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CLINICAL RESEARCH

Residual neuromuscular blockade and late neuromuscular blockade at the post-anesthetic recovery unit: prospective cohort study

Pedro Marcos Silva e Gonçalves [a,*], **Alexandra de Vasconcelos Vieira** [b], **Claudia Helena Ribeiro da Silva** [b], **Renato Santiago Gomez** [a]

[a] *Universidade Federal de Minas Gerais (UFMG), Faculdade de Medicina, Programa de Pós-Graduação em Ciências Aplicadas à Cirurgia e à Oftalmologia, Belo Horizonte, MG, Brasil*
[b] *Hospital Unimed BH – Unidade Contorno, Serviço de Anestesiologia, Belo Horizonte, MG, Brasil*

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Abstract
Introduction and objectives: The use of neuromuscular blockers during surgery represented a landmark for anesthesiology. However, their use can prompt residual Neuromuscular Blockade ($_R$NMB) and objective monitoring of neuromuscular function is crucial to warrant the recovery of muscle strength. The present study aimed to estimate the incidence of $_R$NMB and late Neuromuscular Blockade ($_L$NMB) at the Post-Anesthetic Recovery Unit (PACU).
Method: The study included 85 patients, 43 of which received cisatracurium and 42 of which, rocuronium. The depth of the Neuromuscular Blockade (NMB) was assessed by Train Of Four (TOF). NMB reversal was performed with the administration of neostigmine and atropine.$_R$NMB was defined when a patient presented TOF below 90% at the PACU.
Results: $_R$NMB at the PACU was diagnosed in 39.5% and 40.5% of the patients receiving cisatracurium and rocuronium, respectively (p = 1.0). $_L$NMB at the PACU was found in 32.6% and 16.7% of the patients receiving cisatracurium and rocuronium, respectively (p = 0.131).
Conclusions: The incidence of$_R$NMB remains significant despite the use of intermediate-acting neuromuscular blockers and reversal agents. There was no statistically significant difference in the incidence of $_R$NMB or $_L$NMB in patients receiving cisatracurium or rocuronium. The use of objective NMB monitoring is effective for the diagnosis of $_R$NMB, as well as for treatment management.

* Corresponding author.
E-mail: pedro.marcoss@yahoo.com.br (P.M. Gonçalves).

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Introduction

The introduction of neuromuscular blockers in surgical practice facilitated performance of procedures, especially intrabdominal,[1–4] but in the 1950s, an increase in morbidity and mortality was observed after the use of these agents. Among the complications resulting from neuromuscular blocker drugs, post-operative residual Neuromuscular Blockade ($_R$NMB) has attracted attention.[2,5–7] A multicenter study revealed that half of the anesthesia-related deaths were due to post-anesthetic respiratory depression.[2]

Neuromuscular Blockade (NMB) reversal can be accomplished with anticholinesterase agents, such as neostigmine, or with a specific reversing agent, such as sugammadex.[4,5] In addition to muscarinic side effects, neostigmine has a limited ability to reverse NMB.[8,10] Studies have shown suitable $_R$NMB prevention after administration of a specific neuromuscular blocker reversal agent.[7]

The presence of $_R$NMB can be assessed by clinical assessment or by objective and quantitative methods using neuromuscular transmission monitors. The clinical signs of absence of $_R$NMB revealed false-negative results when compared to objective methods using peripheral nerve stimulation.[2] Clinical methods do not quantify the degree of NMB, so they have been abandoned and replaced by device-based methods.[7,9,11]

Since 2003, with the introduction of the acceleromyograph for neuromuscular function monitoring, TOF $\geq$ 90% measured at the adductor pollicis muscle has been considered the gold standard to define full reversal of NMB.[4,5,9,12,13] Quantitative and objective monitoring of neuromuscular function has proved useful in titrating the dose of both neuromuscular blockers and reversal agents. However, the use of these monitors is far from ideal, since studies have shown that only 10–15% of anesthesiologists routinely use neuromuscular function monitors, and only 18% reported that all workplaces are equipped with this monitor.[11,14] Studies on $_R$NMB incidence at the PACU have shown results from 9% to 47%, with some publications showing even higher rates, indicating that the incidence can reach 88–93%.[3–5,9,15]

The primary objective of the present study was to estimate the incidence of postoperative $_R$NMB on admission to PACU in patients receiving cisatracurium or rocuronium during balanced general anesthesia for laparoscopic cholecystectomy. The secondary objectives were to determine the frequency of late Neuromuscular Blockade ($_L$NMB) and to investigate the occurrence of respiratory events in patients at the PACU.

Method

The study has a prospective observational design. After approval of the protocol by the Research Ethics Committee (Report Number: 2,280,166 and Certificate of Submission for Ethical Appreciation – CAAE: 71086417.3.0000.5121) and signature of the Informed Consent Form, we recruited 100 adult patients to be submitted to laparoscopic cholecystectomy under balanced general anesthesia. The study exclusion criteria comprised patients younger than 18 and older than 50 years, ASA (American Society of Anesthesiologists) physical status III or higher, ASA II patients with respiratory comorbidities, with severe neuromuscular, renal or liver conditions, patients with a Body Mass Index (BMI) greater than 35 and patients repeatedly receiving neuromuscular blockers, as well as drugs interfering with NMB, such as calcium channel blockers, inorganic ions (Mg^{++}, Li^{++}), aminoglycoside antibiotics and halogenated inhalational anesthetics, with the exception of sevoflurane. After complying with study criteria, 85 patients were included so that either cisatracurium or rocuronium was administered intravenously as a neuromuscular blocker of intermediate action. The choice between the two neuromuscular blockers resulted from the preference of the anesthesiologist responsible for anesthetic procedures.

In the operating room, patient monitoring comprised continuous two-lead ECG (DII and V5), pulse oximetry, continuous waveform capnography, anesthetic gas analyzer, automatic non-invasive blood pressure, nasopharyngeal thermometer, and a forced-air convective warming system with blanket to maintain nasopharyngeal temperature between 36 °C and 37 °C. The neuromuscular function of the adductor pollicis muscle was monitored using TOF with an intensity of 50 mA. The TOF result, depicted as the T4/T1 ratio, was expressed as a percentage. The technique was assessed using acceleromyography, with the TOF-Watch®SX model equipment (Organon, Ireland, Limited. Registration with – ANVISA (Brazilian regulatory agency) #80135010006). After prepping the patient's skin with 70% alcohol, the accelerometer transducer was placed over the distal ventral end of the thumb and the device thermometer was positioned over the tenar surface of the patient's left hand. The other fingers were firmly immobilized with adhesive tape. We used the CAL (calibration) mode to determine the supra-maximum threshold and to calibrate the accelerometer transducer.

According to institutional protocol and preference of anesthesiologists, 43 patients received a dose of 0.15 $mg.kg^{-1}$ of cisatracurium and 42 patients received a dose of 0.6 $mg.kg^{-1}$ of rocuronium. Still taking into consideration the institutional protocol, the interval required between the neuromuscular blocker injection and orotracheal intubation was defined as ''ideal neuromuscular blocker time'' and was four minutes for cisatracurium and three minutes for rocuronium. After surgery completion and according to the TOF value found, NMB was reversed with an intravenous injection of neostigmine and atropine. All patients with a TOF value between 90% and 30% received 20 $\mu g.kg^{-1}$ of neostigmine and 10 $\mu g.kg^{-1}$ of atropine. Those with a TOF value < 30% received 40 $\mu g.kg^{-1}$ of neostigmine and 20 $\mu g.kg^{-1}$ of atropine. NMB reversal was performed only after obtaining at least two stimuli in the TOF monitor, characterizing a moderate degree of NMB. The degree of NMB was defined according to the number of responses after the train of four (TOF) and the number of responses after applying a tetanic stimulus (Post-Tetanic Count – PTC). Thus, four categories: intense NMB (TOF = 0 and PTC = 0), deep NMB (TOF = 0 and PTC $\geq$ 1), moderate NMB (TOF = 1 to 3 responses) and recovery from NMB (TOF = 4 up to the T4/T1 ratio $\geq$ 90%).[5,16] After awakening and orotracheal extubation, patients were transferred to the PACU, where the last TOF assessment was performed. Patients showing a TOF value below 90% at the PACU were considered as presenting $_R$NMB.

The following parameters were assessed and recorded in the intraoperative and immediate postoperative period at the PACU: age, ASA physical status, gender, body weight, height, BMI, TOF calibration value, identification and dose of the administered neuromuscular blocker, TOF value after neuromuscular blocker administration, time of orotracheal intubation, duration of surgery, TOF value after surgery completion, name and dose of the neuromuscular blocker reversal agent (if administered), events and complications at the time of reversal, such as additional time required after surgery completion for obtaining two or more TOF responses (moderate NMB level), the need for repeated administration of reversal agents, prolonged awakening and delay for extubation. For the event ''additional time required after surgery completion to obtain two or more TOF responses'', we considered any and entire time required to observe two or more TOF responses after the end of surgery (last port-site skin suture) so that NMB reversal would be possible. Additionally, we recorded the TOF value five minutes after administration of NMB reversal agents, TOF value and time of extubation; and TOF value and PACU admission time. To estimate $_{L}$NMB rate in each patient, a comparative analysis was performed between TOF values at the time of extubation and at admission to PACU. The following adverse events at PACU were recorded to assess respiratory function: decrease in oxygen saturation below 90%, requiring supplement of O_2 via nasal prongs or bag valve mask assisted ventilation.

The sample size was estimated based on the study performed by Morais et al.,[2] who observed 30% $_{R}$NMB (TOF less than 90%) in 40 patients receiving rocuronium and 32% $_{R}$NMB in 53 patients receiving cisatracurium. Supposing a similar $_{R}$NMB rate for each neuromuscular blocker, with a significance level of 5% and test power of 90%, 35 patients receiving rocuronium and 44 patients receiving cisatracurium would be required for the analysis of the primary outcome of our study (sample calculation obtained with the tool available at https://praticaclinica.com.br).

Statistical analysis

All statistical analyses were performed with Graphpad Prism® software, version 5.0 for Windows®. Initially, we performed an exploratory data analysis and calculated the mean or median (25^{th} and 75^{th} percentiles, respectively), standard deviation, absolute frequency, and percentage for the variables as applicable. Quantitative variables were submitted to the Shapiro-Wilk normality test and categorical variables were analyzed using contingency tables and Fisher's exact test. Parametric data were analyzed with Student's *t*-test and nonparametric data with the Mann-Whitney test. We considered the differences statistically significant when the *p*-value obtained in all tests was less than 0.05 (95% significance level).

Results

The flow diagram (Fig. 1) displays the inclusion of the 85 patients that received either cisatracurium or rocuronium. Table 1 shows the demographic characteristics of the patients according to the neuromuscular blocker drug administered.

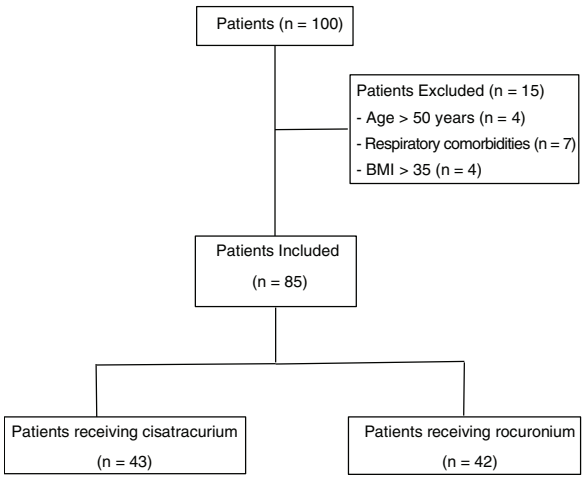

Figure 1 Study flowchart.

There was no statistically significant difference between age, gender, weight and BMI or ASA physical status (Table 1). Patients receiving cisatracurium or rocuronium did not show statistically significant differences neither for the total duration of surgery nor for the partial times analyzed (Table 2).

Table 3 shows the assessment of neuromuscular function performed five minutes after NMB reversal, at orotracheal extubation and at PACU admission. The neuromuscular function assessed by TOF values showed a statistically significant difference between patients receiving cisatracurium and those receiving rocuronium, five minutes after NMB reversal. According to these data, patients receiving rocuronium had a higher median TOF value than patients receiving cisatracurium, that is, 66.5% and 44%, respectively ($p = 0.0414$).

During NMB reversal, the events and incidents were more frequent in patients receiving cisatracurium. After surgery completion, the need to wait additional time for obtaining two or more TOF responses was observed in 30.2% of patients receiving cisatracurium (13/43) compared to 7.1% of patients receiving rocuronium (3/42) ($p = 0.0109$). There was no statistically significant difference between patients receiving cisatracurium and those receiving rocuronium regarding requirement for repeated administration of reversal drugs or concerning delay for awakening and extubation.

Table 4 describes the number of patients with a TOF value below 90% in whom reversal was performed. We excluded two patients from the TOF analysis after five minutes of reversal, as they showed spontaneous recovery of neuromuscular function without requiring neostigmine and atropine administration (one patient received cisatracurium and the other rocuronium).

When stratifying patients in relation to those who were considered to have postoperative $_{R}$NMB, no statistically significant difference regarding the number of patients was observed among the moments analyzed (Table 4).

Adverse events at the PACU were analyzed according to the neuromuscular blocker administered. Only 11.6% (5/43) of the patients receiving cisatracurium presented some type

Table 1 Demographic characteristic of patients receiving cisatracurium or rocuronium.

		Cisatracurium (n = 43)	Rocuronium (n = 42)	*p*
Age (years)				
Mean ± SD		35.16 ± 7.208	36.76 ± 7.457	0.3176[a]
Sex				
n	Male	10 (23.3%)	9 (21.4%)	1.0000[b]
(%)	Female	33 (76.7%)	33 (78.6%)	
Weight (kg)				
Median (25 P–75 P)		72.0 (65.0–82.0)	79.2 (61.0–79.2)	0.2853[c]
	BMI			
	Mean ± SD			
	26.83 ± 3.57	25.87 ± 3.47	0.2169[a]	
Physical status				
n (%)	ASA I	27 (62.8%)	31 (73.8%)	0.3529[b]
	ASA II	16 (37.2%)	11 (26.2%)	

SD, Standard Deviation; BMI, Body Mass Index.
[a] Student *t* test.
[b] Fisherś exact test.
[c] Mann-Whitney test.

Table 2 Intraoperative times and intervals for patients receiving cisatracurium or rocuronium.

	Cisatracurium (n = 43) Median (25 P–75 P)	Rocuronium (n = 42) Median (25 P–75 P)	*p*
Surgery total duration (minutes)	56 (41–65)	54.50 (44.50–67.75)	0.4928[a]
From reversal to extubation (minutes)	15.5 (13.75–18)	16 (12.5–17.5)	0.4641[a]
From end of surgery to extubation (minutes)	18 (15–27)	17 (14–19.25)	0.0715[a]
From end of surgery to PACU (minutes)	30 (25–39)	27 (24–32)	0.0523[a]
From extubation to PACU (minutes)	10 (7–12)	9 (7–13)	0.5781[a]

PACU, Post-anesthesia recovery unit.
[a] Mann-Whitney test.

Table 3 Assessment of the neuromuscular function of patients receiving cisatracurium or rocuronium.

TOF[(a)]	Cisatracurium (n = 43) Median (25 P–75 P)	Rocuronium (n = 42) Median (25 P–75 P)	*p*
Five minutes after reversal	44.0% (23.0–74.0)	66.5% (38.0–77.0)	0.0414[b]
After extubation	81.0% (74.0–96.0)	89.5% (72.0–100.0)	0.6794[b]
On PACU admission	94.0% (83.0–106.0)	94.0% (83.0–105.0)	0.8604[b]

PACU, Post-Anesthesia Recovery Unit.
[a] TOF median values described as T4/T1 ratio percentage.
[b] Mann-Whitney test.

Table 4 Number of patients receiving cisatracurium or rocuronium showing TOF below 90%.

TOF below 90%	Cisatracurium n (%)	Rocuronium n (%)	*p*
After neuromuscular blocker ideal time	40/43 (93.0%)	42/42 (100%)	0.2412[b]
After discontinuation of anesthetic agents	42/43 (97.7%)	41/42 (97.6%)	1.0000[b]
Five minutes after reversal[a]	36/42 (85.7%)	35/41 (85.4%)	1.0000[b]
After extubation	27/43 (62.8%)	21/42 (50.0%)	0.2776[b]
On PACU admission	17/43 (39.5%)	17/42 (40.5%)	1.0000[b]

PACU, Post-Anesthesia Recovery Unit.
[a] Only patients receiving reversal drug were analyzed.
[b] Fisherś exact test.

of adverse event at the PACU, while the rate was 16.7% (7/42) for those receiving rocuronium. There was no statistically significant difference in the occurrence of adverse events at the PACU between patients receiving cisatracurium and those receiving rocuronium ($p = 0.5486$).

Overall, there was an increase in the TOF value at the PACU compared to the value recorded at extubation. Among the patients receiving cisatracurium, the mean increase was 14.53 (± 25.69), and in those receiving rocuronium it was 10.17 (±15.96), with no statistically significant difference ($p = 0.3505$); however, we were not able to exclude the null hypothesis for the difference between the means of increasing the TOF value between extubation and admission to the PACU. $_{L}$NMB occurred in 14 (32.6%) patients receiving cisatracurium, as we found a reduction in the TOF value measured at the PACU compared with the value at extubation. Two of these patients (14.3%) showed decrease in oxygen saturation below 90%, requiring O_2 administration via nasal prongs. The occurrence of $_{L}$NMB at the PACU was also reported in 7 (16.7%) patients receiving rocuronium. Two of these patients (28.6%) required O_2 administration via nasal prongs, due to a decrease in oximetry below 90%. There was no statistically significant difference between patients receiving cisatracurium and those receiving rocuronium regarding the number of patients presenting TOF decrease ($p = 0.1310$). Of the 12 patients showing adverse events at the PACU, only four showed reduction of a TOF value at the PACU compared to the value measurements at extubation.

Discussion

The development of drugs enabling fine-tuning of their onset and end of action has evolved considerably in recent years. A more sophisticated knowledge of pharmacokinetics and pharmacodynamics has provided safer anesthesia and more favorable outcomes for anesthesia and surgery. However, the incidence of $_{R}$NMB remains high, despite the advent of intermediate-action blockers. The present study also showed a significant incidence of $_{L}$NMB at the PACU. According to some authors, these complications may result from ineffective and partial neuromuscular blockade reversal.[2,4,6]

Regarding the assessment of neuromuscular function five minutes after reversal with neostigmine, patients receiving rocuronium had a higher median value of TOF compared to patients receiving cisatracurium. The median values of TOF after extubation and at PACU admission were also higher in patients receiving rocuronium compared to patients receiving cisatracurium, however, the difference was not statistically significant. The incidence of adverse events during NMB reversal was more frequent in patients receiving cisatracurium. These results are corroborated by Mathias and Bernardis (2012), who described greater depth of NMB associated with cisatracurium, and with rocuronium showing a lower incidence of $_{R}$NMB at surgery completion (44%) compared with cisatracurium (57%).[5]

The $_{R}$NMB rate at PACU admission in patients receiving cisatracurium was analogous to the rate found for patients receiving rocuronium, or 39.5% and 40.5% ($p = 1.0$), respectively. This incidence was also observed by Aytac et al. (2016), Ariza et al. (2017), Mathias and Bernardis (2012), Fuchs-Buder et al. (2016) and Murphy et al (2018), who concluded that, despite the introduction of intermediate action neuromuscular blockers, there is still a high incidence (approximately 40%) of incomplete neuromuscular blockade reversal at early stages of post anesthesia recovery.[3–5,8,9]

In the present study, we observed a low number of adverse events at the PACU. They were more frequent in patients receiving rocuronium than in those receiving cisatracurium, although there was no statistically significant difference. These findings can be explained by longer NMB associated to rocuronium. In their study, Feltracco et al. (2016) showed that the time interval from the last administration of the blocker to the administration of reversal was longer in the group that used rocuronium, compared to cisatracurium. This agrees with results showing variability in NMB induced by rocuronium and lasting longer than that induced by cisatracurium.[14]

Late NMB at the PACU was more frequent in patients receiving cisatracurium than rocuronium, or 32.6% and 16.7% respectively, with no statistically significant difference. Likewise, patients receiving cisatracurium showed the greatest reduction in the TOF value at PACU admission when compared with the TOF value found at extubation, although there was no statistically significant difference. As already demonstrated by Mathias and Bernardis (2012), there is deeper NMB after the use of cisatracurium.[5] The occurrence of $_{L}$NMB is also explained by Almeida et al. (2004) These authors stated that, theoretically, $_{L}$NMB can occur after the end of action of neostigmine, since this reversal agent does not displace the neuromuscular blocker from its site of action.[7]

The direct action of neuromuscular blockers on organs other than muscles can cause side effects. Broens et al. (2019) described respiratory depression after rocuronium use, despite full recovery of neuromuscular function revealed by a TOF value over 90%. The authors suggested that the hyperventilation provoked by the response of carotid bodies to hypoxia is impaired by direct action of non-depolarizing neuromuscular blockers after the binding of these drugs to post-synaptic nicotinic receptors located in the cells of the carotid bodies.[17] Therefore, this effect on ventilatory response can influence the adverse events rate at the PACU in patients with complete NMB reversal.

We observed a significant rate (40%) of $_{R}$NMB at the PACU, despite the administration of neostigmine, highlighting that reversal provided by anticholinesterase agents does not guarantee full recovery of neuromuscular function. Neostigmine is known to have a slow and unpredictable onset of action, a ceiling effect and is not effective in reversing deep NMB.[18] In fact, despite the use of acceleromyography monitoring, the high rate of TOF below 90% at the PACU strongly indicates the need to develop more effective methods of NMB reversal.

The present study has some limitations. It is important to mention that the technique for assessing neuromuscular function by acceleromyography is influenced by external factors that can alter the TOF value, impairing the reliability of results. In the patients of this study, the electrodes, sensors and thermometer of the TOF monitor were positioned and fixed to the patient's hand before anesthetic induction and removed only after the last evaluation of the TOF value at the PACU. Despite this, transporting the patient from the operating room to the PACU, moving the patient from the OR

table to the stretcher, changes in room temperature and, invariably, body temperature, in addition to changing the resting site for positioning the hand and fingers to determine the TOF value may have impacted the correct assessment of neuromuscular function at the PACU and, therefore, in the incidence of $_{R}$NMB and $_{L}$NMB. Thus, studies with more sophisticated monitoring techniques are required to improve the accuracy in determining neuromuscular function, especially at the PACU.

In conclusion, a high rate of $_{R}$NMB was observed in patients undergoing general anesthesia and the rate of $_{L}$NMB was practically twice as high in patients receiving cisatracurium compared to those receiving rocuronium, although there was no statistically significant difference. Using objective monitoring of the depth of NMB was essential for the adequate assessment of neuromuscular function recovery. Our results show the need and importance of clinical assessment together with the use of objective monitoring in patients receiving neuromuscular blockers.

Conflicts of interest

The authors declare no conflicts of interest.

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