[17,25] While routine clinical induction often includes opioid co-induction, doing so would have conflated analgesia with hypnosis and biased the ED estimation downward.[41,42] Accordingly, the ED50/95 represents the monotherapy requirement for LOC. In practice, when sufentanil or fentanyl is co-administered, the required ciprofol dose is expected to be lower. Future randomized studies that map ciprofol dosing in the presence of standardized opioid regimens are warranted.

During ciprofol induction, the hemodynamic profile was characterized by a typical, manageable pattern of change. MAP declined after induction, reaching a nadir approximately 5 min after intubation, and then recovered toward baseline. This timing is consistent with prior study,[43] and likely reflects the combined vasodilatory/negative inotropic effects of induction and early maintenance anesthetics together with dissipation of the transient pressor response after intubation and contributions from co-administered agents (eg, opioids). Using our prespecified definitions, hypotension and tachycardia occurred in approximately 40% and 30% of patients, respectively; events were typically early, transient, and responsive to routine measures, and no serious cardiovascular complications were observed.While clinically relevant, the overall rate of circulatory depression appears favorable compared to the higher incidences often associated with propofol induction.[8,44] Our observation that ciprofol offers a less pronounced hemodynamic impact is consistent with recent meta-analytic evidence, which concluded that ciprofol is associated with significantly less circulatory depression and injection pain than propofol.[45] Additionally, the absence of hypoxemia in our cohort, likely due to effective preoxygenation, prompt airway control, and the brief interval between LOC and tracheal intubation, further underscores the reduced incidence of respiratory depression relative to propofol. However, given that morbidly obese patients have reduced functional residual capacity and rapid desaturation kinetics,[46,47] apneic time must still be minimized, and airway adjuncts should be immediately available.

The sequential up-and-down method remains a highly efficient strategy for estimating the ED50, particularly with small sample sizes. We successfully concluded our experiment after achieving eight crossovers, providing ample data for robust analysis. Using probit regression, we calculated both ED50 and ED95 with confidence intervals, and although ED95 estimation in sequential designs involves extrapolation and is less precise, our reasonably narrow confidence bounds reflect a sharp dose-response curve near the ED50. Additionally, to ensure the reliability of our induction success criteria, we employed a dual endpoint—MOAA/S ≤ 1 and BIS < 60 within three minutes—combining behavioral and EEG-based measures of hypnosis, a methodology consistent with recent ciprofol studies.[25] Importantly, to prevent confounding effects on dose estimation, we administered opioids and neuromuscular blockers only after the primary endpoint was met, thereby safeguarding the accuracy of the dose–response assessment of ciprofol.

This study adds to the ciprofol evidence base by focusing on morbidly obese patients undergoing general anesthesia and adopting LBW as the dosing scalar. The integration of continuous hemodynamic monitoring, standardized induction, airway management, and systematic adverse-event capture enhances the internal validity. However, these limitations warrant further research. First, the sample size was determined by the stopping rule intrinsic to the sequential method and was not powered to detect small differences in adverse events or to explore covariates such as sex, degree of obesity, or obstructive sleep apnea status. Moreover, because the up-and-down design yields non-randomized, outcome-defined groups, leading to baseline imbalances (eg, age). Therefore, all between-group comparisons in this study must be interpreted as exploratory and potentially confounded, not as evidence from a comparative trial. Second, generalizability is constrained by eligibility: enrollment required BMI ≥ 35 kg/m^2 with at least one obesity-related comorbidity; under the standard MO definition, our cohort therefore represents the MO-with-comorbidity subset. Although the cohort included individuals with BMI ≥ 40 kg/m^2, all of them also had comorbidity, and the findings may not extend to BMI ≥ 40 kg/m^2 without comorbidity. In addition, the study was single-center and participants were relatively young, so extrapolation to older patients or those with significant cardiopulmonary disease should be cautious. Third, although LBW is a widely advocated scalar, different LBW equations exist. Therefore, we did not compare alternative weight scalars head-to-head. Fourth, ED95 estimation is subject to greater uncertainty. A biased-coin up-and-down or continual reassessment design targeting high quantiles could refine ED95 in future studies. Finally, we used a single-bolus induction paradigm, in which

some clinicians may prefer target-controlled infusion to reach a specific effect-site concentration, and PK/PD modeling in MO would help bridge bolus-based EDs with concentration-guided regimens.

Further research is essential to optimize the use of ciprofol in patients with MO. More randomized studies that map ciprofol dosing in the presence of standardized opioid regimens are warranted. Population PK/PD modeling could clarify how obesity affects ciprofol distribution and clearance, providing valuable data to refine the effect-site targets for target-controlled infusion systems. Additionally, comparative studies evaluating dosing regimens based on TBW, IBW, and LBW during full induction and intubation would help identify the most hemodynamically stable and efficient strategy. Although comparative studies of ciprofol and propofol for anesthesia induction in morbidly obese patients have been conducted, further randomized trials focusing on specific subgroups (eg, varying degrees of obesity or comorbidities) could provide more detailed insights.

Conclusions

In conclusion, using an up-and-down sequential method, we found that the LBW-scaled ED50 and ED95 of ciprofol for LOC during induction in adults with MO were 0.492 and 0.634 $mg.kg^{-1}$, respectively. Hemodynamics were generally well controlled and adverse events were infrequent. These results support LBW-based dosing and provide quantitative guidance for initial bolus selection and titration in patients with MO while underscoring the need for further model-based and comparative studies to optimize anesthetic care in this challenging population.

Data Sharing Statement

All datasets analyzed in this study are included in this article. Further inquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

The study was performed in accordance with the Declaration of Helsinki and was approved by the local institutional Ethics Committee, Lishui People's Hospital (approval number:2024-023-01) and registered in the Chinese Clinical Trial Registry (registration number: ChiCTR2400094305). All the participants provided written informed consent.

Acknowledgments

We sincerely thank all the staff who assisted in this study and all subjects.

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas, took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no conflicts of interest in this work.

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