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Original Article

Comparison of the Onset of Action, Maintenance, and Recovery of Three Weight-based Dosing of Cisatracurium in Patients with Morbid Obesity in Laparoscopic Bariatric Surgery: A Randomized Clinical Trial

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What's Known

- Among the several morbid obesity treatment options, bariatric surgery provides the best outcome and is regarded as a long-term weight-loss solution.
- Obesity affects the pharmacokinetics and pharmacodynamics of the drugs, which makes it a challenging condition for anesthesia management among the patient population. An appropriate dose adjustment of neuromuscular blockers during anesthesia is necessary to provide optimal neuromuscular blockade while also having a suitable recovery time.
- Various cisatracurium dosages were investigated for tracheal intubation and maintenance of neuromuscular blockade in patients with morbid obesity; nonetheless, there is no broad consensus in the literature in this regard.

What's New

- Compared to total body weight dosing, infusion of cisatracurium based on fat-free mass dosing results in a more favorable postoperative situation, less cisatracurium consumption, and a shorter recovery time.
- When compared to total body weight and fat-free mass weight-based dosing, cisatracurium dosing based on ideal body weight does not provide a good surgical situation.
- In contrast to the fat-free mass group, the ideal body weight group required the rescue dose during the maintenance of anesthesia more frequently than the total body weight group.

Abstract

Background: For patients with morbid obesity, different cisatracurium dosage regimens are recommended. This study aimed to compare the onset of action, the sufficiency of neuromuscular blockade during infusion, and the recovery of the three distinct cisatracurium dosage scalars in patients with morbid obesity undergoing laparoscopic bariatric surgery.

Methods: In this randomized clinical trial, 55 patients were scheduled for bariatric surgery at Firoozgar Hospital from March 2020 to August 2021. Using a block randomization method, they were randomly divided into three groups, based on total body weight (TBW group), fat-free mass (FFM group), or ideal body weight (IBW group), to receive a bolus of cisatracurium 0.2 mg/Kg, followed by an infusion of 2 µg/Kg, to maintain a train-of-four (TOF) count≤2. Data were analyzed using SPSS software. $P<0.05$ was considered statistically significant.

Results: The mean time (seconds) to reach TOF0 in the TBW group was significantly shorter (201.89, 95%CI=192.99-210.79; P=0.004) than the IBW group (233.53, 95%CI=218.71-248.34; P=0.01). However, this difference was not statistically significant between TBW and FFM groups (220.83, 95%CI=199.73-241.94; P=0.81) or between FFM and the IBW groups (P=0.23). The rescue dose and increments of cisatracurium infusion were not required in the TBW group, whereas their probability was 4.81 times higher in the IBW group than the FFM group. Furthermore, the TBW and FFM groups had higher mean surgical condition scores than the IBW group ($P<0.001$, and P=0.006, respectively).

Conclusion: Cisatracurium loading and infusion dosing based on FFM provide a comparable onset of action and surgical field condition to the TBW-based dosing with a shorter recovery time. However, IBW-based dosing of cisatracurium was insufficient for laparoscopic bariatric surgery.

Trial Registration Number: IRCT20151107024909N9.

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Keywords ● Anesthesia ● Bariatric surgery ● Clinical trial ● Morbid obesity

Introduction

Obesity, define as a body mass index (BMI) ≥30 Kg/m^2, is associated with an increase in morbidity and mortality.[1-3] Among the different treatments for morbid obesity, bariatric surgery provides the best outcome and is the only effective long-term weight-loss therapy followed by a long-term remission of obesity-related comorbidities.[3-5] Changes in body composition, cardiac output, kidney, and liver structural hemodynamics, and metabolism, that occur with an excessive increase in body weight, affect the drugs' pharmacokinetics and pharmacodynamics and make anesthesia management challenging in these patients.[6-9] Therefore, to provide an optimal operative field and prevent delays in the patient's recovery from neuromuscular blockade (NMB), proper dose adjustment of neuromuscular blockers during anesthesia is required. Failing to do so might result in a longer stay in the operating and recovery rooms, higher expenses, and a decrease in the rate of operation room turnover.

Cisatracurium is a potent intermediate-acting neuromuscular blocker (NMBD). Due to its degradation through Hofmann elimination, the duration of its effect is independent of the hepatic and renal function. In comparison to suxamethonium and rocuronium, cisatracurium does not induce histamine release, and the incidence rate of anaphylaxis following cisatracurium is one-tenth and one-thirteenth lower, respectively.[10, 11] These specific properties of cisatracurium advocate its use in anesthesia management in patients with morbid obesity without predicted difficult intubation. Different cisatracurium dosing regimens were studied for tracheal intubation and maintenance of NMB in patients with morbid obesity, including dosing based on ideal body weight (IBW), lean body weight (LBW), or total body weight (TBW). However, there is no broad consensus in this regard in the literature.[10, 12-14] Given that it is a hydrophilic compound,[10] it seems that cisatracurium is more likely to be distributed in the fat-free part of the body weight. Therefore, this study compared the effects of cisatracurium dosing based on fat-free mass (FFM) with those based on TBW and IBW in patients with morbid obesity. It also examined the onset and sufficiency of NMB during infusion and recovery time.

Patients and Methods

Study Design and Participants

A randomized, double-blinded clinical trial was conducted on 57 patients with morbid obesity scheduled for laparoscopic bariatric surgery at Firoozgar Hospital, affiliated with Iran University of Medical Sciences (Tehran, Iran), from March 2020 to August 2021. The study protocol was approved by the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.FMD.REC 1398.465) and registered in the Iranian Registry of Clinical Trials (IRCT20151107024909N9). Written informed consent was obtained from the patients before enrolling in the study.

The sample size was estimated based on the study of Kralingen and others with a mean time to reach TOF0 of three minutes in the TBW group and four minutes in the IBW group, and a standard deviation of one minute, in both groups.[15] By taking into account an attrition rate of 5%, a sample size of 57 was estimated to achieve a power of 0.85 and a type I error rate (random error) of 0.05.

Using a six-block randomization method, the participants were randomly assigned to three groups. Based on total body weight (TBW group), fat-free mass (FFM group), or ideal body weight (IBW group), the patients were assigned 1:1:1 to receive cisatracurium with a bolus of 0.2 mg/Kg, followed by an infusion of 2 µg/Kg, to maintain a train-of-four (TOF) count≤2.

Two anesthesiologists were involved in the study protocol; one prepared and set the infusion rate of the loading and the infusion dose of cisatracurium, and the other, who was blinded to the study group, supervised anesthesia in accordance with the study protocol and gathered the data. All the procedures and operative field scorings were performed by a single surgeon who was blinded to the patient study group.

Patients with morbid obesity aged between 18 to 60 years, the American Society of Anesthesiologists physical status (ASA-PS)≥2, a BMI of more than 35 Kg/m^2, and normal renal and hepatic function were included in the study. A history of neuromuscular disease, treatment with known medicines that interfere with neuromuscular transmission, allergy to cisatracurium, and predicted difficult intubation were all the exclusion criteria.

Patients Preparation

The bioelectrical impedance analysis (BIA, In-body 720, Biospace, Korea) was used to determine the patients' weight (i.e., TBW), and body composition (including FFM) was determined the day before the surgery. Patients were recommended to avoid eating and drinking three hours before BIA testing, to urinate at least 30 minutes before testing, and to drink enough fluid for 24 hours before the testing

was performed. IBW was calculated using the Robinson formula [i.e., Ideal Body Weight (Kg)=52 Kg (for men) or 49 Kg (for women)+0.75 Kg per centimeter over 152 cm].

Anesthesia Protocol

Upon entering the operating room, routine monitoring including electrocardiography, non-invasive blood pressure monitoring and peripheral blood oxygen saturation monitoring, thermometer, capnography, acceleromyography (TOF-Watch SX monitoring system, Organon, Ireland), and Bispectral Index (BIS) monitoring (BISPECTRAL VISTA monitoring system; Covidien company, USA) were performed on the patients. After the patient was sedated, the electrodes of the neuromuscular monitoring were placed to stimulate the ulnar nerve using surface electrodes, and the device was calibrated. The skin temperature was maintained above 32 °C. A 20-gauge catheter (Lars Medicare, India) was used to cannulate two antecubital veins, one from each upper limb, and a load of 5 mL per TBW of warm isotonic fluids was started. For six minutes, the patients were placed in the ramp position and pre-oxygenated with 100% O_2.

Induction and Maintenance of Anesthesia

All the patients in the three groups were given midazolam 2 mg (Darou Paksh, Iran) and fentanyl 2 µg/Kg (Caspian Tamin Pharmaceutical Co., Iran), based on TBW, two minutes before anesthesia was administered. Anesthesia was induced with propofol 2 mg/Kg (Fresenius Kabi Austria GmbH, Austria) (IBW). Cisatracurium 0.2 mg/Kg (Alborz Daru, Iran), based on the study group's body weight, was administered after the proof of ventilation. By the time TOF reached zero, the trachea was intubated.

Anesthesia was maintained with propofol infusion to keep the BIS range from 40-60. The lungs were mechanically ventilated with a tidal volume of 8 mL/Kg (IBW), and the rate of breathing was adjusted to maintain end-tidal CO_2 between 30-35 mmHg.

After TOF reached zero, an infusion of cisatracurium was started at a dose of 2 µg/Kg/min based on TBW, FFM, or IBW, according to the study group. NMB was monitored every 12 sec. If the TOF count was ≥2, or there was any evidence of muscle contraction (i.e., visible diaphragm movement, return of spontaneous breathing, or the patient's movement), a rescue dose of cisatracurium, 0.05 mg/Kg based on TBW, was administered, and the infusion rate was increased by 10%.

Recovery of NMB and Tracheal Extubation

Cisatracurium infusion was discontinued, as the trocars were removed, and the propofol infusion was discontinued at the end of the procedure. When a TOF count of four was detected, neostigmine 40 µg/Kg (Caspian Tamin Pharmaceutical Co., Iran) plus atropine 20 µg/Kg (Darou Pakhsh, Iran) was administered. Then, the trachea was extubated, when the patient was awake, alert, and spontaneously breathing, and the TOF ratio was ≥90%.

Data Recording

Time from the administration of cisatracurium intubating dose to TOF count reaches zero (defined as the onset of action in this study), the number of patients required the rescue dose of cisatracurium 0.05 mg/Kg, time from discontinuation of cisatracurium infusion to TOF count reaches four, and TOF ratio to 50%, 75%, and 100%, as well as total cisatracurium consumptions, were all recorded. The surgical field condition was scored by the surgeon using the following five-point Likert scale: score 1: Very bad; score 2: Bad (poor); score 3: Medium (acceptable); score 4: Good; and score 5: Excellent.[16] The variable selection method employed in this study was based on the literature review conducted in the field of research area where relevant theories predominated.[17-19]

Study Outcomes

The primary outcome was the time to reach TOF zero in three cisatracurium dose regimens based on TBW, FFM, and IBW. The secondary outcomes included comparing the adequacy of the infusion dose, the recovery time to TOF 4, and the TOF ratio of 50%, 75%, and 100%, following these three dosing scalars.

Statistical Analysis

Data were analyzed using SPSS software, version 28.0 (Armonk, NY: IBM Corp). The Kolmogorov-Smirnov test was used to evaluate the normal distribution of the data. Chi square and Fisher's exact tests were used to compare categorical variables between the three study groups. One-way analysis of variance (ANOVA) was used to compare independent quantitative variables with normal distribution between the groups. LSD *post hoc* test was used to make all potential comparisons between the groups. $P<0.05$ was considered statically significant.

Results

A total of 57 patients were enrolled in the study, of which 55 completed the study. At the

beginning of anesthesia, one patient in the TBW group declined to participate in the study. The procedure was canceled in one patient in the FFM group due to a change in surgical plan. No patient was excluded from the study during the intervention, data gathering, or statistical analysis (figure 1).

As indicated in table 1, the study groups were comparable in terms of age, sex, height, BMI, the type of surgery, the mean duration of surgery, and cisatracurium infusion (P=0.40, P≥0.999, P=0.54, P=0.91, P=0.87, P=0.76, P=0.70, respectively). The LSD *post hoc* test indicated that the time to reach zero TOF was shorter in the TBW group (201.89 sec, 95%CI=192.99-210.79) than the IBW group (233.53 sec, 95%CI=218.71-248.34; P=0.004). However, neither the difference between TBW and FFM groups (220.83 sec, 95%CI=199.73-241.94; P=0.81) nor the difference between the FFM and the IBW groups (P=0.23) was statistically significant (table 2). According to the results of the study, there were significant differences between the three study groups in the need for a rescue dose and an increase in cisatracurium infusion during the maintenance of anesthesia (P=0.008). As a result, patients in the TBW group did not require the rescue dose. The rescue dose was administered to four patients in the FFM group at least once, with a total of five doses. In contrast, eleven patients in the IBW group received a total of 17 doses. The probability of requiring a rescue dose and increments of cisatracurium was 4.81 times higher in participants receiving cisatracurium based on IBW than those receiving cisatracurium based on FFM. The overall amount of consumed cisatracurium was higher in the TBW group than in the FFM and IBW groups (P<0.001) (table 2).

All the time durations from discontinuation of cisatracurium infusion to reach a TOF count of four, TOF ratios of 50%, 75%, and 100% were significantly longer in the TBW group than in the other two groups. However, LSD *post hoc* test revealed no significant difference between the FFM and IBW groups (P=0.85, P=0.94, P=0.66, P=0.92, respectively; table 3).

As shown in table 4, surgical conditions were significantly different between the study groups (P<0.001). The LSD *post hoc* test showed that the mean surgical condition score was similar between the TBW and FFM groups (P=0.14), while it was less favorable in the IBW group than the TBW group (P<0.001) and FFM group (P=0.006).

Discussion

According to the findings of this study, patients receiving cisatracurium based on FFM had similar onset of action, adequacy of NMB during cisatracurium infusion, and surgical condition score with those receiving cisatracurium based on TBW, while the recovery time was faster.

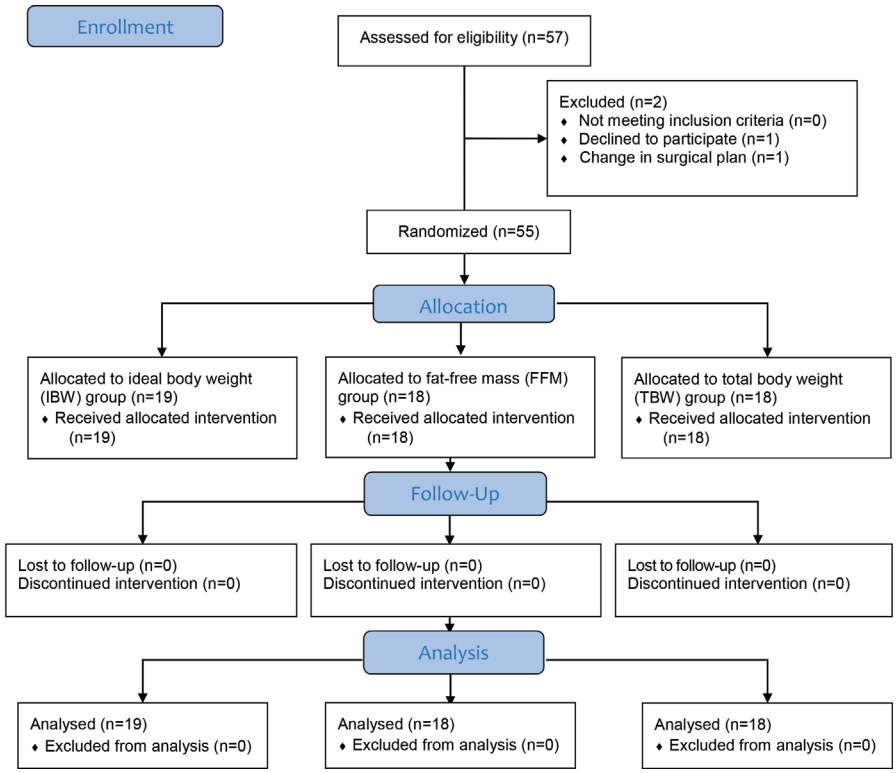

Figure 1: The figure represents the CONSORT flow diagram of the present study.

Table 1: Demographic data and type of surgery in different groups

Variables		TBW group (n=18)	FFM group (n=18)	IBW group (n=19)	P value
Age (Mean±SD)		40.33±10.58	37.17±7.64	41.89±12.86	0.40*
Height (cm)		162.67±7.44	165.72±8.95	164.68±8.74	0.54*
Weight (Kg)		127.84±29.73	133.83±22.59	129.79±25.71	0.78*
BMI(Kg/m^2)		47.88±8.61	48.65±6.82	47.59±6.64	0.91*
Sex	Male	5 (27.8%)	4 (22.2%)	5 (26.3%)	≥0.999
	Female	13 (72.2%)	14 (77.8%)	14 (73.7%)	
Type of Surgery	Sleeve	13 (72.2%)	11 (61.1%)	14 (73.7%)	0.87**
	Mini-bypass	2 (11.1%)	3 (16.7%)	1 (5.3%)	
	Classic bypass	3 (16.7%)	4 (22.2%)	4 (21.1%)	

Data were expressed as mean±SD or frequency (%). *One-way ANOVA, **Fisher's exact test; BMI: Body Mass Index; FFM: Fat-free Mass; IBW: Ideal Body Weight; TBW: Total Body Weight. P<0.05 was considered statically significant.

Table 2: Comparison of the outcomes in different groups

Variables		TBW group (N=18) (mean±SD)	FFM group (N=18) (mean±SD)	IBW group (N=19) (mean±SD)	P value
TOF 0 (sec)		201.89±17.891	220.83±42.443	233.53±30.738	0.002*
Surgery duration (min)		63.44±22.16	66.88±19.46	68.89±25.58	0.76*
Total cisatracurium (µg)		40,100.56±13340.52	21,479.06±5,259.09	21,712.89±7,313.68	<0.001*
Cisatracurium duration (min)		54.01±22.07	58.48±21.23	60.29±25.28	0.70*
Number of patients who received rescue dose	0	18 (100%)	14 (77.8%)	8 (42.1%)	0.008**
	1	0 (0%)	3 (16.7%)	9 (47.4%)	
	2	0 (0%)	1 (5.9%)	1 (5.3%)	
	>2	0 (0%)	0 (0%)	1 (5.3%)	

Data were expressed as mean±SD or frequency (%). *One-way ANOVA, **Chi Square test; FFM: Fat-free Mass; IBW: Ideal Body Weight; TBW: Total Body Weight; TOF: Train-of-four. P<0.05 was considered statically significant.

Table 3: Recovery profile of neuromuscular block in different groups

Time from discontinuation of cisatracurium infusion to reach	TBW group (N=18) (mean±SD)	FFM group (N=18) (mean±SD)	IBW group (N=19) (mean±SD)	P value
TOF Count 4 (min)	22.03±9.27	13.54±6.05	13.10±5.53	<0.001*
TOF Ratio 50% (min)	31.36±11.76	20.38±8.38	20.61±8.17	0.001*
TOF Ratio 75% (min)	39.64±14.10	26.47±10.94	24.79±9.07	<0.001*
TOF Ratio 100% (min)	44.53±13.38	31.34±12.38	31.74±9.64	0.002*

Data were expressed as mean±SD. *One-way ANOVA, FFM: Fat-free Mass; IBW: Ideal Body Weight; TBW: Total Body Weight; TOF: Train-of-four. P<0.05 was considered statically significant.

Table 4: Surgical condition score in different groups

Variable	TBW group (N=18) (mean±SD)	FFM group (N=18) (mean±SD)	IBW group (N=19) (mean±SD)	P value
Surgical condition score	4.22±0.43	3.89±0.58	3.26±0.87	<0.001*

Data were expressed as mean±SD. *One-way ANOVA; FFM: Fat-free Mass; IBW: Ideal Body Weight; TBW: Total Body Weight. P<0.05 was considered statically significant.

The increase in fat mass and FFM were not parallel with weight gain.[14, 20, 21] Furthermore, the body fat fraction varied with age, sex, ethnicity, and even muscle strength. Therefore, women had higher body fat fractions than men, and patients with larger BMIs had lower body fat fractions than those with higher muscle strength.[22, 23] Consequently, although different formulas were proposed, no single formula could be used for all patients.[24] Body composition can be measured with different methods, each of which has some limitations. In the present study, FFM was measured using BIA. This inexpensive, easy, and non-invasive method measures tissue impedance based on a cylindrical body model with constant conductivity.[25] BIA were shown to underestimate fat mass and overestimate FFM compared to dual-energy X-ray absorptiometry (DXA). The use of multi-frequency BIA, however, significantly reduces this bias. As different

multi-frequency InBody analyzers produce small individual errors, BIA has been suggested as a surrogate for dual-energy X-ray absorptiometry when it is not available.[26] In this study, BIA was used to measure FFM. Although it was not expensive, it had some expenses for the patient or the health care system. Following bariatric surgery, BIA was routinely used for patients' weight loss follow-up in this center.

A few studies investigated the effects of cisatracurium in patients with morbid obesity and those with normal weight. Geng and colleagues found a correlation between larger BMIs and longer recovery time of cisatracurium.[27] They reported that when cisatracurium 0.2 mg/Kg was administered based on real body weight (i.e., TBW), the clinical duration and the recovery time were longer in overweight patients (BMI>28) than normal-weight patients (BMI<24) undergoing TIVA anesthesia. Leykin and others conducted a study on women with morbid obesity (BMI>40) and reported that cisatracurium 0.2 mg/Kg had a faster onset of action when administered based on TBW than IBW.[9] TBW-based dosing of cisatracurium had a faster onset of action in patients with morbid obesity than individuals with normal weight. They also indicated that the duration of action of TBW-based cisatracurium in patients with morbid obesity and in normal-weight patients was longer than IBW-based dosing of cisatracurium in patients with morbid obesity. The findings of the present study were consistent with those of Leikin and others, in that, based on TBW, compared with IBW, the onset of action was shorter, and the duration of action of cisatracurium was longer in individuals with obesity. It should be noted that in previous studies, different dosing regimens in patients with obesity were compared with normal-weight patients, whereas in the current study, all the patients had morbid obesity, as the aim of the study was to determine appropriate dosing, and to the best of our knowledge, such comparison has not yet been made.

Although the findings of all studies were not consistent, certain studies indicated that deep NMB (post-tetanic number of contractions of 1-2) versus moderate block (number of TOF 1-2) improved and provided a stable surgical condition in laparoscopic bariatric surgery.[28, 29] The current study also found that higher weight-based doses provided deeper levels of the NMB and better surgical conditions. The TOF count in the TBW group was zero at all times recorded during the procedure, and no patients in this group received a rescue dose or had an increase in cisatracurium infusion. Extra boluses and increments in cisatracurium infusion dose were most frequently required in the IBW group; nevertheless, the postoperative condition was the least favorable in this group, indicating that IBW-based dosing was insufficient for cisatracurium in patients with obesity. However, the surgical condition was comparable in the TBW and FFM groups.

Obesity has consequences for the respiratory system due to fat deposition in different parts of the body and systemic inflammation. Lung capacities, including expiratory reserve volume, functional residual capacity, and total lung capacity are decreased, particularly in patients with an android pattern of body fat deposition. Obesity also impairs respiratory muscle performance, resulting in a decrease in airway luminal diameter and an increase in airway collapsibility pressure and labor of breathing.[2] There is also a correlation between obesity and asthma, chronic obstructive pulmonary disease, obesity hypoventilation syndrome, and obstructive sleep apnea.[2, 3] According to the findings of the present study, which were consistent with previous studies, the recovery of NMB was significantly longer in the TBW group than the other two groups. While the larger cisatracurium dose administered to the TBW group in the current study resulted in a deeper level of NMB and a better surgical field than the IBW group, it was at the expense of the prolonged recovery time, making this dosing undesirable in patients with morbid obesity, who might already have respiratory function impairment due to obesity and were at risk of respiratory depression due to residual effects of other anesthetic agents, such as opioids and hypnotics. The prolonged residual NMB impacts the tracheal extubation time. Therefore, the cisatracurium dosing based on TBW may not be prudent in bariatric surgeries, in which the surgery typically lasts 1-2 hours on average, and the NMB is required during pneumoperitoneum, which lasts almost until the end of the procedure, with no time left for the NMB recovery during the procedure.

The loading dose of a medicine can be determined by the volume of distribution (V_d).[30] The V_d for hydrophilic drugs is correlated to lean body weight (similar to FFM).[21] It was shown that the volume of distribution, and elimination of half-lives, as well as clearance of cisatracurium based on FFM in patients with morbid obesity were comparable with normal-weight patients.[31] In the present study, Cisatracurium dosing based on FFM provided a comparable onset of action and surgical condition compared to dosing based on TBW. Besides, FFM resulted in better surgical conditions and fewer rescue

doses, but similar NMB recovery compared to dosing based on IBW. Therefore, according to the findings of the present study and review of the previous studies, FFM seemed to be a reasonable loading and maintenance dose for patients with morbid obesity undergoing bariatric surgery. The main limitation of our study was the coincidence with the coronavirus disease pandemic and intermittent lockdowns making data gathering so long.

Conclusion

Based on the findings of the current study, cisatracurium dosing based on TBW prolonged NMB recovery time and increased cisatracurium consumption, despite providing a favorable surgical condition. However, dosing based on FFM provided surgical conditions comparable to TBW dosing, but shorter NMB recovery time, which was comparable with IBW dosing. Therefore, dosing based on FFM was the most appropriate choice for cisatracurium in patients with morbid obesity undergoing bariatric surgery.

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Authors' Contribution

F.R. and S.S. contributed to designing the study, data acquisition, analysis, and interpretation; drafting the article, and revising it; S.D.M., T.Y., and E.P. contributed to data acquisition, analysis, and drafting the article. All authors contributed to the final approval of the version to be published and are accountable for the accuracy or integrity of the research work.

Conflict of Interest: None declared.

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