Comparison of the effect of rocuronium dosing based on corrected or lean body weight on rapid sequence induction and neuromuscular blockade duration in obese female patients

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ABSTRACT

الأهداف: لمقارنة بداية الإصابة، مدة العمل، والظروف التنبيب الرغامي في المرضى الذين يعانون من السمنة المفرطة عند الجرعة التنبيب من rocuronium على تصحيح وزن الجسم (CBW) مقابل وزن الجسم الغث (LBW) لتعريفي تسلسل السريع.

الطريقة: أجريت هذه الدراسة المرتقبة بها في مستشفى نيومن للدراسات والبحوث، أنقرة، تركيا خلال الفترة ما بين أغسطس 2013م ومايو 2014م . وتم اختيار أربعين مريضاً يعانون من السمنة المفرطة من الإناث وقسموا عشوائياً إلى مجموعتين لإجراء عملية جراحية بالمنظار تحت التخدير. مجموعة (CBW) n = 20 وردت 1.2 ملغ / كغ rocuronium بناء على CBW ، ومجموعة (LBW) n = 20 وردت 1.2 ملغ / كغ rocuronium على أساس LBW. تم إجراء التنبيب الرغامي لمدة 60 ثانية بعد حقن ارتخاء العضلات، وجرى تقييم ظروف التنبيب. من إبهام اليد تم رصد النقل العصبي والعضلي باستخدام acceleromyography. سجلت في البداية، وقت اكتئاب من twitch tension انقباض إلى 95% من قيمته السيطرة، ومدة العمل، الذي يعرف بأنه الوقت المناسب لتحقيق استجابة تحفيز واحدة لتدريب من أربعة (T1).

النتائج: لا توجد فروق ذات دلالة إحصائية بين المجموعات في ظروف التنبيب أو الوقت يصيب (60–50 ثانية متوسط، 26،5–22،5 المجال الربعي [IQR]). وكانت مدة العمل لفترة أطول كثيرا في (60 CBW دقيقة الوسيط، 12 IQR؛) من مجموعة (35 LBW دقيقة الوسيط، 16IQR؛ $p<0.01$).

الخاتمة: المرضى الذين يعانون من السمنة المفرطة، الجرعات من 1.2 ملغم / كغم rocuronium على أساس LBW تعطي القصبة الهوائية تنبيب ممتازة أو جيدة في غضون 60 ثانية بعد تناوله، ولا تحتاج مدة طويلة.

Objectives: To compare onset time, duration of action, and tracheal intubation conditions in obese patients when the intubation dose of rocuronium was based on corrected body weight (CBW) versus lean body weight (LBW) for rapid sequence induction.

Methods: This prospective study was carried out at Numune Education and Research Hospital, Ankara, Turkey between August 2013 and May 2014. Forty female obese patients scheduled for laparoscopic surgery under general anesthesia were randomized into 2 groups. Group CBW (n=20) received 1.2 mg/kg rocuronium based on CBW, and group LBW (n=20) received 1.2 mg/kg rocuronium based on LBW. Endotracheal intubation was performed 60 seconds after injection of muscle relaxant, and intubating conditions were evaluated. Neuromuscular transmission was monitored using acceleromyography of the adductor pollicis. Onset time, defined as time to depression of the twitch tension to 95% of its control value, and duration of action, defined as time to achieve one response to train-of-four stimulation (T1) were recorded.

Results: No significant differences were observed between the groups in intubation conditions or onset time (50-60 seconds median, 30-30 interquartile range [IQR]). Duration of action was significantly longer in the CBW group (60 minutes median, 12 IQR) than the LBW group (35 minutes median, 16 IQR; $p<0.01$).

Conclusion: In obese patients, dosing of 1.2 mg/kg rocuronium based on LBW provides excellent or good tracheal intubating conditions within 60 seconds after administration and does not lead to prolonged duration of action.

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The World Health Organization defines obesity as a worldwide epidemic disease.[1] More than half of the population is reported to be overweight, and nearly 20-35% is obese in the United States and Europe.[2] In Turkey, 30.3% of the population is obese and 34.6% is overweight.[3] This means that obesity has become a healthcare problem not only for developed but also for developing countries. Since the rate of obesity is expected to increase further in the future,[2] anesthesiologists are being more frequently confronted with obese patients in their daily work. In obese patients, mask ventilation can be difficult; in addition, pulmonary aspiration risk is higher, and the period of apnea time before desaturation is shorter.[4] Therefore, many clinicians prefer rapid sequence induction (RSI) technique in obese patients.[5] Rocuronium is an aminosteroid, non-depolarizing, neuromuscular blocking drug used in RSI at an optimal dose of 1.2 mg/kg.[6] Both fat and lean body mass are greater in obese patients when compared with non-obese patients of similar age, height, and gender.[7] These differences considerably influence the apparent volume of distribution of drugs in obese patients. Furthermore, increases in cardiac output and total blood volume and changes in regional blood flow can impact peak plasma concentration, clearance, and elimination half-life of many anesthetic agents.[7-9] As a consequence, clinicians face difficulties in calculating neuromuscular blocking agent doses in obese patients. Dosing based on total body weight (TBW) may cause overdose and prolonged duration of action.[9] Thus, in some studies, dosing is recommended to be based on ideal body weight (IBW),[9,10] which is calculated by subtracting 106 from the height in cm for women and 102 from the height in cm for men.[11] However, this causes all patients of the same height to receive the same dose and does not take into account the variation in body composition related to obesity.[12] Corrected body weight (CBW) is another scalar used for dosing neuromuscular blocker agents.[11] Because of greater volume of distribution in obese patients, it is proposed that dosing should be based on CBW for sufficient onset time and peak of action.[13] The scalar of lean body weight (LBW) is obtained by subtracting the fat mass from TBW;[12] this correlates with early distribution kinetics of drugs[14] and drug clearance.[15] Therefore, LBW is proposed as the ideal weight scalar for dosing in morbidly obese patients.[12] However, it has also been claimed that LBW cannot be used without normalization since it results in underdosing.[16] Calculation, advantages, and disadvantages of weight scalars are shown in **Table 1**. Earlier studies on dosing rocuronium in obese patients were performed with 0.6 mg/kg rocuronium based on TBW, CBW, and IBW, and with 1.2 mg/kg rocuronium based on IBW. However, we hypothesized that LBW is more appropriate for dosing in obese patients during RSI practice due to the sufficient onset time and shorter duration of action. In the present study, we evaluated the intubation conditions, onset time, and duration of action in patients with a body mass index (BMI) greater than 30 kg/m^2 when 1.2 mg/kg rocuronium was dosed based on LBW and CBW for RSI.

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Methods. This study was carried out between August 2013 and May 2014 in accordance with the principles of Helsinki Declaration and after receiving approval from the ethics committee of Ankara Numune Training and Research Hospital, Ankara, Turkey. In this prospective, randomized, double-blind study, we studied 40 patients scheduled for laparoscopic surgery under general anesthesia. Inclusion criteria were: female; age between 18 and 65 years; American Society of Anesthesiologists (ASA) status I-III; and BMI ≥30 kg/m^2. Exclusion criteria were: neuromuscular disease; treatment with medication known to interfere with neuromuscular transmission; known impaired renal or hepatic function; known allergy to the study drugs; and expected difficult airway. Prestudy power analysis using a 10 minutes (min) standard deviation (SD), and a difference of 10 min in time to reappearance of T1 between the CBW and LBW groups indicated that 17 patients in each group (5% type 1 error risk, 80% power) would be sufficient. We estimated a 10 min SD and a difference of 10 min in time to reappearance of T1 based on a previous study.[11] Considering possible adverse events and patients with an unexpected difficult airway, we selected 40 patients at the pre-anesthetic assessment who met the inclusion criteria, and obtained written informed consent from each patient. All patients who met the inclusion criteria were approached to participate in the study. There was no patient who did not accept the study, or whose operation was postponed. All patients fasted from midnight and took nonparticulate antacids to minimize the risk of aspiration pneumonitis; no premedication was given. A peripheral intravenous (IV) access was established, and all patients received routine monitoring (Datex-Ohmeda, Helsinki,

Finland) consisting of noninvasive arterial blood pressure, pulse oximetry, and electrocardiography. Neuromuscular transmission was monitored and recorded using acceleromyography of the adductor pollicis muscle (TOF-Watch SX, Organon, Dublin, Ireland). After carefully cleaning the skin, 2 pediatric surface electrodes were placed over the ulnar nerve, 3-6 cm from the wrist of the patient. The acceleration transducer was mounted on the thumb, and the hand was fixed to the operating table with plaster but did not limit thumb movement. A temperature sensor was secured on the volar aspect of the hand, and peripheral skin temperature was maintained above 32°C by an upper body air-warming device. The response to ulnar nerve stimulation was recorded with a TOF-Watch SX (Organon, Dublin, Ireland), and data were collected on a laptop using the TOF-Watch SX monitor program.

Patients were randomly and equally separated into 2 groups based on a computer-generated list of random numbers that were placed in opaque sealed envelopes. One group was given 1.2 mg/kg rocuronium (Curon® 50 mg/5 mL [Mustafa Nevzat, Istanbul, Turkey]) based on LBW, and the other group was given 1.2 mg/kg rocuronium based on CBW. The following formulas were used in the calculations:

LBW: (9270 × TBW)/ (8780 + 244 × BMI);[17]

CBW: IBW + (TBW - IBW) × 0.4;[11] and

IBW: Height (cm) - 106[11]

In the operating room, an unblinded nurse opened the sealed envelope and calculated the CBW or LBW value. Then, the nurse calculated the dose of rocuronium and placed it into a 20 mL syringe; the remaining volume was filled with 0.9% sodium chloride before administration. All other medical staff and the patients were blinded to the dose of rocuronium. The patients were positioned in a ramped position and were spontaneously ventilated with 100% oxygen by a snug-fitting face mask for 5 min. Anesthesia was induced with propofol 2.5 mg/kg and fentanyl 1 μg/kg, both based on CBW. After loss of eyelid and corneal reflexes, and no response to the verbal order "open your eyes", a 50-Hz tetanic stimulus was applied for 5 seconds. Following baseline stabilization, supramaximal stimulation and calibration were carried out using the built-in calibration function (CAL 2), and the intubation dose of rocuronium was then injected IV in less than 5 seconds. Neuromuscular monitoring was started using single-twitch stimulation of 0.1 Hz. The Sellick maneuver was not performed in order to avoid interference with evaluation of intubation conditions. Endotracheal intubation was carried out 60 s after injection of the muscle relaxant, and the intubation conditions were assessed by an anesthesiologist certified in difficult airways and with over 10 years of clinical experience. The evaluation of intubation conditions was based on good clinical research practice (GCRP) guidelines for pharmacodynamic neuromuscular studies.[18] Ease of laryngoscopy, position and/or movement of the vocal cords, and reaction to intubation were evaluated as excellent, good, or poor.[18] Cormack-Lehane grading and maneuvers used to improve the glottis view were recorded. Ventilation was performed with 50% nitrous oxide in oxygen, and end-tidal pCO_2 (carbon dioxide) was maintained between 30 and 35 mmHg (Datex-Ohmeda S/5, Avance, USA). Anesthesia was maintained with sevoflurane with an end-tidal concentration of 1.7-2.4% in 3 L/min fresh gas flow. Onset time, defined as the time from the start of the rocuronium injection to depression of the twitch tension to 95% of its control value was recorded. After 95% depression of the control twitch was obtained, neuromuscular stimulation was changed to train-of-four (TOF). The TOF was measured at every 15 seconds automatically. Duration of action, defined as the time from the start of the rocuronium injection to achievement of one response to TOF stimulation (T1) was recorded. After the reappearance of T1, if the neuromuscular blockade was insufficient for surgery, supplementary rocuronium (10 mg) was given. At the end of surgery, if TOF ratio was <90%, neostigmine (2.5 mg) and atropine (one mg) were given. The trachea was extubated when the patient was fully awake, and TOF ratio was ≥90%.

The Statistical Package for Social Sciences for Windows version 15 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The data were shown as the number of patients, or median and range. The Mann-Whitney U test was used for comparison of continuous data, and the chi-square test was used for comparison of categorical data. A $p<0.05$ was considered statistically significant. The Hodges-Lehmann estimate of the difference in medians between the 2 groups, 95% confidence intervals (CI) for the differences in medians, and interquartile ranges (IQR) were calculated.

Results. All 40 patients participated in the study since their tracheas could be intubated and no adverse events were observed. The type of surgeries that patients underwent in the 2 groups are shown in **Table 2**. There were no demographic differences between the groups (**Table 2**). In the LBW group, the median LBW was 50 kg. In the CBW group, the median CBW was 74 kg. A comparison of doses, neuromuscular properties, and intubation conditions of the 2 groups are shown in

Table 1 - Calculation, advantages, and disadvantages of weight scalars.

Calculations	Advantages	Disadvantages
Total body weight (TBW)	Easy calculation Proposed dosing for normal weight subjects[12]	May cause overdose and prolonged duration of action in obese patients[9]
Ideal body weight (IBW)		
For female: Height (cm)-106[11]	Shorter duration of action[9,10]	Causes all patients of the same height to receive the same dose[12]
For male: Height (cm)-102[11]		Does not take into account the variation in body composition related to obesity[12] May result in underdosing[12]
Lean body weight		
For female: (9270 × TBW) / (8780 + 244 × BMI)[17]	Correlates with cardiac output[14] Correlates with early distribution kinetics of drugs[14]	May result in underdosing[16]
For male: (9270 × TBW) / (6680 + 216 × BMI)[17]	Correlates with drug clearance[15]	
Corrected body weight		
IBW + (TBW - IBW) × 0.4[11]	Sufficient onset time and peak of action[13]	May cause prolonged duration of action[11]

BMI - body mass index

Table 2 - Demographic data of the 2 groups included in this study.

Parameters	CBW group, n=20	LBW group, n=20	*P*-value
Age, years*	42 (25-64)	43.5 (21-64)	0.55
Body weight, kg*	111.5 (73-140)	105 (85-151)	0.93
Height, cm*	157.5 (145-165)	157 (147-170)	0.82
Body mass index, kg/m²*	45.2 (31.6-57)	45.35 (31.1-59.7)	0.82
Mallampati score, 1:2:3:4	10:4:6:0 (50%:20%:30%)	10:5:5:0 (50%:25%:25%)	0.72
Neck circumference, cm*	40.5 (30-47)	40 (33-47)	0.36
Sterno-mental distance, cm*	15.5 (14-20)	16 (14.5-20)	0.29
Cormack-Lehane grade, 1:2:3:4	11:9:0:0 (55%:45%:0:0)	10:8:2:0 (50%:40%:10%:0)	0.48
BURP maneuver, n (%)	5 (25)	4 (20)	1.00
Type of surgery†	11:2:5:2	9:1:10:0	

*median (range). CBW - corrected body weight, LBW - lean body weight, BURP - backward-upward-rightward pressure of the larynx, †laparoscopic sleeve resection, laparoscopic gastric bypass, laparoscopic cholecystectomy, laparoscopic inguinal hernia repair

Table 3 - Comparison of neuromuscular properties and intubation conditions of patients.

Parameters	CBW group (n=20)	LBW group (n=20)	*P*-value
Intubation dose of rocuronium, mg*	89 (64 - 106)	60 (52 - 75)	<0.01
Onset time, seconds*	50 (20 - 90)	60 (30 - 110)	0.10
Time to reappearance of T1, minutes*	60 (37 - 90)	35 (15 - 70)	<0.01
Conditions for intubation, excellent:good:poor	15:5:0	14:6:0	0.72

*median (range), CBW - corrected body weight, LBW - lean body weight

Table 3. Intubation dose of rocuronium was significantly greater in the CBW group (89 mg) compared with the LBW group (60 mg, $p<0.01$). The median onset time was: 50 s (IQR: 30) in the CBW group; and 60 s (IQR: 30) in the LBW group (difference in median: -10; 95% CI: -30 to 0; $p=0.10$). The median time to reappearance of T1 was different between groups: 60 min (IQR: 12) in the CBW group, and 35 min (IQR: 16) in the LBW group (difference in median 28, 95% CI: 19-37; $p<0.01$). Tracheal intubation was performed at the first attempt in all patients of both groups. Tracheal intubating conditions were excellent or good in all patients, without statistical significance ($p=0.72$). At the end of surgery, neostigmine (2.5 mg) and atropine (one mg) were administered to all patients since none had a TOF ratio ≥90%.

Discussion. We found that in obese patients, a rocuronium dose of 1.2 mg/kg based on both LBW and CBW provided clinically acceptable tracheal intubating conditions 60 s after administration. However, dosing based on LBW resulted in shorter duration of action. Adamus et al[19] showed that the onset time was shorter and the clinical duration of rocuronium was increased in female patients, and claimed that females were more sensitive than males to a single bolus dose of rocuronium. For that reason, our study included only female patients to avoid possible wrong decisions due to gender difference. The RSI is commonly considered standard for anesthesia induction in obese patients since pulmonary aspiration risk increases and an apnea period of even one min may cause hypoxemia.[20] The optimal rocuronium dose for complete neuromuscular blockade at the time of tracheal intubation is 1.2 mg/kg during RSI.[6] Therefore, 1.2 mg/kg is the dose of rocuronium we applied in our study.

The primary endpoint of our study was the duration of action in the 2 groups. Leykin et al[9] studied a rocuronium dose of 0.6 mg/kg based on IBW or TBW in morbidly obese patients, and found that the duration of action was 55.5 min when rocuronium was administered based on TBW, and 22.3 min when based on IBW. On the other hand, Meyhoff et al[11] used a rocuronium dose of 0.6 mg/kg based on IBW or CBW in morbidly obese patients, and found that the duration of action was 21 min when administered based on IBW and 28-31 min when based on CBW. Both studies emphasized that dosing of rocuronium in morbidly obese patients should be based on IBW to avoid prolonged duration of action. In another study[21] of RSI in morbidly obese patients, administration of 1.2 mg/kg rocuronium based on IBW resulted in a duration of action of 52.2 min. We found the duration of action to be 35 min when 1.2 mg/kg rocuronium was administered based on LBW and 60 min when based on CBW, confirming that dosing based on LBW resulted in a shorter duration of action than dosing based on IBW. The difference in results between our study and that of Gaszynski et al[21] using IBW might be because patients were taller in that study compared to our present study, and all patients of the same height received the same dose.

Studies have also been carried out with non-obese patients. Schultz et al[22] studied rocuronium doses and duration of action to be: 0.6 mg/kg - 21 min; 0.9 mg/kg - 33.8 min, and 1.2 mg/kg - 47.7 min in non-obese patients. Magorian et al[6] found durations of action of 37 min at 0.6 mg/kg, and 73 min at 1.2 mg/kg when rocuronium was administered in non-obese patients. It was seen that the duration of action when rocuronium was administered at 1.2 mg/kg based on LBW in obese patients as in our present study was even shorter than the ones when rocuronium was administered 1.2 mg/kg in non-obese patients. The secondary endpoints of our study were onset time and intubation conditions in the 2 groups. Leykin et al[9] observed that the onset time was 77 s when rocuronium (0.6 mg/kg) was administered based on TBW, and 87.5 s when based on IBW. Meyhoff et al[11] observed that the onset time was 85 s when dosing of rocuronium (0.6 mg/kg) was based on IBW, and 80-84 s when based on CBW. However, a rocuronium dose of 0.6 mg/kg results in insufficient onset times (greater than one min), and so may not be appropriate for RSI. Gaszynski et al[21] observed that the onset time was 43.8 s when rocuronium (1.2 mg/kg) was administered based on IBW. In our study, we found the onset time to be 50 s in the CBW group, and 60 s in the LBW group, and both times were suitable for RSI. We found no statistical significance between the groups, but this may be because onset time was our secondary endpoint. Gaszynski et al[21] reported that intubation conditions 60 s after injection of rocuronium were excellent, or good in all but 2 patients. In our study, the trachea was intubated at the first attempt 60 s after administration of rocuronium in all patients, and intubation conditions were excellent or good, meaning clinically acceptable, based on GCRP in all patients in both groups.

Postoperative residual curarization (PORC) can cause postoperative pulmonary complications, such as aspiration, pneumonia, and atelectasis.[23] The incidence of PORC correlates with the duration of action of the neuromuscular blocking agents.[24] Our findings showed that incidence of PORC may be decreased by the use of LBW during RSI in obese patients because the duration of action obtained when rocuronium was administered at 1.2 mg/kg based on LBW in obese patients was close to that for a rocuronium dose of 0.6 mg/kg in non-obese patients.

A limitation of our present study was that supplementary rocuronium injections were performed irregularly. Therefore, we could not evaluate time to T1 recovery to 25% of the control value, or time to a 90% TOF ratio. As a novel finding, rocuronium 1.2 mg/kg based on LBW can be used safely in obese patients during RSI, since the tracheal intubating conditions were clinically acceptable within 60 s after administration, and the duration of action was close to that when 0.6 mg/kg rocuronium was given to non-obese patients. Further studies are needed comparing the neuromuscular properties of rocuronium in adjusted doses based on CBW and LBW on men as the pharmacodynamic behavior of the drug may differ according to gender.

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