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SCIENTIFIC ARTICLE

Sugammadex by ideal body weight versus 20% and 40% corrected weight in bariatric surgery – double-blind randomized clinical trial

Nádia Maria da Conceição Duarte [a,*], Ana Maria Menezes Caetano [a],
Silvio da Silva Caldas Neto [a], Getúlio Rodrigues de Oliveira Filho [b],
Gustavo de Oliveira Arouca [a], Josemberg Marins Campos [a]

[a] Universidade Federal de Pernambuco (UFPE), Hospital das Clínicas, Departamento de Cirurgia, Recife, PE, Brazil
[b] Universidade Federal de Santa Catarina (UFSC), Florianópolis, SC, Brazil

Abstract

Background and objectives: The weight parameters for use of sugammadex in morbidly obese patients still need to be defined.

Methods: A prospective clinical trial was conducted with sixty participants with body mass index ≥ 40 kg.m^{-2} during bariatric surgery, randomized into three groups: ideal weight (IW), 20% corrected body weight (CW20) and 40% corrected body weight (CW40). All patients received total intravenous anesthesia. Rocuronium was administered at dose of 0.6 mg.kg^{-1} of Ideal weight for tracheal intubation, followed by infusion of 0.3–0.6 mg.kg^{-1}.h^{-1}. Train of four (TOF) was used to monitor depth of blockade. After spontaneous recovery TOF-count 2 at the end of surgery, 2 mg.kg^{-1} of sugammadex was administered. Primary outcome was neuromuscular blockade reversal time to TOF ≥ 0.9. Secondary outcome was the occurrence of postoperative residual curarization in post-anesthesia recovery room, searching the patient's ability to pass from the surgical bed to the transport, adequacy of oxygenation, respiratory pattern, ability to swallow saliva and clarity of vision.

Results: Groups were homogenous in gender, age, total body weight, ideal body weight, body mass index, type and time of surgery. The reversal times (s) were (mean $\pm$ standard deviation) 225.2 ± 81.2, 173.9 ± 86.8 and 174.1 ± 74.9 respectively, in the IW, CW20 and CW40 groups ($p = 0.087$).

Conclusions: No differences were observed between groups with neuromuscular blockade reversal time and frequency of postoperative residual curarization. We concluded that ideal body weight can be used to calculate sugammadex dose to reverse moderate neuromuscular blockade in morbidly obese patients.

* Corresponding author.
  E-mail: nadiaduarte2011@gmail.com (N.M. Duarte).

Uso de sugamadex pelo peso corporal ideal *versus* corrigido em 20% e 40% em cirurgia bariátrica – ensaio clínico randômico e duplo-cego

Resumo

Justificativa e objetivos: Os parâmetros de peso para o uso de sugamadex em pacientes com obesidade mórbida ainda precisam ser definidos.

Métodos: Um ensaio clínico prospectivo foi realizado com sessenta participantes com índice de massa corporal $\geq 40\,kg.m^{-2}$, submetidos a cirurgia bariátrica, randomizados em três grupos: peso ideal (PI), peso corrigido em 20% (PC20) e peso corrigido em 40% (PC40). Todos os pacientes receberam anestesia intravenosa total. Rocurônio foi administrado em dose de $0,6\,mg.kg^{-1}$ para intubação traqueal pelo peso ideal, seguido de infusão ($0,3$ a $0,6\,mg.kg^{-1}.h^{-1}$). A sequência de quatro estímulos (TOF) foi usada para monitorar a profundidade do bloqueio. Após recuperação espontânea da segunda resposta do TOF ao final da cirurgia, $2\,mg.kg^{-1}$ de sugamadex foi administrado. O desfecho primário foi o tempo de reversão do bloqueio neuromuscular até obter TOF $\geq 0,9$. O desfecho secundário foi a ocorrência de curarização residual pós-operatória na sala de recuperação pós-anestésica, avaliando a capacidade do paciente para passar do leito cirúrgico para o de transporte, adequação da oxigenação, padrão respiratório, habilidade para deglutir saliva e clareza de visão.

Resultados: Os grupos foram homogêneos quanto ao gênero, idade, peso corporal total, peso corporal ideal, índice de massa corporal, tipo e tempo de cirurgia. Os tempos de reversão (segundos) foram (média $\pm$ desvio padrão) $225,2 \pm 81,2$, $173,9 \pm 86,8$ e $174,1 \pm 74,9$, respectivamente, nos grupos PI, PC20 e PC40 ($p = 0,087$).

Conclusões: Não foram observadas diferenças entre os grupos quanto ao tempo de reversão do bloqueio neuromuscular e frequência de curarização residual pós-operatória. Concluímos que o peso corporal ideal pode ser usado para calcular a dose de sugamadex para reverter o bloqueio neuromuscular moderado em pacientes com obesidade mórbida.

Introduction

Obesity is currently a major health problem worldwide and is associated with a disproportionate increase in adipose tissue in relation to lean body mass.[1] Individualized criteria taking into account composition modifications should be used to calculate doses for this kind of patient.[2] However, the compounds used for anesthesia are developed in studies with patients without comorbidities or with only one (such as kidney or liver disease). This strategy excludes morbidly obese patients. Data for this particular population are obtained after drugs have already been approved by regulatory agencies and made commercially available. The use of ideal or total body weight for administration of drugs in morbidly obese patients may result in insufficient or excessive doses, adverse effects and/or poor clinical outcomes.[3,4]

In laparoscopic abdominal surgeries, especially bariatric ones, muscle relaxation facilitates pulmonary ventilation and establishes adequate conditions for surgery.[5] Some authors advocate the use of deep neuromuscular blockade to reduce the risk of physiopathological repercussions of pneumoperitoneum and accidental lesions caused by surgical instruments.[6] But more recent studies disagree with this statement, because they found no advantage of deep against the moderate block.[7] Anyway, incomplete reversal of motor blockade at the end of surgery is associated with lack of protection of airways, owing to poor functioning of the larynx muscles, with consequent increase in postoperative morbidity and mortality related to bronchoaspiration, hypoxemia, athelectasia, pneumonia and other complications.[8] In this situation, systematic monitoring and adequate reversal of motor blockade are protective factors and their use should be encouraged and monitored by health services.[9,10]

Sugammadex, a modified gamma-cyclodextrin, is the first direct neuromuscular blocker antagonist[11] capable of shortening blockade reversal time and reducing side-effects associated with residual postoperative curarization or the use of neostigmine and atropine.[12] However, the recommended dose is based on initial publications that have not factored in the peculiarities of morbidly obese patients.[13,14] More recent studies of morbid obesity and sugammadex have produced conflicting findings.[15–20]

The possibility of immediate reversal of any level of neuromuscular blockade with sugammadex have enabled more liberal use of rocuronium, providing adequate relaxation until the completion of laparoscopic surgery.[21,22] Continuous infusion of rocuronium has been studied and successfully used, to obtain and maintain specific target concentration in plasma and in the effector site, providing a more stable and efficient level of blockade[23]; its use on this basis, followed by sugammadex-induced reversal, may be a good option for anesthesia in morbidly obese patients. However, it is still necessary to establish which body weight parameters doses of sugammadex should be based on for antagonism of this pattern of neuromuscular blockade.

The present study compared neuromuscular blockade reversal time induced by continuous infusion of rocuronium and the occurrence of residual postoperative paralysis in

morbidly obese patients undergoing laparoscopic bariatric surgery, using three different doses of sugammadex, calculated for ideal weight, ideal weight plus 20% of excess weight or ideal weight plus 40% of excess weight. The hypothesis was that sugammadex effects swifter reversal of neuromuscular blockade, when administered at a dose calculated on the basis of ideal weight plus 40% of excess weight.

Methods

This study was approved by the Institutional Review Board and conducted in accordance with the Declaration of Helsinki. All patients were informed about and invited to take part in the study and only included after signing the written informed consent.

A prospective, double-blind randomized clinical trial was conducted with sixty adult participants with body mass index (BMI) over $40 \, kg.m^{-2}$, of both gender, aged between 18 and 70 years, undergoing elective laparoscopic bariatric surgery (sleeve gastrectomy or Roux-en-Y gastric by-pass).

The exclusion criteria were: known neuromuscular disease (such as myasthenia gravis), use of drugs that interfere with neuromuscular transmission, allergy to drugs used in the study, kidney failure, any incidents resulting in alteration or discontinuation of the anesthesia or surgical procedure, calculation error in administration of drugs involved, malfunctioning of neuromuscular functioning monitor, inability to obtain a moderate level of motor blockade (TOF count = 2) at the time of reversal with sugammadex or the occurrence of complications relating to anesthesia or surgery making postoperative follow-up of the research subject impossible.

Corrected body weight takes into account the fact that obese individuals increase lean body mass in a way that is not proportional to fat gain. Thus, CW20 and CW40 were defined, respectively, as ideal weight plus 20% and 40% of the difference between total and ideal body weight.

The participants were randomly assigned to three groups, according to the body weight parameter used to calculate the dose of sugammadex administered at the end of the surgical procedure to reverse neuromuscular blockade: ideal body weight (IW), IW plus 20% of excess weight (20% corrected body weight – CW20) and IW plus 40% of excess weight (40% corrected body weight – CW40).

Ideal weight was defined as height (cm) − 100 for men and height (cm) − 110 for women.[24]

During anesthesia and surgery, the monitoring routine was maintained using electrocardiography, non-invasive arterial pressure; pulse oximetry, capnography, thermometer and acceleromyography based peripheral nerve stimulator (TOF-Watch® SX; Organon Ltd., Dublin, Ireland).

All the patients received total venous general anesthesia, with a target-controlled infusion of propofol and continuous infusion of remifentanil. Rocuronium was the neuromuscular blocker, administered at a dose of $0.6 \, mg.kg^{-1}$ of ideal weight for tracheal intubation, followed by infusion of $0.3–0.6 \, mg.kg^{-1}.h^{-1}$.

Monitoring of neuromuscular activity followed the Good clinical research practice in pharmacodynamic studies of neuromuscular blocking drugs.[25] A combination of the ulnar nerve and adductor pollicis muscle was used, with 2 electrodes fixed to the ulnar surface of the wrist. The acceleration transducer was positioned on the ventral and distal side of the thumb. The other four fingers were immobilized with adhesive tape to allow free movement of the thumb.

The TOF-Watch® SX information for each patient was registered on a TOF-Watch® SX Monitor, Organon Ltd., Dublin, Ireland digital storage program, installed on a research-specific computer receiving data continuously in real time through an optic cable.

After anesthesia was induced and consciousness lost, calibration of the neuromuscular functioning monitor began and the supramaximal stimulus was obtained automatically. After stabilization of the signal, $0.6 \, mg.kg^{-1}$ of rocuronium bromide was injected intravenously, for ideal weight, to facilitate tracheal intubation. Continuous infusion began shortly afterwards, with doses between 0.3 and $0.6 \, mg.kg^{-1}.h^{-1}$ also for ideal weight. Four 0.2 ms pulses at a frequency of 2 Hz (TOF) were emitted by the monitor every 15 s during the surgical procedure. The aim during anesthesia was to maintain intraoperative deep neuromuscular blockade, with TOF count = 0 and a Post-Tetanic Count (PTC) of less than 5 responses – increase or reduction in speed of infusion was effected by adjusting these parameters. The infusion of rocuronium was terminated when the surgeon commenced a review of the peritoneal cavity.

After completion of the last suture line in the abdominal wall and recovery from TOF-count 2, the blockade was reversed using an intravenous dose of $2 \, mg.kg^{-1}$ sugammadex, based on three different body weight calculations – ideal, 20% corrected and 40% corrected – according to group.

Blockade reversal was conducted by a research assistant aware of which group the participant was assigned. He prepared a syringe with the dose of sugammadex, according to the weight parameter established for that particular group. The syringe was further filled up with 0.9% physiological saline to a total volume of 10 mL, in such a way that the main researcher was unaware of the dose being administered and, hence, of the group to which the patient had been assigned.

After initiation of injection of sugammadex, the neuromuscular functioning monitor continually measured TOF every 15 s. The time taken to reverse the blockade was measured from the beginning of injection using a digital stop watch and the TOF-Watch® SX program.

Full reversal was defined as a TOF rate equal to or greater than 0.9 on three consecutive measurements. The reversal time was recorded as the first of these three measurements.

After awakening from anesthesia, tracheal extubation and ensuring adequate conditions for transfer from the operating theater, each patient was referred to the Post-Anesthesia Care Unit (PACU), where they remained for at least 2 h and were evaluated for appearance and need for treatment of clinical signs of muscular weakness. Clinical tests were carried out on leaving the operating theater, every 20 min at PACU and immediately prior to being moved from PACU to the ward, searching the patient's ability to pass from the surgical bed to the transport with little or no help, adequacy of oxygenation, respiratory pattern, ability to swallow saliva and clarity of vision.

A TOF-Watch® SX monitor was made available for use in PACU, if clinical evidence of residual curarization was

Table 1 Demographic data of patients and anesthetic-surgical procedures.

Variable	Group			p-value
	IW (N = 20)	CW20 (N = 19)	CW40 (N = 17)	
Female – n (%)	13 (65.0)	10 (52.6)	13 (76.5)	0.328
Age (years) – mean (SD)	35.9 (11.6)	33.2 (7.1)	34.9 (9.3)	0.668
Sleeve gastrectomy – n (%)	18 (90.0%)	14 (73.7%)	13 (76.5%)	0.451
Total weight (kg)	119.7 (14.3)	119.3 (15.4)	123.4 (21.8)	0.735
Ideal weight (kg)	61.7 (12.6)	64.4 (14.1)	57.9 (13.0)	0.353
BMI – mean (SD)	42.2 (2.5)	41.3 (1.2)	44.7 (4.1)	0.051
Surgery time (min) – mean (SD)	145.2 (31.5)	131.7 (29.5)	129.5 (40.9)	0.311

N, number of participants per group; n, number of participants per variable; SD, standard deviation; BMI: body mass index; IW, ideal weight; CW20, ideal weight plus 20% excess weight; CW40, ideal weight plus 40% excess weight.

Table 2 Comparison of groups regarding neuromuscular blockade reversal time.

Reversal time (s)	Group			p-value
	IW (N = 20)	CW20 (N = 19)	CW40 (N = 17)	
Mean (SD)	225.2 (81.2)	173.9 (86.8)	174.1 (74.9)	0.088
Minimum–maximum	120–395	85–360	48–320	
95% confidence interval	187.2–263.2	132.1–215.8	135.6–212.7	

N, 56 patients; SD, standard deviation; IW, ideal weight; CW20, ideal weight plus 20% excess weight; CW40, ideal weight plus 40% excess weight.

detected. An extra dose of 2 mg.kg^{-1} of sugammadex should be administered to any patient objectively diagnosed with residual paralysis, using the same body weight parameter as the group to which they have been allocated in the study.

The primary outcome of the research was the neuromuscular blockade reversal time, defined as time in seconds taken to obtain TOF $\geq$ 0.9. The secondary outcome was frequency of occurrence of postoperative residual curarization in the post-anesthesia care unit.

The statistical calculations for the study were performed using SPSS for Windows Version 21.0 (Statistical Package for the Social Science – SPSS, Chicago, IL), with a level of significance of 0.05.

Given the level of significance of 0.05 and power of 0.9, using the G* Power, a statistical power analysis program, we estimated that 54 participants should be included in the study. However, anticipating possible losses during collection, the sample size was set at 60 participants, with 20 in each group.

Analysis of variance (ANOVA) was used for the quantitative variables. The mean and median were used to sum up information and the standard deviation to indicate the variability of data.

Pearson Chi-square test or Fisher's exact test in categorical variables was used to compare the frequency of distribution of the groups.

Results

Sixty patients were selected for the study, but four were excluded due to malfunction of neuromuscular monitor (01 in the CW20 group and 01 in the CW40) and error calculating of the sugammadex dose (02 in the CW40 group). Thus, the sample consisted of 56 participants, 20 (35.7%) in the IW group, 19 (33.9%) in the CW20 group and 17 (30.4%) in the CW40 group.

The groups were homogeneous in terms of gender, age, total body weight, ideal body weight, BMI, and type and time of surgery (Table 1).

There was no statistically significant difference between the groups for neuromuscular blockade reversal time (Table 2).

No patient in the study showed signs of postoperative residual curarization in PACU. Thus, no one was evaluated with TOF or received additional dose of sugammadex.

Discussion

The present study found no difference between groups for neuromuscular blockade reversal time and no patients with postoperative residual curarization in PACU.

Both rocuronium and sugammadex are hydrophilic compounds and have no affinity for fatty tissue. Rocuronium, both in bolus and in continuous infusion, is administered based on ideal weight. And sugammadex's inactivation of rocuronium occurs at a molecular level at a proportion of 1:1.[11] The findings of this study, therefore, are not contradictory from a biochemical and pharmacological point of view. The efficiency of the three regimens employed was confirmed by the absence of complications in the post-anesthesia care unit, which could be attributed to postoperative residual curarization or return of motor blockade.

The similarity between groups, regarding to the time to reverse the motor block, conflicts with the findings of others authors who argue for the use of corrected weight 40%[15,16] or total body weight for sugammadex.[17]

The results of the present study do not accord with those of Van Lancker et al.,[15] who found that the use of sugammadex based on ideal or ideal plus 20% weight delayed the reversal of neuromuscular blockade. These authors found that there was no difference between ideal weight plus 40% and total weight and concluded that sugammadex is effective for reversal of rocuronium blockade after recovery from the second TOF response, with $2 \, \text{mg.kg}^{-1}$, based on ideal weight plus 40%. However, even in the ideal weight and 20% corrected weight groups, which had significantly longer recovery times, these authors did not find a significantly longer duration for tracheal extubation or opening of the eyes, nor any postoperative complications related to residual curarization. This may point to a weak clinical correlation with the results, whose difference, though significant, was just a little larger than sixty second between the longest and shortest times for achieving full motor recovery in the groups (IW = 188.9, CW 20% = 154.6, CW 40% = 112.5 and total weight = 128.8). Given that, at this point, all the patients were intubated, being monitored and under medical supervision, awaiting recovery from TOF 0.9, it is questionable whether this minute does much to corroborate the conclusion that doses of sugammadex based on ideal weight or 20% corrected weight are insufficient. A methodological variation between the present study and that of Van Lancker et al.[15] can also justify the differences in the results found. While in this study we used the formula ''ideal weight plus 20% or 40% of excess weight'' for calculation of the corrected body weight for sugammadex administration, that authors used the formula ''ideal weight plus 20% or 40%''. This difference between the calculations may have resulted in higher corrected weights, with consequent higher sugammadex doses, given to the groups 20% and 40% of corrected weights in the European study.

Neither did the results of the present study confirm those of Laurado et al.,[16] who compared sugammadex using adjusted ideal weight by level of neuromuscular blockade in laparoscopic bariatric surgeries. These authors used $2 \, \text{mg.kg}^{-1}$ sugammadex to reverse moderate blockade (classified as two or more TOF responses) and $4 \, \text{mg.kg}^{-1}$ for deep blockade (classified as TOF 0 and 12 or fewer PTC responses). In both groups, sugammadex was administered for ideal weight. The authors found a delay in motor recovery and high rates of patients responding to sugammadex slowly or not at all. They concluded that the use of sugammadex based on ideal weight is insufficient or unsafe for moderate or deep blockade. Two aspects of the study, however, should be considered: first, the groups studied – moderate and deep blockade – were not randomized, a methodological shortcoming recognized by the authors themselves; second, unusually for management of recovery from motor blockade, the authors accepted a maximum time of only 2 min for reversal of moderate blockade and 3 min for deep blockade. After this, if the TOF did not reach a level of 0.9, a second $2 \, \text{mg.kg}^{-1}$ dose of sugammadex was administered in either group. In a self-analysis of this course of action, the authors agree that if more time had been allowed for recovery from blockade before administering the second dose, more patients who used sugammadex on the basis of ideal weight could have achieved a TOF of over 90%, which would have modified the conclusions. In our opinion, the indication of the second dose of sugammadex so soon after the initial dose added biases on the findings on insufficient recovery of neuromuscular blockade when it was used sugammadex based on ideal weight and, equally, on the possible complications arising from the use of such calculation that were not actually found.

On the other hand, the findings of the present study concur with those of other publications on the subject,[18,20] which did not have patients with complications related to residual curarization and concluded that the use of sugammadex based on ideal weight is safe for quick recovery from motor blockade in morbidly obese patients.

There is no universally valid scale for categorization of patients in the post-anesthesia care unit, in terms of their motor function after use of blockers and antagonists. So, this study did not classify the different patients according to their state of muscular function in the post-anesthesia care unit. This may be a limitation of the study, since the use of a specific scale for this type of observation, be it ordinal, interval or ratio, would facilitate supervision and comparison of the patients and the results of similar studies. However, this limitation is not exclusive of this study and we suggest that future studies can establish and validate a scale for this purpose.

Summary

We conclude that the administration of $2 \, \text{mg.kg}^{-1}$ of sugammadex, calculated by the ideal body weight provides full and timely reversal of moderate neuromuscular blockade induced by a continuous infusion of rocuronium, in morbidly obese patients undergoing laparoscopic bariatric surgery. This calculation parameter is safe in terms of occurrence of postoperative residual curarization and there is no need for higher doses of sugammadex based on body weight plus 20% or 40% of excess weight.

Conflicts of interest

The authors declare no conflicts of interest.

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