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Half-dose sugammadex with neostigmine versus full-dose sugammadex for reversal of rocuronium in laparoscopic bariatric surgery

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Abstract

Background: Sugammadex reverses rocuronium more effective than neostigmine during deeper neuromuscular blockade levels. Relying upon the high cost of sugammadex we hypothesized that combined neostigmine with half-dose sugammadex (1.2 mg/kg) would be as effective as the full dose (2.4 mg/kg IBW) in reversing rocuronium-induced deep neuromuscular block in obese patients. A multimodal approach would be an effective cost saving strategy, while preserving the advantages of this novel agent.

Patient and methods: A prospective randomized study done on 50 morbid obese patients undergoing elective laparoscopic sleeve gastrectomy operation. Patients were allocated into two groups each of 25. Group NS received sugammadex 1.2 mg/kg and neostigmine 50 μg/kg with atropine 20 μg/kg. Group S received sugammadex 2.4 mg/kg and 10 mL of normal saline.

Primary outcome: Interval between administration of reversal and reaching TOF of 90%.

Secondary outcomes: Total dose of rocuronium (mg), duration between last dose rocuronium and reverse, number of patients reached TOF of 90% within 5 min, duration between IV reversal and extubation, and the number of patients with residual neuromuscular blockade.

Results: Number of patients who reached TOF 90% within 5 min, the interval between reversal and 90% TOF, the interval between reversal and extubation were comparable between the study groups.

Conclusion: As regards neuromuscular blocker reversal in obese patients, the neostigmine 50 μg/kg plus sugammadex half dose (1.2 mg/kg) is as effective as full-dose sugammadex (2.4 mg/kg) alone.

Trial registration: Institutional Research Board: (IRB code number): MS/17.12.195 on 16 January 2018.

Keywords: Sugammadex, Neostigmine, Morbid obese, Laparoscopic sleeve gastrectomy, Rocuronium

Background

The global age-standardized prevalence of obesity nearly doubled from 6.4% in 1980 to 12.0% in 2008. Half of this rise occurred in the 20 years between 1980 and 2000, and half occurred in the 8 years between 2000 and 2008 (Stevens et al., 2012). Laparoscopic sleeve gastrectomy (LSG) is an innovative approach to the surgical management of morbid obesity (Shi et al., 2010). There is recent trend in the literature that advocates for the maintenance of deep levels of muscle relaxation till the end of surgery, mainly in laparoscopic surgery, for better surgical conditions and outcome (Dubois et al., 2014).

Despite supplemental oxygen therapy, morbidly obese subjects, with or without obstructive sleep apnea (OSA), experience frequent oxygen desaturation episodes post-

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operatively, suggesting that perioperative management strategies in morbidly obese patients undergoing laparoscopic bariatric surgery should include measures to prevent post-operative hypoxemia including adequate reversal of neuromuscular blockade (Ahmad et al., 2008). Rocuronium bromide is a non-depolarizing muscle relaxant with a rapid onset of activity, used in modern anesthesia to facilitate endotracheal intubation by providing skeletal muscle relaxation. It is used for both standard endotracheal intubation and rapid sequence induction (RSI) (Perry et al., 2008).

Neostigmine is used to reverse the effects of non-depolarizing muscle relaxants such as rocuronium at the end of surgeries, provided that recovery criteria are fulfilled. It binds to the active sites of acetyl cholinesterase enzyme so the enzyme can no longer break down the acetylcholine molecules allowing for its accumulation at the post-synaptic membrane and activation of its receptors (Howland et al., 2006). It has a moderate duration of action, usually 2 to 4 h. Sugammadex is a new reversal agent that works differently than cholinesterase inhibitors. It binds with high affinity to rocuronium in the blood forming very tight water-soluble complexes, decreasing its plasma concentration and creating a concentration gradient between the plasma and the neuromuscular junction. This process results in movement of rocuronium molecules from neuromuscular junction back into plasma results in rapid recovery from the neuromuscular blockade (Naguib, 2007).

Sugammadex, if given in appropriate doses, has the ability to reverse the neuromuscular blocking effect of rocuronium more rapidly and effectively than neostigmine, especially from deeper levels of neuromuscular blockade (NMB) (Della Rocca et al., 2013). It also has been shown that within 5 min, 98% of patients would recover a train of four (TOF) ratio of 0.9 from a moderate rocuronium blockade with sugammadex versus only 11% of patients with neostigmine (Blobner et al., 2010).

However, the high cost of this drug is prohibitive and is a significant limitation for its routine use in many institutions, especially when relatively high doses are required (Kopman & Naguib, 2015). Combination of neostigmine 50 μg/kg and sugammadex 2 mg/kg is less effective than sugammadex 4 mg/kg, as regards patients who achieved full recovery from rocuronium-induced deep NMB within 5 min in non-obese patients (BMI < 35) (Aouad et al., 2017). Regarding the high cost of sugammadex, multimodal reversal approach would be an effective cost-saving strategy, while preserving the advantages of this novel agent. The ED90 of sugammadex was proved to be 2.4 mg/kg (Silva et al., 2017). Elective laparoscopic sleeve gastrectomy (LSG), the greater curvature, and the stomach fundus vertical resection parallel to the lesser curvature. The principle of LSG is to lead food from the esophagus to the antral part and directly into the duodenum. Despite that LSG was previously considered not only a restrictive procedure but also enhance weight loss by producing anorexia through the removal of the ghrelin-producing cells from the gastric fundus (Sippey et al., 2016).

We hypothesized that the combination of neostigmine with half-dose sugammadex (1.2 mg/kg of ideal body weight (IBW) would be as effective as the full dose (2.4 mg/kg IBW) [119] in reversing rocuronium-induced deep NMB in obese patients.

Aim of the work is to create a cheaper effective multimodal muscle relaxant reversal strategy in morbid obese patients by comparing the effectiveness of half dose of sugammadex 1.2 mg/kg and neostigmine 50 mic/kg and full dose of sugammadex 2.4 mg/kg ideal body weight in *morbid obese patients* as regards interval between administration of reversal and reaching 90% on TOF as the primary outcome.

Procedure

Methods

This is a prospective, randomized, double-blinded, controlled study conducted over a year starting at 20 January 2018 in Mansoura Gastroenterology Center (GEC). After approval from the institutional research board (IRB)-code number: MS/17.12.195 on 16 January 2018, Faculty of Medicine, Mansoura University. This present study included 50 patients who were ASA II–III, of both sexes, aged 18–65 years, and all were morbid obese (BMI > 35), underwent elective laparoscopic sleeve gastrectomy operation. All patients were interviewed and written informed consents were obtained from them. Patients were excluded from the study according to the following criteria: patient refusal, pregnancy or breastfeeding, renal dysfunction defined as creatinine > 1.2 mg/dl, known hepatic disease, allergy to rocuronium or sugammadex, and patients receiving medications known to interfere with the neuromuscular transmission and neuromuscular diseases.

Randomization

Patients were randomly allocated by a computer-generated randomization table, and group assignments were concealed in sealed opaque envelopes into 2 equal groups: study group (NS) (25 patients): patients received sugammadex and neostigmine with atropine, control group (S) (25 patients): patients received sugammadex with normal saline. All drug dosing was according to the ideal body weight.

Anesthetic management

All patients were assessed pre-operatively for medical history, physical examination, and laboratory evaluation

(complete blood picture, coagulation profile, liver function and renal function tests). All patients were premedicated with intramuscular midazolam (0.05 mg/kg) 30 min before anesthesia. On the patient's arrival to the operative theater standard monitoring connected (ECG, non-invasive blood pressure measurement, and pulse oximetry) then an 18–20 G peripheral venous cannula was inserted. The anesthesiologist involved in the performance of the study was blinded to group allocation. After patient enrollment that matches inclusion and exclusion criteria, patients were allocated into one of two groups: neostigmine plus sugammadex group (group NS) received sugammadex 1.2 mg/kg (Bridion 2 ml vial 100 mg/ml MSD company) and neostigmine 50 μg/kg with atropine 20 μg/kg. The sugammadex group (group S) received sugammadex 2.4 mg/kg and 10 mL of normal saline (all drugs were given according to the ideal body weight).

General anesthesia was induced by IV lidocaine 1.5 mg/kg, IV fentanyl 100 mic, and propofol in a dose of 2 mg/kg and the ulnar nerve was stimulated supramaximally with repetitive train of four (TOF) stimuli. After TOF monitor calibration, IV rocuronium 0.6 mg/kg was administered. Patients were intubated after sixty seconds and ventilated with 40% O2 in air.

Maintenance of anesthesia was achieved using isoflurane. Depth of the NMB was monitored by TOF electrodes attached to the proximal medial aspect of the forearm along the ulnar nerve. The hand was lying freely on the arm board and kept warm by using a forced-air warming blanket. Rocuronium was given by incremental boluses of 10 mg to maintain deep NMB (TOF count = 0) till the end of surgery. An anesthetist not included in patient care randomly assigned patients to one of two groups according to computer generated table of random numbers. The group assignment was kept in opaque sealed envelopes which were opened sequentially before study drug administration. Study drugs were drawn in two separate syringes, were diluted to a total volume of 10 ml with normal saline, and were labeled with the randomization number.

The anesthesiologist collecting the data and administering the reversal was blinded to group allocation. At the end of surgery, patients in group NS received sugammadex 1.2 mg/kg and neostigmine 50 μg/kg with atropine 20 μg/kg, and patients in group S received sugammadex 2.4 mg/kg and 10 ml of normal saline. For a better assessment of the muscle relaxant recovery profile in both groups, we divided the studied patients into two categories according to the time between the last dose of muscle relaxant and the time of reversal; less than 15 min and more than 15 min then recovery profile was compared in both categories. The times from reversal administration to 90% recovery of TOF ratio, and to extubation was recorded. The number of patients who recovered 90% TOF ratio within 5 min, systolic blood pressure (SBP), and heart rate (HR) before, after 1 and 5 min of reversal administration were recorded. Patients who did not achieve 90% TOF ratio recovery within 10 min from study drug administration were identified as patients with residual blockade (for those patients, it was planned to proceed with unbinding and to supplement with additional sugammadex 2 mg/kg for patients in group NS). In the post-anesthesia care unit (PACU), the reoccurrence of signs of residual neuromuscular blockade (rNMB) including nystagmus, laryngospasm, weakness, inability to sustain head lift, uncoordinated movements, or desaturation (SpO2 < 94%) were monitored by one of the investigators who were blinded to group allocation. All patients were observed for at least one hour following which they were discharged if they met standard discharge criteria.

Post-operative assessment

Patients were discharged from PACU only when they reached an Aldrete score of 10 (i.e., when they were able to move all extremities in response to a request, able to breathe deeply and cough freely, stable systemic blood pressure [± 20% of pre-anesthetic level], fully awake, and had oxygen saturation > 94% while breathing room air). Any post-operative side effects, e.g., nausea, vomiting, bradycardia, hypotension, excessive sedation, hallucination, nightmares, or diplopia were recorded. Patients who experienced nausea or vomiting received ondansetron 4 mg IV as a rescue antiemetic.

Outcome variables

Primary outcome

The interval between administration of reversal and reaching TOF of 90%.

Secondary outcome

Total dose of rocuronium (mg), duration between last dose rocuronium and reverse, number of patients reached 90% TOF within 5 min, duration between IV reversal and extubation, and the number of patients with residual neuromuscular blockade (defined as TOF less than 0.9 within 10 min). Muscle relaxant recovery profile in both groups also for patients who received reversal within less and more than 15 min after the last dose of rocuronium. Hemodynamics: blood pressure and heart rate [before reversal, after 1 min, after 5 min]. Blood gases variables: PH, PaO2 (mmHg), PaCO2 (mmHg), and SaO2 (%) at [Basal, at PACU, 3 h post-operatively].

A sample size calculation using power analysis and sample size software program (pass) version 15.0.5 for Windows (2017) with the interval between administration of reversal and reaching 90% on TOF as the primary

outcome. The alternate hypothesis relayed up on the effect size and was considered as the absence of difference between treatment modalities used in both of the study groups, regarding the interval between administrations of reversal and reaching 90% on TOF (non-inferiority design). To the best of our knowledge, no previous studies were conducted using the after mentioned drug combinations in morbidly obese patients with BMI ≥ 35 and only one study was conducted by Aouad M etal. (2017) (Aouad et al., 2017) on normal BMI non-obese population, so we used an effect size of 0.45 for sample size calculation. A non-inferiority margin of 0.45 was set as the target similarity between the study groups. A sample size of 21 patients in each group is needed to achieve 80% power (1-β or the probability of rejecting the null hypothesis when it is false) in the proposed study using one-sided, two-sample *t* test with a significance level (α or the probability of rejecting the null hypothesis when it is true) of 5%. The coefficients of variation of both groups are assumed to be 0.5, a 20% drop-out is expected, so a total of 25 patients will be enrolled in each group.

Statistical analysis

IBM's SPSS Statistics (statistical package for the social sciences) for Windows (version 25, 2017) was used for statistical analysis of the collected data. Shapiro-Wilk test was used to check the normality of the data distribution in continuous variables. Continuous variables were expressed as mean and standard deviation while categorical ones were expressed as number and percentage. Independent samples *t* test and Mann-Whitney independent samples test were used to compare normally and abnormally distributed continuous variables with no follow-up readings respectively. For longitudinal data (follow-up data), repeated measures ANOVA or generalized linear models were used according to the fulfillment of their hypotheses. Fisher exact test was used for intergroup comparison of nominal and ordinal data using the crosstabs function. Comparison of follow-up and basal values (intra-group) was conducted using Wilcoxon signed ranks test and McNemar test for ordinal and nominal data respectively. All tests were conducted with a 95% confidence interval. Charts were generated using SPSS' chart builder. *P* (probability) value < 0.05 was considered statistically significant.

Results

For the 55 patients enrolled, 50 patients completed the study protocol. Two patients refused surgery, and three patients did not fulfill the inclusion criteria as shown in the study flow chart (Fig. 1). Patient characteristics were comparable between the two groups (Table 1).

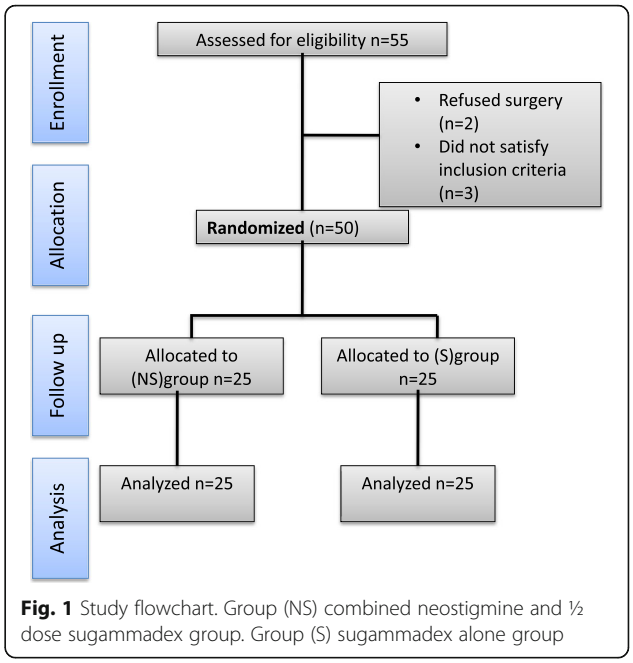

Fig. 1 Study flowchart. Group (NS) combined neostigmine and ½ dose sugammadex group. Group (S) sugammadex alone group

We found no statistically significant difference between NS group and S sugammadex in the duration of surgery, anesthesia and end tidal isoflurane concentration at the end of the surgery, total dose of rocuronium and interval between the last dose of rocuronium and reverse (Table 2).

The number of patients who reached TOF of 90% within 5 min, the interval between reversal and TOF of 90%, the interval between reversal and extubation were comparable between the two groups with *P* value 0.26, 0.15, and 0.07, respectively (Table 3).

The interval between reversal administration and 90% TOF and interval between reversal administration and extubation were significantly higher in NS groups with *P* value 0.4 in patients who received reversal within less than 15 min of the last dose of rocuronium. However, there was no significant difference in recovery profile of both groups in patients who received within more than 15 min after the last dose of rocuronium (Table 4).

In regard to heart rate and systolic blood pressure, before reversal, after reversal administration by 1 min and 5 min, there was statistically significant increase in heart rate after 1 min (75.12 ± 13.12) in NS group compared to 64 ± 14.69 in S group with *P* value 0.007; otherwise, no statistically significant difference between the two groups (Table 5). Comparison of arterial PH, oxygen saturation, oxygen tension, and carbon dioxide tension levels in the studied groups showed no significant difference in between the study groups (Table 6).

Table 1 Demographic data of the studied groups

Variable	NS group (n = 25)	S group (n = 25)	95% CI of mean difference	P value
Age (year)	31.7 ± 7.4	34 ± 11.1	-7.6 , 3.1	0.45[a]
BMI (kg/m^2)	38.9 ± 7.1	42 ± 7.5	-7.2 , 1.1	0.13[a]
Ideal weight (kg)	59.7 ± 5.7	62.4 ± 7.8	-6.6 , 1.1	0.14[b]
Sex				
Male	1 (4%)	6 (24%)	0.02 , 0.38	0.1[c]
Female	24 (96%)	19 (76%)		

Data are expressed as mean and standard deviation or a number and (percentage). 95% CI: 95% confidence interval. [a]Mann Whitney independent samples test, [b]independent samples t-test, [c]Chi square test. *p is significant when ˂ 0.05. *Abbreviations*: *BMI* body mass index, *KG* kilogram, *M*^{2} square meter, *n* number, *group (NS)* half dose sugammadex plus neostigmine, *group (S)* full dose sugammadex group

Discussion

This double blind prospective randomized study was designed to evaluate the effectiveness of half dose of sugammadex 1.2 mg/kg and neostigmine 50 μg/kg compared to full dose of sugammadex 2.4 mg/kg in obese patients as regards interval between the administration of reversal of muscle relaxant and reaching 90% on TOF. In our study, combined half-dose sugammadex (1.2 mg/kg) with neostigmine 50 μg/kg was non-inferior to full-dose sugammadex (2.4 mg/kg) alone regarding the time interval from giving the reversal till reaching TOF of 90% (334.1 s ± 99.8 s in NS sugammadex with neostigmine group compared to 294.1 s ± 95.0 s S group). The interval from giving reversal to extubation is comparable between the two groups. No recurarization was discovered in PACU.

Applying half dose of sugammadex (1.2 mg\kg of IBW) to reverse a deep level of neuromuscular blockade brought the patient to a more shallow levels of block and the residual blockade was efficiently reversed by neostigmine. Calvey et al. (1979) (Calvey et al., 1979) documented that neostigmine might take up to 15 min to reach its peak effect which considered a major disadvantage in comparison with speed of sugammadex. This advantage of sugammadex was not lost in NS group since approximately 90% of patients reached full recovery within 5 min. Moreover, the onset of neostigmine is after 2 min despite the full effect might take up to 15 min.

Taking into consideration the high cost of sugammadex, this study showed that using half dose of sugammadex with neostigmine may be more economic compared to full dose of sugammadex, especially in busy operating rooms in tertiary centers through use of less quantities of sugammadex. Sugammadex antagonize rocuronium blockade in a dose-dependent relationship (Pühringer et al., 2010), reach full recovery faster than neostigmine (Blobner et al., 2010).

As regards time interval from giving reversal and to reach TOF of 90% and in line with our results, Aouad M and colleagues (Aouad et al., 2017) randomly allocated patients to receive sugammadex 4 mg/kg versus sugammadex 2 mg/kg with neostigmine 50 μg/kg and glycopyrrolate 10 μg/kg (group NS) as reversal of rocuronium deep NMB in non-obese patients. Aouad found no statistical difference between both groups as regards the time to achieve TOF of 90% which was 180.9 ± 96.8 s in group S and 228.2 ± 83.9 s in group NS, the shorter time could be attributed to higher doses of sugammadex as it works in a dose-dependent manner.

Another supporting study done by Cheong et al. 2015 (Cheong et al., 2015) compared the time to TOF of 90%

Table 2 Duration of surgery, duration of anesthesia, end tidal isoflurane concentration at the end of the surgery, total rocuronium dose and the interval between the last dose and reverse

Variable	NS group (n = 25)	S group (n = 25)	95% CI of mean difference	P value
Surgery Duration (minutes)	106.6±12.7	113.8±29.4	-20.3,5.8	0.15[a]
Anesthesia Duration (minutes)	113.5 ± 12.3	120.8 ± 28.9	-19.9, 5.4	0.14[a]
Et- isoflurane Conc. at the end of surgery (%)	1.33 ± 0.31	1.29 ± 0.37	-0.18, 0.22	0.92[a]
Total dose of Rocuronium (mg)	88 ± 11.1	90.2 ± 22.3	-12.2, 7.8	0.66[b]
D.LRO-Rev. (minutes)	14.1 ± 7.74	15.12 ± 7.67	-5.41, 3.36	0.64[b]

Data are expressed as mean and standard deviation. 95% CI: 95% confidence interval. [a]Mann Whitney independent samples test, [b]Independent samples t-test. *p is significant when ˂ 0.05. *Abbreviations*: *Et* End tidal, *Conc.* Concentration, *D.LRO-Rev.* Duration between last dose rocuronium and reverse, *group (NS)* half dose sugammadex plus neostigmine, *group (S)* full dose sugammadex group

Table 3 Muscle relaxant recovery profile in both groups

Variable	NS group (n = 25)	S group (n = 25)	95% CI of mean difference	P value
P.NO- 90% TOF within 5 minutes	10 (40%)	15 (60%)	-0.07,0.47	0.26[a]
D. R - 90% TOF (seconds)	334.1 ± 99.8	294.1 ± 95.0	-15.4, 95.4	0.15[b]
D. R-Extubation (seconds)	426.2 ± 98.5	376 ± 90.4	-3.6, 103.9	0.07[b]

Data are expressed as mean and standard deviation. 95% CI: 95% confidence interval. [a]Mann Whitney independent samples test, [b]independent samples t-test. *p is significant when ˂ 0.05.
All the patients reach 90% TOF ratio before 10 minutes after reverse administration in both groups
No signs of residual blockade were documented in PACU in both groups
Abbreviations: *group (NS)* half dose sugammadex plus neostigmine, *group (S)* full dose sugammadex group. *P.NO- 90% TOF within 5 minutes* Number of patients reached 90% TOF within 5 minutes, *D. R - 90% TOF (seconds)* Duration between IV reversal and 90% TOF (seconds), *D. R-Extubation*, Duration between IV reversal and extubation

recovery in 4 reversal groups: sugammadex 2 mg/kg (S2), sugammadex 1 mg/kg (S1), sugammadex 1 mg/kg + neostigmine 50 μg/kg (SN) and neostigmine 50 μg/kg alone (N) and found that group SN showed significantly shorter recovery time than group S1 and N in similarity to our study results. Furthermore, the recovery time from moderate NMB of 183 s in group S2 and 204 s in group SN were shorter than the recovery times from deep NMB in our study (294.1 s ± 95.0 s in group S and 334.1 s ± 99.8 s in group NS) that may be attributed to our deeper blockade levels in our study and also to the less total amount of rocuronium in the previous study.

Furthermore, and in accordance to our study, Kakinuma et al. 2013 (Kakinuma et al., 2013) proved that the combined use of sugammadex and neostigmine was more effective than the use of sugammadex alone in the setting of profound neuromuscular blockade induced by rocuronium. In Kakinuma study, sugammadex 1 mg/kg were administered in the control group and sugammadex 0.5 mg/kg and neostigmine 40 μg/kg were administered in the experimental group 5 min after administration of rocuronium 0.6 mg/kg. The time to TOF of 90% recovery was 29.9 ± 7.5 min in the control group and 18.8 ± 8.9 min in the experimental group.

Table 4 Muscle relaxant recovery profile in both groups for patients who received reversal within less and more than 15 minutes after the last dose of rocuronium

Variable	NS group (n = 12)	S group (n = 13)	95% CI of mean difference	P value
Anesthesia Duration				
< 15 minutes	108.25±12.66	115.43±26.12	-24.3 , 9.9	.39[a]
>15minutes	118.38±10.13	126.58±31.82	-27.4,11	.39[a]
Surgery Duration				
< 15 minutes	100.8 ± 12.56	108.6 ± 26.44	-25.1, 9.6	0.36[a]
>15minutes	112 ± 10.6	119.6 ± 32.5	-27.2, 12.1	0.41[a]
Et- isoflurane Conc. at the end of surgery				
< 15 minutes	1.34±.32	1.53±.28	-0.44,0.05	0.12[a]
>15minutes	1.49±0.29	1.28±0.36	-0.06 , 0.5	0.12[a]
Total dose (mg)				
< 15 minutes	82.5±9.89	91.92±26.89	-26.4,7.6	0.26[a]
>15minutes	93.08±9.9	88.33±16.97	-7.1,16.6	0.41[a]
D. R - 90% TOF (seconds)				
< 15 minutes	385.1 ± 74.9	307.1 ± 97.1	5.8 , 150.1	0.04[*,a]
>15minutes	287 ± 98.9	280 ± 94.7	-73.2, 87.3	0.89[a]
D. R-Extubation (seconds)				
< 15 minutes	472.0 ±78.6	384.7 ± 99.0	12.9, 161.7	0.04[*,a]
>15minutes	384 ± 98.5	366.6 ± 83.3	-58.5 , 93.1	0.65[a]

Data are expressed as mean and standard deviation. 95% CI: 95% confidence interval. [a]Mann Whitney independent samples test. [*]p value is significant when ˂ 0.05. *Abbreviations*: *group (NS)* half dose sugammadex plus neostigmine, *group (S)* full dose sugammadex group, *Et* End tidal, *Conc.* Concentration, *D.R - 90% TOF* duration (seconds) between IV reversal and 90% TOF, *D.R-Extubation* Duration between IV reversal and tracheal extubation

Table 5 Hemodynamic comparison before and after administration of reversal: HR&SBP

Variables		NS group (n = 25)	S group (n = 25)	95% CI of mean difference	P value
HR	**Before reversal**	65.36 ± 12.13	59.48 ± 13.03	-13.04; 1.28	0.11[a]
	After 1 minute	75.12 ± 13.20	64.00 ± 14.69	-19.06; -3.18	0.007*[,b]
	After 5 minutes	71.24 ± 18.25	68.08 ± 20.17	-14.10; 7.78	0.56[b]
SBP	**Before reversal**	124.48 ± 11.50	118.56 ± 21.75	-15.82; 3.98	0.24[b]
	After 1 minute	128.44 ± 19.33	121.72 ± 18.54	-17.49; 4.05	0.22[b]
	After 5 minutes	130.52 ± 29.46	127.64 ± 15.47	-16.26; 10.50	0.67[b]

Data are expressed as mean and standard deviation. 95% CI: 95% confidence interval
Abbreviations: *group (NS)* half dose sugammadex plus, *group (S)* full dose sugammadex group, *HR* Heart rate, *SBP* systolic blood pressure. [a]Mann Whitney independent samples test, [b]Independent samples t-test. *p is significant when < 0.05

However, the results of this study are difficult to extrapolate into clinical anesthesia, given that the dosage of sugammadex was too small despite profound neuromuscular blockade.

Our study showed that number of patients reached 90% TOF at 5 min was 40% in half-dose group and 60% in full-dose group compared to Aouad and his colleagues (Aouad et al., 2017) 89% and 96% respectively which can be explained that they used higher doses than doses we used.

In this present study, there was no significant difference in both groups as regards interval between giving reverse and extubation; 426.2 ± 98.5 s in NS, 376 ± 90.4 s in S group in agreement with Aouad M. and his colleagues (Aouad et al., 2017) who found that time from giving reversal drug to extubation was 504 ± 186 s in group S and 544 ± 176 s in group NS, Aouad attributed this delay occurred during recovery phase to dexmedotomidine.

This present study proved that in patients who received reversal within less than 15 min after the last dose of rocuronium there was significant increase in both the time interval between reversal and reaching 90% TOF and time interval between IV reversal and extubation at the end of operation in group NS compared to group S while this statistical difference disappeared in patients who received reversal within more than 15 min after the last dose of rocuronium.

On the other hand, Cammu et al. 2017 (Cammu et al., 2017) reversed rocuronium in 18 volunteers subdivided into three groups: group N received 50 μg/kg neostigmine, group S received 2 mg/kg sugammadex, and group NS received 50 μg/kg neostigmine plus 2 mg/kg sugammadex 3 min later. Cammu concluded that electro-myographic activity of the diaphragm and surface electromyogram on the intercostal muscles were increased after sugammadex alone compared with neostigmine but adding sugammadex after neostigmine reduced

Table 6 Comparison of arterial PH, Oxygen saturation Oxygen tension and carbon dioxide tension levels in the studied groups

Variables		NS group (n = 25)	S group (n = 25)	95% CI of mean difference	P Value
PH	Basal	7.38 ± 0.02	7.36 ± 0.01	-0.002, 0.015	0.12
	At PACU	7.34 ± 0.08	7.31 ± 0.02	-0.026, 0.027	1
	Three hours post-operatively	7.37 ± 0.03	7.36 ± 0.01	-0.007, 0.013	0.59
PaO2 (mmHg)	Basal	88.1 ± 4.2	88 ± 3	-2, 2.1	0.97
	At PACU	177.6 ± 33.3	178.3 ± 15.2	-15, 13.8	0.93
	Three hours post-operatively	91.2 ± 4.1	89.7 ± 3.1	-0.5, 3.6	0.13
$PaCO_2$ (mmHg)	Basal	35.9 ± 3	36.7 ± 2.7	-2.4, 0.8	0.32
	At PACU	37.6 ± 3.7	39.6 ± 3.8	-4.2, 0.8	0.06
	Three hours post-operatively	34.4 ± 3.1	34.8 ± 2.8	-2.1, 1.3	0.6
SaO2%	Basal	96.9 ± 1.2	97 ± 1.3	-0.86, 0.54	0.65
	At PACU	98 ± 1.1	97.6 ± 1.4	-0.31, 1.1	0.26
	Three hours post-operatively	97.4 ± 1.2	97.4 ± 1.4	-0.71, 0.79	0.92

Data is expressed as mean and standard deviation. 95% CI: 95% confidence interval. *Abbreviations*: *group (NS)* half dose Sugammadex plus neostigmine, *group (S)* full dose sugammadex group. All drug dosing was according to the ideal body weight. *PaO2* arterial Oxygen tension, *PaCO2* arterial carbon dioxide tension, *SaO2* arterial Oxygen saturation, *PACU* post anesthesia care unite. p is significant when < 0.05

the electro-myographic activity of the diaphragm compared with sugammadex alone. Unlike the diaphragm, intercostal EMG was preserved with neostigmine followed by sugammadex and could be attributed to neostigmine early injection prior sugammadex by 3 min that would produce a residual neuromuscular block, a fact documented long time back by Magorian et al. 1990 *(Magorian et al., 1990)* that neostigmine efficacy is limited because when in the deep block, the maximum concentration of acetylcholine that can be thus achieved is often not sufficient to overcome the effect of the muscle relaxant, and ineffective reversal results (ceiling effect). Even if a second booster dose of neostigmine is given it would never speed of recovery. However, in our research there was just a delay in full power recovery as observed clinically and confirmed by TOF but not to the extent of residual neuromuscular blockade.

There was moderate transient increase in heart rate in NS group after 1 min which disappeared at 5 min, a result could be attributed to atropine induced anticholinergic effect. In current study, there was no statistical difference in both groups as regard PH, SaO_2, PaO2, CO_2 in basal ABG, at PACU and 3 h post-operative documenting the effective reversing action and post-operative safety of using the combination of half-dose sugammadex and neostigmine in rocuronium deep relaxation in morbid obese patients.

Study limitations

1- We could not measure the profound neuromuscular blockade using post-tetanic contraction before administering reversal agents (not available).
2- Further dose assessment studies in obese patients are required on larger scale of patients.
3- Relatively long time to extubation may be attributed to the high isoflurane depth of anesthesia needed targeting motionless hand during TOF measurements. Further researches are recommended for using propofol in place of increasing the inhalational anesthetic dosing.

Conclusion

As regards neuromuscular blocker reversal in obese patients, the neostigmine 50 μg/kg plus sugammadex half dose (1.2 mg/kg) is as effective as full-dose sugammadex (2.4 mg/kg) alone given within more than 15 min from last dose of rocuronium, while sugammadex 2.4 mg/kg is superior within less than 15 min.

Abbreviations

AChE: Acetylcholine esterase; Ach: Acetylcholine; ASA: American Society of Anesthesiologists; BMI: Body mass index; CI: Choline esterase inhibitor; ED90: Effective dose 90; ERV: Expiratory reserve volume; IBW: Ideal body weight; LBW: Lean body weight),; LSG: Laparoscopic sleeve gastrectomy; NMB: Neuromuscular blocker; NMBAs: Neuromuscular blocking agents; NMJ: Neuromuscular junction; PACU: Post-operative anesthetic care unit; PORC: Post-operative residual curarization; RV: Residual volume; TBW: Total body weight; TOF: Train of four

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Not applicable.

Ethical approval and consent to participate

This prospective randomized double-blinded controlled study conducted over a year starting at 20 January 2018 in Mansoura Gastroenterology Center (GEC). After approval from the institutional research board (IRB)-Code number: MS/17.12.195 on 16 January 2018, Faculty of Medicine, Mansoura University, included 50 patients who were ASA II–III, of both sexes, aged 18–65 years, and all were morbid obese (BMI > 35) underwent elective laparoscopic sleeve gastrectomy operation. All patients were interviewed and written informed consents were obtained from them. Patients were exclude from the study according to the following criteria: patient refusal, pregnancy or breast-feeding, renal dysfunction defined as creatinine> 1.2 mg/dl, known hepatic disease, allergy to rocuronium or sugammadex, and patients receiving medications known to interfere with the neuromuscular transmission neuromuscular diseases. Consent to participate is available upon request.

Authors' contributions

MA analyzed and interpreted the patient data, formulated the study conception and hypothesis, supervised data collection and its statistics, sample size calculation, writing manuscript, and statistical analysis of the study, manuscript final writing and manuscript submission. MN collected the study data, helped in writing manuscript. AM helped in data evaluation, manuscript formulation and study step by step supervision. SE helped in study hypothesis layout, statistical analysis of the study, manuscript final writing. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/ or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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