

# Use of neuromuscular blockers and neostigmine for general anesthesia and its association with neuraxial blockade

## A retrospective study

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### Abstract

This research aimed to assess the use of neuromuscular blockers (NMB) and its reversal, associated or not with neuraxial blockade, after general anesthesia.

This retrospective study analyzed 1295 patients that underwent surgery with general anesthesia at Prof. Dr. José Aristodemo Pinotti Hospital in 2013. The study included patients aged >1 year, with complete, readable medical charts and anesthetic records.

Rocuronium (ROC) was the most used NMB (96.7%), with an initial dose of 0.60 (0.52–0.74) mg/kg and total dose of 0.38 (0.27–0.53) mg/kg/h. In 24.3% of the cases, neuraxial blockade was associated with a significantly longer anesthesia ( $P < .001$ ) than in cases without neuraxial block, regardless of technique (total intravenous (TIV) vs intravenous and inhalational (IV+IN)). In 71.9% of the cases, a single dose of NMB was used. Patients under TIV general anesthesia associated with neuraxial blockade had a lower total dose of ROC (mg/kg/h) in comparison with TIV GA alone (0.30 (0.23–0.39) and 0.42 (0.30–0.56) mg/kg/h, respectively,  $P < .001$ ). The same was observed for patients under IV+IN GA (0.32 (0.23–0.41) and 0.43 (0.31–0.56) mg/kg/h, respectively,  $P < .001$ ). The duration of anesthesia was longer according to increasing number of additional NMB doses ( $P < .001$ ). Dose of neostigmine was 2.00 (2.00–2.00) mg or 29.41 (25.31–33.89)  $\mu$ g/kg. The interval between neostigmine and extubation was >30 minutes in 10.9% of cases.

The most widely used NMB was ROC. Neuroaxial blockade (spinal or epidural) was significantly associated with reduced total dose of ROC (mg/kg/h) during general anesthesia, even in the absence of neuromuscular monitoring and regardless of general anesthetic technique chosen. In most cases, neostigmine was used to reverse neuromuscular block. The prolonged interval between neostigmine and extubation (>30 minutes) was neither associated with total doses of ROC or neostigmine, nor with the time of NMB administration. This study corroborates the important role of quantitative neuromuscular monitors and demonstrates that neuraxial blockade is associated with reduced total ROC dose. Further studies are needed to evaluate the possible role of neuraxial blockade in reducing the incidence of postoperative residual curarization.

**Abbreviations:** ANOVA = analysis of variance, ASA = American Society of Anesthesiologists, BMI = body mass index, GA = general anesthesia, IV + IN = intravenous and inhalational, NMB = neuromuscular blocker(s), NON-ROC = all other neuromuscular blockers, except for rocuronium, PORC = postoperative residual curarization, ROC = rocuronium, TBW = total body weight, TIV = total intravenous.

**Keywords:** anesthetic technique, neostigmine, neuraxial blockade, neuromuscular blockers, rocuronium

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*Implication statement:* This retrospective study evaluated the use of neuromuscular blocking agents in a tertiary hospital in Brazil. This analysis may promote the development of strategies to improve use of NMB, reducing the incidence of residual neuromuscular block in postanesthetic care units and its complications in this institution and in other services.

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## 1. Introduction

Since 1954, after a study published by Beecher and Todd, the use of neuromuscular blockers (NMB) has been associated with increased perioperative mortality. The adequate reversal of NMB at the end of surgery, either spontaneously or by pharmacologic means, reduces the risk of undesired effects of these drugs. It is known that the occurrence of postoperative residual curarization (PORC) is related to a number of complications, particularly respiratory, and a longer stay in the postanesthetic care unit.<sup>[1–4]</sup>

The introduction of intermediate-acting NMB into clinical practice has decreased the occurrence of PORC; however, its incidence is around 56% and still considered elevated.<sup>[2,5–7]</sup> Furthermore, the low use of neuromuscular monitoring and undesired effects of inadequate neostigmine doses have sparked a discussion on the use or nonuse of reversal agents.<sup>[8]</sup> Thus, the study of the use of NMB and their reversal agents is mandatory in clinical practice.

Previous surveys, usually conducted by distributing questionnaires to anesthesiologists, have shown a heterogeneous preference regarding the use of NMB and their reversal agents. There is a significant increase in the use of intermediate-acting drugs, with considerable emphasis on rocuronium (ROC), particularly after the introduction of Suggamadex into clinical practice.<sup>[9–12]</sup>

It is believed that analysis of NMB use, along with other factors (e.g., anesthetic technique, dose, and time each drug is used), may promote the development of strategies, aimed at optimizing reversal of NMB and possibly reduce the complications related to its use in clinical practice. The purpose of this study is to show the frequency and characteristics of NMB use and their reversal agents in patients undergoing general anesthesia (GA), with or without neuraxial blockade, in a tertiary hospital in Brazil.

## 2. Materials and methods

This is a retrospective, analytical study, carried out at the surgical center of “Professor Doutor José Aristodemo Pinotti Women’s Hospital” at the State University of Campinas. The project was approved by the National Research Ethics Committee on September 2014, under Ethical Approval Certificate, number 38414514.9.0000.5404 and report number 896,589. Data collection was based on a review of anesthesia records. The ethical committee granted the study a waiver of informed consent.

The study included cases with complete and readable anesthetic charts of female patients, over the age of 1 year, undergoing GA during the year of 2013. In all the cases, the following parameters were evaluated: demographic characteristics (age, weight, height, body mass index (BMI), and American Society of Anesthesiologists (ASA – physical status); anesthetic technique (total intravenous (TIV) or intravenous and inhalational (IV+IN), associated or not with neuraxial blockade; duration of anesthesia (time between NMB injection and conclusion of anesthesia) and surgery; neuromuscular blocking agent, reversing agent (neostigmine), doses used and time of administration; intervals between the first dose of NMB and neostigmine, between the last dose of NMB and neostigmine and between neostigmine injection and conclusion of anesthesia (time of extubation or removal of intubated patient from the operating room).

For the analysis of ROC dose, a BMI  $\geq$  or  $<$  30 kg/m<sup>2</sup> was considered. Total body weight (TBW) was used for patients with a BMI  $<$  30 kg/m<sup>2</sup> and ideal body weight for subjects with BMI  $\geq$  30 kg/m<sup>2</sup>.<sup>[13–15]</sup> TBW was considered to calculate the dose of neostigmine.<sup>[16]</sup>

To calculate the total dose of NMB (mg/kg/h), the interval from the first dose of NMB until neostigmine was considered. In cases where neostigmine was not used, the duration of anesthesia (interval between the initial dose of NMB and conclusion of anesthesia) was considered.

The period between the initial dose of NMB and reversal with neostigmine was analyzed. To assess the interval between the last NMB dose and time of NMB reversal, cases were distributed into intervals  $\geq$  45 or  $<$  45 minutes. The interval between neostigmine injection and extubation was evaluated to determine whether this period was  $>$  30 or  $\leq$  30 minutes.

### 2.1. Statistical analysis

The sample size for this study was calculated based on the use of neuromuscular blockers in other countries, described on previous studies.<sup>[2,9,11,17]</sup> Since most data are based on surveys and there are very few studies on this topic in Brazil, we considered results from a large, single-center, prospective, observational study to calculate sample size,<sup>[2]</sup> which encountered ROC to be the most frequently used NMB, with a rate of 76%. Based on the fact that ROC is the most widely available NMB at our institution, we anticipated an incidence of use of rocuronium of 80%. For this analysis we divided NMB into 2 groups: ROC and NON-ROC (all other NMB, except ROC). Considering a dichotomous endpoint, 1-sample study, power 80% and  $\alpha=5\%$ , the calculated sample size was  $n=861$ . Taking into account the surgical volume at our institution and allowing for losses due to incomplete medical records and anesthetic charts, we reviewed data for the period of 12 consecutive months prior to the beginning of the study.

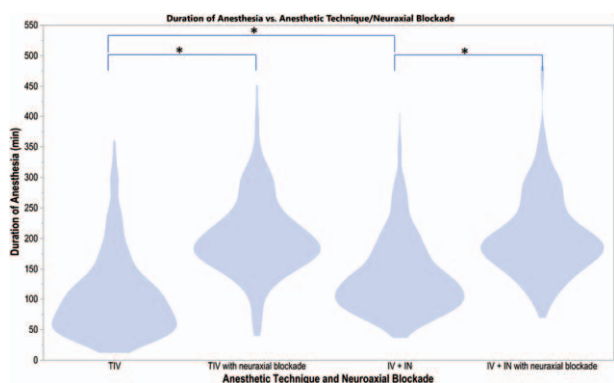
For comparisons of categorical data, the  $\chi^2$  and Fisher exact tests were used. Numerical data were compared using analysis of variance (ANOVA), Tukey test, Mann–Whitney *U* test, or the Kruskal–Wallis H-test, as appropriate. Patients with missing data on medical records and anesthetic charts, such as weight, dose of anesthetic drugs used, duration of anesthesia and surgery, and other relevant information, were excluded from the study. Results from variables for which the sample did not follow a normal distribution were expressed as median and interquartile range (range between the first quartile and the third quartile)—median (q1–q3).

For statistical analysis, software R (R Foundation for Statistical Computing, Vienna, Austria, 2016) was used. Another

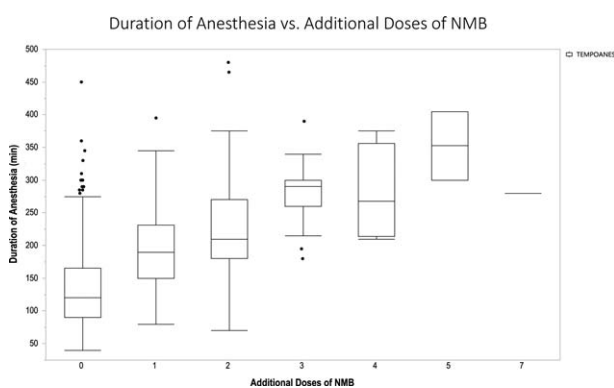
**Table 1**  
Patient demographic data; duration of anesthesia and surgery (n = 1295).

Age, y	48.00 (37.00–59.00)
Weight, kg	67.00 (59.00–78.00)
BMI, kg/m <sup>2</sup>	26.67 (23.43–30.48)
Height, cm	160.00 (154.00–164.00)
ASA physical status (1–5)	
1	291 (22.5%)
2	695 (53.7%)
3	264 (20.4%)
4	38 (2.9%)
5	7 (0.5%)
Duration of anesthesia, min	130.00 (90.00–185.00)
Duration of surgery, min	80.00 (45.00–130.00)

Values expressed in median (q1–q3); number of patients (%—percentage of patients). ASA=American Society of Anesthesiologists, BMI=body mass index.



**Figure 1.** Comparisons (violin plots) of duration of anesthesia (minutes) according to general anesthetic technique associated or not with neuraxial blockade. Kruskal–Wallis test and Tukey test ( $P < .001$ ).

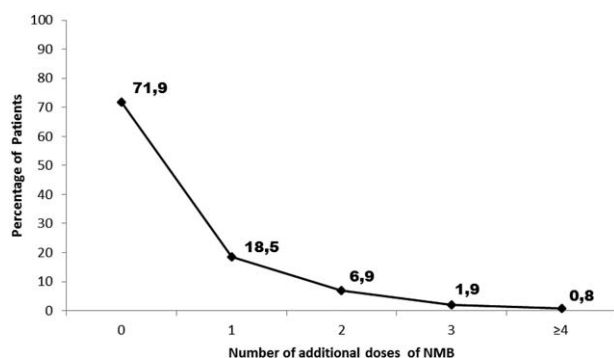


**Figure 2.** Duration of anesthesia versus number of additional doses of rocuronium. Kruskal–Wallis test and Tukey test ( $P < .001$ ).

software (JMP, Version 13.0, SAS Institute Inc, Cary, NC, 2016) was used to generate graphs and plots.

### 3. Results

In the study period, a total of 1313 patients were selected, 18 of whom were excluded due to missing data. Medical charts and data of 1295 patients were analyzed. Neuromuscular monitoring was not used in any of the cases.



**Figure 3.** Percentage of patients according to number of additional doses of NMB. NMB=neuromuscular blocker.

**Table 2**

**Analysis of total dose of rocuronium according to the general anesthesia technique (TIV or IV+IN) and association or not with neuraxial blockade (spinal or epidural).**

Variables (N)	Dose total rocuronium (mg/kg/h) <sup>*</sup>	P value <sup>†</sup>
TIV without neuraxial blockade (272)	0.42 (0.30–0.56)	<.0001
TIV and epidural block (73)	0.26 (0.20–0.35)	
TIV without neuraxial blockade (272)	0.42 (0.30–0.56)	.018
TIV and spinal block (64)	0.34 (0.27–0.42)	
IV+IN without neuraxial blockade (510)	0.42 (0.31–0.56)	<.0001
IV+IN and epidural block (63)	0.31 (0.23–0.40)	
IV+IN without neuraxial blockade (510)	0.42 (0.31–0.56)	.002
IV+IN and spinal block (90)	0.32 (0.23–0.42)	

IV+IN=intravenous and inhalational anesthesia, N=number of patients, TIV=total intravenous anesthesia.

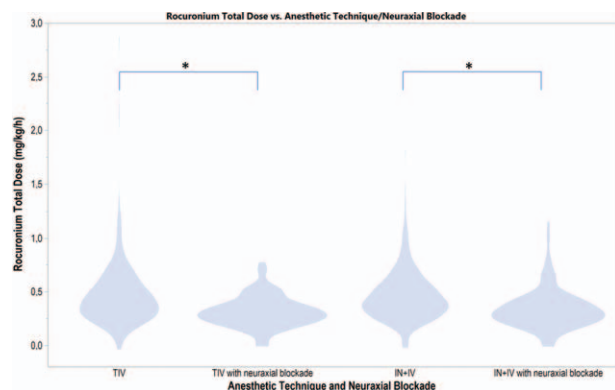
<sup>\*</sup> Values expressed in median (q1–q3).

<sup>†</sup> Mann–Whitney test.

Patient demographic data, duration of anesthesia, and surgery are shown in Table 1. The most commonly used anesthetic technique was IV+IN (55.9%), followed by TIV (44.1%). Neuraxial blockade was associated with general anesthesia in 24.3% of the cases and the mean duration of anesthesia in these cases was significantly longer ( $P < 0.01$ ), in comparison with techniques without neuraxial block. When neuraxial blockade was not associated, the Tukey test showed that the duration of anesthesia in patients undergoing TIV anesthesia was significantly shorter ( $P < .001$ ) in comparison with those receiving IV+IN anesthesia (Fig. 1).

The duration of anesthesia increased and was significantly longer ( $P < .001$ ) according to the number of additional doses of NMB used (Fig. 2). However, in 71.9% of the cases, a single dose of NMB was used and no additional doses were given (Fig. 3).

A neuromuscular blocking agent was not used in 12.4% ( $n = 160$ ) of patients. In patients undergoing GA and receiving any neuromuscular blocker ( $n = 1135$ ), rocuronium was used in 96.7% of the cases ( $n = 1097$ ), followed by cisatracurium 2.2% ( $n = 25$ ), atracurium 0.4% ( $n = 5$ ), pancuronium 0.4% ( $n = 5$ ), and succinylcholine (as a single NMB agent) 0.3% ( $n = 3$ ). Therefore, for further data analysis on NMB used, only cases receiving ROC were considered. All NMB doses were administered by bolus; no continuous infusion of NMB was used.



**Figure 4.** Comparisons (violin plots) of total dose of rocuronium (mg/kg/h) according to general anesthetic technique, associated or not with neuraxial blockade. Kruskal–Wallis test and Tukey test ( $P < .001$ ).

**Table 3**

**Distribution of patients according to the interval (> or ≤ than 30 min) between neostigmine and extubation and the interval (≥ or < than 45 min) between the last dose of NMB and neostigmine.**

Interval between neostigmine and extubation	Interval between last dose of NMB and neostigmine				P value*
	Interval <45 min		Interval ≥45 min		
	n	%	n	%	
Interval ≤30 min	56	83.58	839	89.54	.15
Interval >30 min	11	16.42	98	10.46	

NMB = neuromuscular blocker(s).

\*  $\chi^2$  test.

The initial dose of ROC was 0.60 (0.52–0.74) mg/kg and total dose was 0.38 (0.27–0.53) mg/kg/h, regardless of anesthetic technique and whether it was associated or not with neuraxial blockade (n = 1097).

In patients receiving TIV GA, a total dose of ROC (mg/kg/h) was significantly lower ( $P < .001$ ) when neuraxial blockade was associated (0.30 (0.23–0.39) mg/kg/h), in comparison with cases without neuraxial blockade (0.42 (0.30–0.56) mg/kg/h). The same was observed in patients undergoing IV + IN GA (0.32 (0.23–0.41) mg/kg/h and 0.43 (0.31–0.56) mg/kg/h, respectively,  $P < .001$ ). When analyzed separately, both spinal and epidural blocks were associated with a significantly reduced total dose of rocuronium when compared with patients under the same general anesthetic technique, but without an associated neuroaxial blockade (Table 2). In patients receiving neuraxial blockade, there was no difference in the total dose of rocuronium (mg/kg/h) when the anesthetic technique was compared ( $P = .36$ ). The same occurred in patients without neuraxial blockade ( $P = .99$ ) (Fig. 4).

Among patients receiving any competitive NMB (n = 1132), neostigmine was used in 89.4% of the cases (n = 1012), at a total dose of 2.00 (2.00–2.00) mg or 29.41 (25.31–33.89)  $\mu$ g/kg. In 10.61% (n = 120), there was no NMB reversal. In 42.4% of the cases, the dose of neostigmine was >30  $\mu$ g/kg and, in only 2.4% of the cases, >50  $\mu$ g/kg. The time between the administration of the initial dose of NMB and reversal with neostigmine was 110.00 (75.00–155.00) minutes. In cases where additional doses of NMB were used, the time between the last NMB dose and reversal with neostigmine was 70.00 (55.00–100.00) minutes. In patients in whom there was no NMB reversal, the time between the initial NMB dose and extubation (duration of anesthesia) was 180.00 (105.00–205.00) minutes, with a significant difference ( $P = .03$ ), in comparison with those receiving neostigmine (140.00 (105.00–190.00) minutes). None of the cases in this study received sugammadex.

In 10.9% of the cases, the interval between neostigmine administration and extubation was > 30 minutes. The distribution of patients according to interval (> or ≤ than 30 minutes) between neostigmine and extubation was no different ( $P = .15$ ) when divided according to the interval (≥ or < than 45 minutes) between the last dose of NMB and neostigmine (Table 3). There was no significant difference in the total dose (mg/kg/h) of ROC

( $P = .15$ ) or neostigmine ( $P = .88$ ) after patient distribution according to the interval between neostigmine use and extubation (> or ≤ than 30 minutes) (Table 4).

#### 4. Discussion

This retrospective study was based on the review of medical records and anesthetic charts. Despite the fact that we cannot guarantee information obtained from these sources is a true representation of reality, we considered it to be as close as possible and to the best knowledge of the hospital's clinical staff. However, this is a limitation and a possible bias that we cannot disconsider completely.

The most widely used NMB in this institution during the study period was ROC, as also demonstrated in recent studies from other institutions.<sup>[7,9,18]</sup> In the majority of cases, a single dose of NMB was administered. This may have been related to the duration of most anesthesia (approximately 2 hours), a result similar to those described in other studies.<sup>[2,18]</sup>

In this study, the use of neostigmine in 89.4% of cases for the reversal of neuromuscular block contradicts data from studies conducted in other countries, where routine pharmacologic reversal of neuromuscular block is performed by only a minority of anesthesiologists.<sup>[17,19]</sup> Although 71.9% of patients received a single dose of NMB and the mean duration of anesthesia was 142 minutes, reversal with neostigmine is still necessary, especially in the absence of neuromuscular monitoring. A study by Debaene et al<sup>[2]</sup> showed that the incidence of neuromuscular blockade is high even after a single dose of NMB in surgical procedures lasting 2 hours or more. However, routine use of neostigmine, in the absence of monitoring, does not eliminate the risk of residual blockade.<sup>[20,21]</sup> Thus, it is essential to use quantitative neuromuscular monitoring and study the incidence of PORC in the postanesthetic care unit.

The mean dose of neostigmine observed in this study was 2.02 mg or 30.18  $\mu$ g/kg, which is similar to that observed by Kotake et al.<sup>[22]</sup> Those authors found a mean dose of 33  $\mu$ g/kg in a prospective study, when NMB reversal was performed without the aid of neuromuscular monitoring.<sup>[22]</sup> However, other studies<sup>[18,23]</sup> have reported the use of doses (2.5 and 3.2 mg) slightly higher than those described in this study. Therefore, the mean neostigmine dose

**Table 4**

**Analysis of total dose of rocuronium and neostigmine according to interval between neostigmine use and extubation (≤ 30 or > 30 min).**

Variables	Interval ≤30 min*	Interval >30 min*	P value†
Dose total rocuronium, mg/kg/h	0.38 (0.28–0.52)	0.42 (0.30–0.54)	.15
Dose total neostigmine, $\mu$ g/kg	29.41 (25.31–33.89)	28.84 (25.64–33.33)	.88

\* Values expressed in median (q1–q3).

† Wilcoxon test.



used in this institution was shown to be lower than the dose recommended (40–70  $\mu\text{g}/\text{kg}$ ) in the literature in situations in which neuromuscular monitoring showed evidence of a deep or even a moderate or superficial blockade.<sup>[24–29]</sup>

However, it is well known that high doses of neostigmine are not exempt from unwanted effects, particularly when administered in the presence of complete recovery from the neuromuscular block ( $T4/T1 \geq 0.9$ ). In this case, it may lead to muscle weakness and affect function of the genioglossus muscle and diaphragm.<sup>[8,30,31]</sup> These events may be related to both a depolarizing block and an open-channel block, possibly associated with excessive doses of neostigmine.<sup>[32,33]</sup> In addition, muscarinic side effects of neostigmine have been described, such as nausea and vomiting, bradycardia, prolongation of the Q-T interval of the electrocardiograph, bronchoconstriction, stimulation of salivary glands, miosis, and increased intestinal tone.<sup>[34]</sup>

In the absence of neuromuscular monitoring, routine use of adequate neostigmine doses is currently recommended to minimize the occurrence of PORC and its deleterious effects. Therefore, the introduction of quantitative neuromuscular monitoring into clinical practice is mandatory and urgent, since it may contribute to the prevention of excessive doses of neostigmine and its adverse effects.<sup>[21,24]</sup> It is known that clinical judgement is insufficient to correctly determine the need for reversal of NMB and the adequate use of neostigmine.<sup>[4,9,21]</sup> However, decision on reversal of NMB is still based on clinical judgement, notably in settings where neuromuscular monitoring is not widely available or routinely used.<sup>[35]</sup> Previous studies have shown that anesthesiologists usually elect NMB reversal based on the moment and dose of the last NMB administration and qualitative judgement of the adequacy of the breathing pattern.<sup>[35]</sup> We believe this was also most likely the case in our institution, even though it was not the objective of this study to determine the decision-making process.

Previous studies have demonstrated potentiation of NMB by volatile anesthetics, with a resultant decrease in the total dose of these drugs.<sup>[36–39]</sup> The mechanism behind this interaction has still not been fully elucidated. Potentiation may occur due to several factors: effect of volatile agents on acetylcholine receptor channels; action on the central nervous system, causing reflex medullary depression and contributing to tone reduction with skeletal muscular relaxation; decreased postjunctional synaptic membrane sensitivity to depolarization caused by acetylcholine; and increased muscle blood flow, allowing a higher amount of NMB to reach the site of action.<sup>[40,41]</sup>

Nevertheless, in this study, the difference observed in the total dose of NMB between patients undergoing IV+IN and TIV anesthesia is correlated with the presence or absence of neuraxial blockade and not with the inhalational agent. Our study did not show any association with lower doses of NMB in anesthetics using inhalational agents when compared with TIV anesthetics. This result may be due to the absence of neuromuscular monitoring. Potentiation of neuromuscular block by volatile agents may have gone undetected by the anesthesiologist and did not imply a decreased dose of NMB used.

In prolonged anesthetics, additional doses of NMB were used more frequently. However, when the total dose of rocuronium was evaluated in  $\text{mg}/\text{kg}/\text{h}$ , taking into account the duration of anesthesia, this dose was lower in patients receiving neuraxial blockade. As described in clinical and experimental studies, the use of lower doses of NMB may be justified not only by the motor block caused by local anesthetics, but also by the interaction between local anesthetics and NMB.<sup>[42–46]</sup> However, there is still

controversy over the mechanisms behind this interaction, which seems to be multifactorial and due to different mechanisms. In the presynaptic region, local anesthetics alter motor fiber conduction and reduce the release of acetylcholine. In the postsynaptic region, local anesthetics lead to receptor desensitization, cause temporary occlusion of nicotinic receptor channels, and interfere in the process of excitation-contraction coupling of the muscle fiber.<sup>[42,43,46–49]</sup> Previous authors have found that neuraxial blockade can be related to reduction on the needed dose of NMB during GA or delayed recovery to TOF ratio of 0.9 when unchanged doses of NMB are administered.<sup>[45,47]</sup> These reports were prospective studies with smaller group of patients and with the aid of neuromuscular monitoring.

An interval longer than 30 minutes between neostigmine administration and extubation occurred in 10.9% of cases, suggesting that incomplete recovery of neuromuscular block occurred in these patients. Compared with patients in whom the interval was  $\leq 30$  minutes, this longer time until extubation had no relationship with the interval between the initial dose of NMB and neostigmine use, the interval between the last dose of NMB and neostigmine use, the total dose of rocuronium ( $\text{mg}/\text{kg}/\text{h}$ ) or dose of neostigmine. We hypothesize that these patients perhaps exhibited a wider interval between neostigmine administration and extubation due to insufficient or excessive doses of neostigmine, or the drug was given at an inappropriate time. Furthermore, the residual effects of central nervous system depressants inherent to other drugs used in GA (opioids, hypnotics, etc.) must be considered.

In summary, our current study evidences that in a real-life setting, even in the absence of neuromuscular monitoring, neuroaxial blockade (spinal or epidural) is significantly associated with reduced total dose of NMB during GA. This is of paramount importance, especially in settings without quantitative neuromuscular monitoring, as it endorses previous recommendations that regional anesthesia may be used as a strategy to prevent residual paralysis.<sup>[50]</sup> Additionally, our findings sustain worldwide publications suggesting that currently used neostigmine doses are below recommendations when quantitative neuromuscular monitors are not used in clinical practice.

## 5. Conclusion

The main neuromuscular blocking agent used was rocuronium. In patients receiving neuraxial blockade, the total NMB dose (in  $\text{mg}/\text{kg}/\text{h}$ ) was lower, regardless of general anesthetic technique. In the majority of cases, neostigmine was used to reverse neuromuscular block, at doses lower than recommended, and without neuromuscular monitoring. The prolonged interval between neostigmine and extubation ( $> 30$  minutes) did not correlate with the total dose of rocuronium, total dose of neostigmine or time of NMB administration. The results of this study corroborate the role of quantitative neuromuscular monitors and the need of adjusting doses of neostigmine in settings where quantitative neuromuscular monitors are not available. Neuraxial blockade was associated with reduced doses of NMB during GA and Future studies are needed to evaluate the possible role of neuraxial blockade in reducing the incidence of PORC.

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