Relationship between the muscle relaxation effect and body muscle mass measured using bioelectrical impedance analysis: A nonrandomized controlled trial

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Abstract

Objective: The dose of neuromuscular blocking drugs is commonly based on body weight, but using muscle mass might be more effective. This study investigated the relationship between the effect of neuromuscular blocking drugs and muscle mass measured using bioelectrical impedance analysis.

Methods: Patients who were scheduled for elective surgery using a muscle relaxant were screened for inclusion in this study. Under intravenous anaesthesia, 12 mg or 9 mg of rocuronium was administered to males and females, respectively; and the maximal relaxation effect of T1 was measured using a TOF-Watch-SX® acceleromyograph.

Results: This study enrolled 40 patients; 20 males and 20 females. For both sexes, the maximal relaxation effect of T1 did not correlate with the body weight-based dose of neuromuscular blocking drugs (males, $r^2 = 0.12$; females, $r^2 = 0.26$). Instead, it correlated with the dose based on bioelectrical impedance analysis-measured muscle mass when injected with the same dose of rocuronium (males, $r^2 = 0.78$, female, $r^2 = 0.82$).

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Conclusions: This study showed that the muscle relaxation effect of rocuronium was correlated with muscle mass and did not correlate with body weight when using the same dose. Therefore, a muscle mass-based dose of neuromuscular blocking drugs is recommended.

Introduction

It is important to use the appropriate doses of neuromuscular blocking drugs (NMBDs) during general anaesthesia because the use of an inappropriate dose may cause various problems, such as pressure injury due to the use of a mechanical ventilator, cardiovascular disturbances due to sympathetic nerve stimulation or delayed recovery from anaesthesia due to sustained muscle relaxation.[1] According to several previous studies, the use of NMBDs dosed according to real body weight (RBW) provided poor conditions for tracheal intubation or prolonged its onset time.[2–4] Therefore, some studies concluded that ideal body weight (IBW) is more appropriate for the dosing of NMBDs.[4,5] However, for nonobese patients, overestimation of NMBD dose determined using IBW prolonged the duration of action of NMBDs.[6] Therefore, the dose based on IBW or RBW may not accurately predict the desired muscle relaxation effect of NMBDs.

Neuromuscular blocking drugs are distributed mainly in lean tissues.[7] NMBDs specifically bind to acetylcholine receptors at the neuromuscular junction, a synapse between the skeletal muscle and a motor neuron, and the loss of muscle mass leads to a decrease in the relaxation effect of NMBDs.[7–9] Therefore, muscle mass may be an important factor to determine the effective dose of NMBDs.

There are several methods available for evaluating body composition, such as biopelectrical impedance spectroscopy,[10] magnetic resonance imaging,[11] bioelectrical impedance analysis (BIA)[12] and dual energy X-ray absorptiometry (DXA).[10] Among them, DXA has traditionally been used for measuring body composition and to validate reference methods.[13] However, DXA is not always practical as it has a relatively high cost, is time consuming and involves radiation exposure, which limits multiple measurements or individual use. Unlike DXA, BIA is more practical and a viable alternative for measuring body composition.[14–17] BIA is a relatively easy-to-use, noninvasive, portable, safe and reproducible method for assessing body composition.[12,13] Further, BIA has high test–pretest reliability and accuracy.[14–17] Correlations between BIA and DXA were acceptable for the whole population, including children, adolescents and adults with a body mass index classified as normal, overweight or obese.[14,18–20]

This current study was designed to test the hypothesis that muscle mass measured using BIA may be a better way to calculate the appropriate dose of NMBDs and accurately predicting their effects. Therefore, the primary endpoint of the

present study was to evaluate whether the maximum muscle relaxation effect of NMBDs correlated more closely with muscle mass or RBW. The secondary end-point of this study was to evaluate the elapsed time for which T1 was decreased to 50% and whether this correlated with muscle mass or RBW.

Patients and methods

Patient population

This nonrandomized controlled trial recruited consecutive patients with an American Society of Anesthesiologists physical status of I or II, who were aged 20 to 64 years and were scheduled for elective surgery between January 2016 and May 2016 in the Department of Anaesthesiology and Pain Medicine, Korea University Anam Hospital, Seoul, Republic of Korea. For men, height in the range of 170–175 cm and weight in the range of 70–75 kg; and for women, height in the range of 158–163 cm and weight in the range of 53–58 kg were the inclusion criteria. The height and weight criteria were in line with the standard adult height of the Korean population and the ideal weight for the corresponding height.[21] Patients with a history of neuromuscular disorder, diabetes mellitus, liver function disorder, kidney function disorder, those who were receiving medications known to influence neuromuscular function (e.g. aminoglycosides or phenytoin) and those who were receiving magnesium treatment were excluded.

The study was approved by the Institutional Ethics Committee of Korea University Anam Hospital (no. ED15263). Written informed consent was obtained from all patients. The protocol was registered before starting patient enrolment at clinicaltrials.gov (NCT02617433).

Bioelectrical impedance analysis

All patients fasted for 8 h before BIA and received maintenance doses of fluid. BIA was performed using the InBody 770 body composition analyser (Biospace, Seoul, Republic of Korea) on the day of surgery. The test was carried out by trained research nurses. The InBody 770 body composition analyser has in-built hand and feet electrodes. Patients wore a normal patient gown and were advised to stand barefooted in the upright position with their feet on the feet electrodes on the machine platform and their arms abducted with hands gripping the electrodes on the handles.

Anaesthesia

After BIA, patients received 2 mg of midazolam intramuscularly and were sent to the operating theatre. After applying standard noninvasive monitoring, anaesthesia was induced with remifentanil and propofol using a target-controlled infusion system (Base Primea; Fresenius-Vial, Brézins, France). The targeted effect-site concentration of propofol for induction was $4 \pm 1\,\mu g/ml$ in the Schneider model and $3 \pm 1\,ng/ml$ for remifentanil in the Minto model.[22,23] When the patient lost consciousness, ventilation was applied through a face mask (end-tidal partial pressure of carbon dioxide, 35 to 45 mmHg) with a 50% oxygen–air mixture. Neuromuscular monitoring was then started. The patient's central temperature was monitored using an ear thermometer.

Neuromuscular monitoring

Neuromuscular monitoring was carried out according to international guidelines.[24] The ulnar nerve was stimulated by train of-four (TOF) using a TOF-Watch-SX® accelero-myograph (Organon, Dublin, Ireland). Surface electrodes (3M™ Red Dot™; 3M Health Care, Neuss, Germany) were placed

on cleaned skin over the ulnar nerve proximal to the wrist. The distance between the centres of the two electrodes was kept at 3–4 cm. The piezoelectric probe of the acceleromyograph was attached to the tip of the thumb. The arm was fixed with an armboard and kept in the same position during the study. A temperature sensor, fixed at the distal end of the forearm, ensured that the skin temperature of the monitored arm was maintained at $> 32°C$. In addition, central temperature was maintained $> 35°C$ using warming blankets (3M^{TM} Bair Hugger^{TM}; Arizant Healthcare, Eden Prairie, MN, USA). Data were registered and stored on a computer using TOF-Watch SX® software (version 2.5; Organon).

First, before calibration of the TOF-Guard® unit (Organon), a 5-s and 50-Hz supramaximal tetanic stimulus (250 stimuli) was administered at the ulnar nerve. Previous work has shown that the period required for baseline stabilization is shortened considerably by this procedure.[25,26] Immediately thereafter, the patient's arm and acceleration transducer was repositioned and calibration of T1 was performed. After initial T1 calibration, several additional minutes of TOF stimulation (every 15 s) were allowed for baseline stabilization. A second T1 calibration was performed and 12 mg for males and 9 mg for females of rocuronium (Esmeron®; MSD Korea, Seoul, Republic of Korea) was administered for 5 s. This dose was determined by the ED_{50} of rocuronium.[27,28]

Train of-four is a method of monitoring muscle relaxation, which measures the decrease in magnitude of the first twitch compared with a pre-relaxant stimulus. The T1 value is the first twitch of the TOF over time. To confirm the relationship between muscle mass and the degree of muscle relaxation from NMBDs, the maximal neuromuscular relaxation effect to the T1 value (maximal suppression of T1) and the elapsed time from the injection of rocuronium to the maximal neuromuscular relaxation effect to T1 (elapsed time for which T1 was decreased to 50%) were recorded.[29] Differences in T1 were defined as the following: observed T1 value of first twitch subtracted by the observed twitch height value of T1 when the NMBD effect was at its maximal level. To compare the elapsed time to reach the same degree of muscle relaxation, the elapsed time for which T1 was decreased to 50% was recorded. In patients that showed fewer than three twitches, only T1 was analysed. After completion of the neuromuscular monitoring, surgery was then initiated and anaesthesia was maintained with propofol and remifentanil.

Statistical analyses

All data were analysed using the R statistical software package (version 3.3.2; R Foundation for Statistical Computing, Vienna, Austria) and were reported as mean $\pm$ SD unless otherwise indicated. The sample size was determined based on a previous study that described the suitable sample size for regression analysis.[30] The regression analysis required at least 20 cases per independent variable. In this current study, there was only one independent variable (muscle mass), therefore, 20 patients of each sex were required. We enrolled 22 patients of each sex to account for potential loss of data during the study period. Relationships between muscle mass and the maximal relaxation effect of T1 and the duration of T1 were assessed using the Pearson correlation coefficient. In addition, linear regression analyses were performed. A $P < 0.05$ was considered statistically significant.

Results

This nonrandomized controlled trial initially recruited and screened 22 males and 22
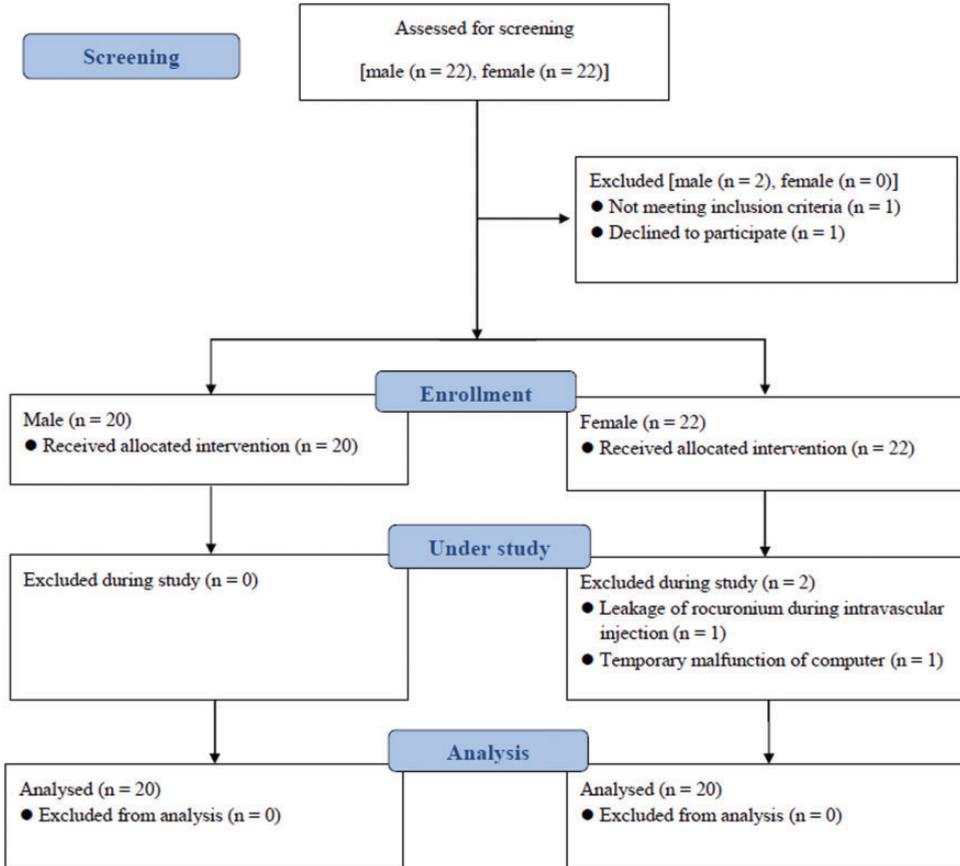
Figure 1. Flow diagram of the progression of patients undergoing elective surgery through this study of the relationship between the muscle relaxation effect and body muscle mass measured using bioelectrical impedance analysis.

females. Two patients of each sex were excluded. One male patient refused to join the study and the other male patient had diabetes mellitus. A female patient was excluded because of leakage of rocuronium during the intravascular injection. The other female patient was excluded because of the temporary malfunction of a computer. A flow diagram of the progression of patients undergoing elective surgery through this study is shown in Figure 1. Data from 40 patients were included in this study. The demographic characteristics and muscle mass of the patients are shown

in Table 1. In this current study, nine patients showed fewer than three twitches, and in these patients only T1 was analysed. The results of TOF-Watch-SX® acceleromyograph are described in Table 2.

Maximal suppression of T1 is presented in Figure 2. For both sexes, the maximal suppression of T1 did not correlate with body weight (males, $r^2 = 0.12$; females, $r^2 = 0.26$); however, it did correlate with measured muscle mass when injected with the same dose of rocuronium (males, $r^2 = 0.78$; females, $r^2 = 0.82$). Therefore, the relaxation effect of rocuronium

showed a strong negative correlation with measured muscle mass using BIA in both groups.

The difference in T1 at different body weights and muscle masses is shown in Figure 3. The difference between the initial and maximal value of T1 did not correlate with body weight (males, $r^2 = 0.07$; females, $r^2 = 0.34$); however, it correlated with measured muscle mass when injected with the same dose of rocuronium (males, $r^2 = 0.78$; females, $r^2 = 0.79$).

The elapsed time for which T1 was decreased to 50% is shown in Figure 4. In male patients, this did not correlate with body weight ($r^2 = 0.04$); however, it did correlate with measured muscle mass ($r^2 = 0.55$) when injected with the same dose of rocuronium. In female patients, the elapsed time

for which T1 was decreased to 50% did not correlate with body weight ($r^2 = 0.17$) or measured muscle mass ($r^2 = 0.04$) when injected with the same dose of rocuronium.

Discussion

This current study has shown that the muscle relaxation caused by rocuronium was not related to RBW when using the same dose of rocuronium. Rather, the muscle relaxation of rocuronium was associated with muscle mass. When the same dose of rocuronium was administered, the effect of maximal muscle relaxation was measured by TOF and showed a correlation with muscle mass. Similarly, the elapsed time for which T1 was decreased to 50% was also correlated with muscle mass rather than with the RBW.

Maximal suppression of T1 means that the maximal effect of NMBD has been reached. In previous studies, T1 was used to demonstrate the effect of muscle relaxation.[30–32] Individual muscle tension data were expressed as the final maximal inhibition of T1 when injecting the same dose of rocuronium (percentage of tension at the final level).[31] This approach allows for an accurate relationship between the relaxation effect of NMBD and muscle mass. Using T1, these current results suggested that the muscle relaxation effect of rocuronium was not correlated with RBW, but instead was associated with muscle mass.

Table 1. Demographic and clinical characteristics of the patients ($n = 40$) who were enrolled in this study of the relationship between the muscle relaxation effect of rocuronium and body muscle mass measured using bioelectrical impedance analysis.

	Males $n = 20$	Females $n = 20$
Age, years	36.70 ± 12.41	52.42 ± 8.55
Height, cm	172.24 ± 2.21	159.56 ± 2.27
Weight, kg	71.90 ± 2.24	55.35 ± 2.27
Muscle mass, kg	32.72 ± 3.74	21.84 ± 1.82

Data presented as mean $\pm$ SD.

Table 2. Measured maximal suppression of T1 and onset time of the patients ($n = 40$) who were enrolled in this study of the relationship between the muscle relaxation effect of rocuronium and body muscle mass measured using bioelectrical impedance analysis.

	Males $n = 20$	Females $n = 20$
Maximal suppression of T1, %	21.40 ± 15.71	27.32 ± 11.88
Difference of T1, %	77.35 ± 16.50	70.00 ± 10.92
Onset time, s	185.55 ± 56.91	213.37 ± 60.07

Data presented as mean $\pm$ SD.

T1, first twitch of the train of-four; difference of T1, difference between initial and maximal effect of T1; onset time, time from end of injection to maximal effect of T1.
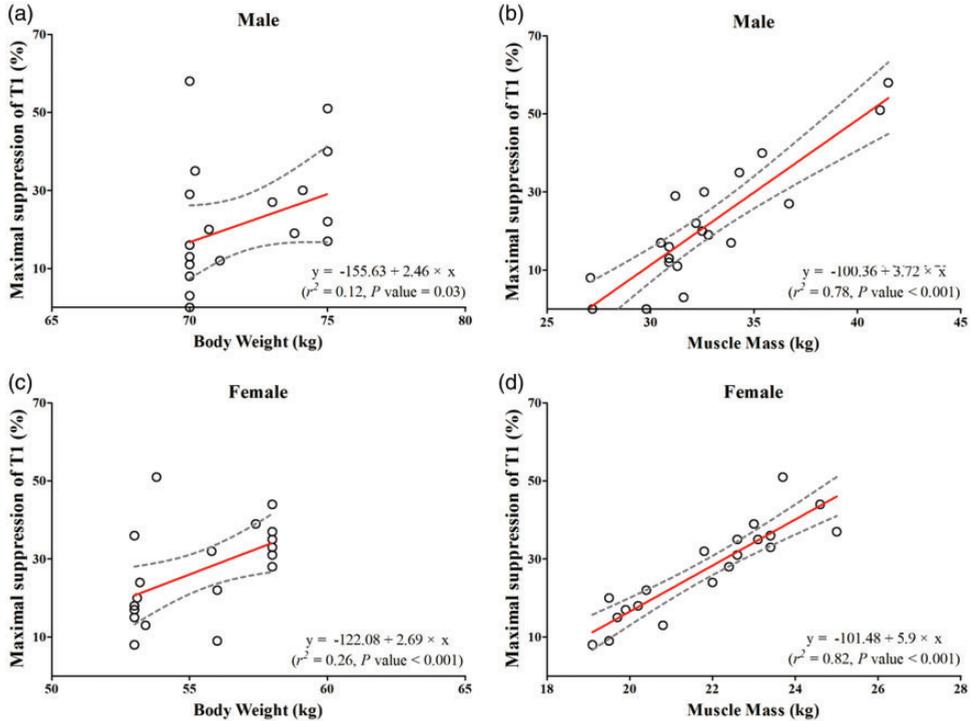
Figure 2. Maximal suppression of T1 at different body weights and muscle masses. (a) Maximal suppression of T1 at different body weights in male patients ($n = 20$) and (b) maximal suppression of T1 at different muscle masses in male patients ($n = 20$). (c) Maximal suppression of T1 at different body weights in female patients ($n = 20$) and (d) maximal suppression of T1 at different muscle masses in female patients ($n = 20$). T1, first twitch of the train of-four. Overlapping data points might result in less than 20 individual points per figure.

When the same rocuronium dose was administered, there was less muscle relaxation when the muscle mass was higher. A previous study also revealed that obese patients with lower muscle mass needed a lower dose of rocuronium.[5] Therefore, it was considered that rocuronium dose calculated using the IBW was more appropriate for adequate anaesthesia.[5]

This current study recorded the elapsed time for which T1 was decreased to 50% because analysing the time to maximum effect can be difficult due to various factors when comparing muscle relaxation. This current study found that the elapsed time for which T1 was decreased to 50% was associated with muscle mass measured using BIA. However, the RBW was not associated with the elapsed time for which T1 to decrease to 50%. Previous studies also showed that rocuronium dosed according to RBW provided a long duration of action in morbidly obese patients.[4,5] The relaxation effect of NMBDs was more than double in the RBW group (55 min) compared with the IBW group (22 min).[6] These findings indicate that the effects of muscle relaxation vary for each calculation method, which means that a new accurate calculation method is needed to provide adequate anaesthesia. In this current study, the muscle mass was measured and
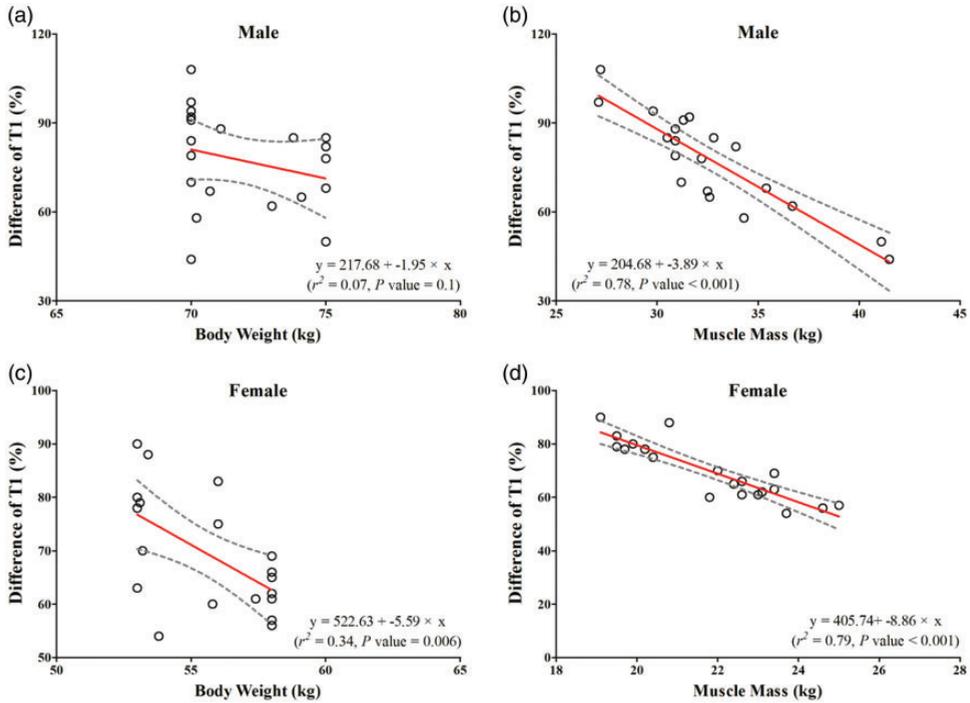
Figure 3. Difference in T1 at different body weights and muscle masses. (a) Difference in T1 at different body weights in male patients ($n = 20$) and (b) difference in T1 at different muscle masses in male patients ($n = 20$). (c) Difference in T1 at different body weights in female patients ($n = 20$) and (d) difference in T1 at different muscle masses in female patients ($n = 20$). T1, first twitch of the train of-four; difference in T1, difference in T1 value from first twitch to maximal stimulation. Overlapping data points might result in less than 20 individual points per figure.

its correlation with the muscle relaxation effect was confirmed.

In female patients, this current study did not find a relationship between muscle mass and the elapsed time for which T1 was decreased to 50%. It is difficult to explain this finding. However, in our opinion, it was not thought to be because of the study setting. This current analysis studied a standard population with minimal comorbidity in a highly standardized anaesthetic setting. Anaesthesia conditions and measurements remained constant because the same equipment and investigators was used throughout the study. Intravenous anaesthetics were used to reduce the potentiation of the muscle relaxation effect of NMBDs by

inhalation anaesthetics. The muscle relaxation effect of rocuronium was evaluated objectively with neuromuscular monitoring. One possible explanation for this finding in female patients is that the differences in muscle mass between individual women was not large enough to show any meaningful results.

In this current study, muscle mass was measured using BIA. Many early research studies on BIA revealed that it was a useful instrument for measuring body composition; however, many did not consider providing an accurate measurement of body composition.[18,33–35] Single-frequency BIA may have problems with its accuracy that result in overestimation of muscle mass in
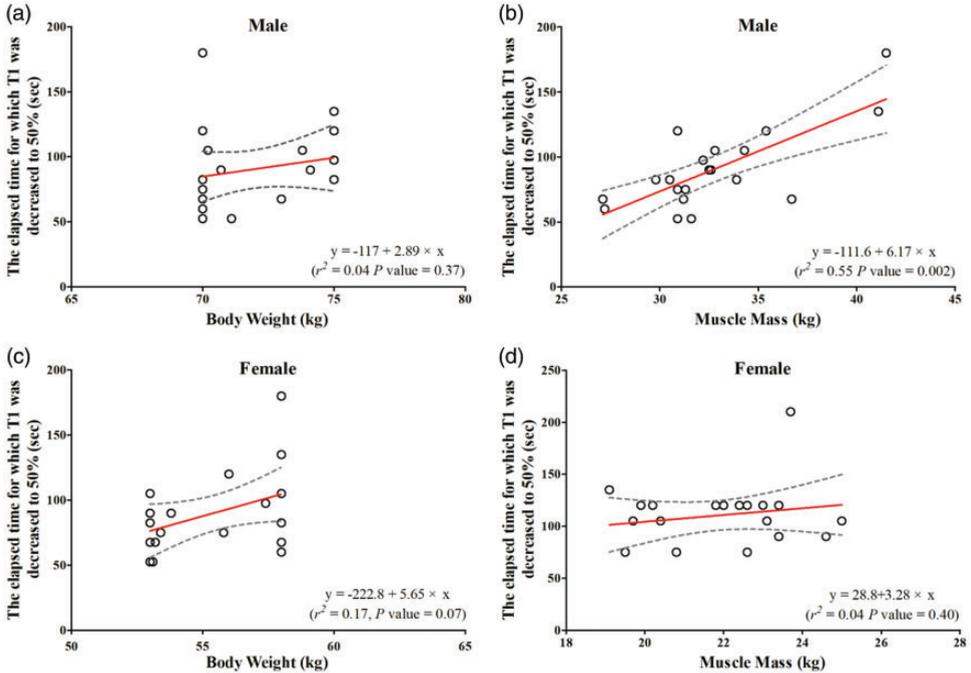
Figure 4. The elapsed time for which T1 was decreased to 50% at different body weight and muscle mass. (a) The elapsed time for which T1 was decreased to 50% at different body weight in male patients ($n = 20$) and (b) the elapsed time for which T1 was decreased to 50% at different muscle mass in male patients ($n = 20$). (c) The elapsed time for which T1 was decreased to 50% at different body weight in female patients ($n = 20$) and (d) The elapsed time for which T1 was decreased to 50% at different muscle mass in female patients ($n = 20$). T1, first twitch of the train of-four; the elapsed time for which T1 was decreased to 50%, duration from first twitch of T1 to decrease by 50%. Overlapping data points might result in less than 20 individual points per figure.

men and underestimation or overestimation of muscle mass in women.[36,37] However, technological improvements in recent years have made BIA a more reliable and more acceptable way of measuring body composition.[35] Multi-frequency BIA devices like the InBody 770 body composition analyser may have several advantages over previous single-frequency BIA devices. For example, a study in healthy young adults observed that there were no differences between BIA and DXA in fat mass comparison; furthermore, a slight overestimation using BIA in men may be considered physiologically acceptable.[35] A previous study showed that BIA is a valid method to estimate body composition, including muscle mass, in adults classified as having a normal body weight.[18] BIA accurately assessed changes in body composition with weight loss and provided superior cross-sectional estimates of body composition compared with DXA.[20] Therefore, muscle mass measured using BIA was sufficient to elucidate the relationship between muscle mass and the effect of NMBDs, as shown in this current study.

There were several limitations in the present study. Clinically, ED_{95} and ED_{50} are widely used by researchers to study the effects of drugs. In particular, ED_{95} is useful for determining the dose of NMBD

(e.g. for tracheal intubation). The degrees of muscle relaxation using TOF is expressed in three ways (i.e. %, count or 0), which made it difficult to compare between groups. In addition, the TOF count with a higher dose of rocuronium sometimes became zero within 1 min after injection. This time period is too short to detect differences between groups because TOF stimulation is repeated every 15 s. Accordingly, this may have reduced the chance of detecting differences when using a higher dose of rocuronium (i.e. ED_{95}). Therefore, the current study decided to use ED_{50} in this first trial to determine the dose of rocuronium and whether the effect of rocuronium was associated with muscle mass. Thus, further research may be needed to investigate the effect of ED_{95}.

In conclusion, the relaxation effects of rocuronium may be associated with muscle mass measured using BIA. In addition, the demand for rocuronium may be increased as muscle mass increases. Therefore, dosing of rocuronium based on muscle mass rather than RBW may be a better option for accurate estimation of muscle relaxation and, ultimately, patient safety.

Author contributions

Conceptualization: Kim YH, Choi YJ, Lee YS. Data curation: Bae GE, Yu JH, Yoon SZ, Kang HW, Lee KS, Kim JH. Formal analysis: Kim YH, Choi YJ, Bae GE, Yu JH, Yoon SZ, Kang HW, Lee KS, Kim JH, Lee YS. Writing, original draft: Kim YH, Choi YJ, Lee YS. Writing, review and editing: Kim YH, Choi YJ, Lee YS, Kang HW.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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