Original Article

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Incidence of postoperative residual neuromuscular blockade – A multicenter, observational study in Portugal (INSPIRE 2)

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Abstract

Background: Although the use of neuromuscular blocking agents (NMBAs) optimizes surgical conditions and facilitates tracheal intubation, it can lead to residual neuromuscular blockade (RNMB), with postoperative complications. This study aimed to assess RNMB incidence and management in Portugal.

Methods: Prospective observational study of patients admitted for elective surgery requiring general anesthesia with non-depolarizing NMBAs between July 2018 and July 2019 at 10 Portuguese hospitals. The primary endpoint was the proportion of patients arriving at postanesthesia care unit (PACU) with a TOF ratio <0.9.

Results: A total of 366 patients were included, with a median age of 59 years, and 89.1% classified as ASA II or III. Rocuronium was the most used NMBA (99.5%). A total of 96.2% of patients received a reversal agent, 96.6% of which sugammadex and 3.4% neostigmine. Twenty patients displayed a TOF ratio <0.9 at PACU arrival, representing an RNMB incidence of 5.5% (95% CI, 3.1%–7.8%). Only two patients displayed a TOF ratio <0.7. RNMB incidence was 16.7% with neostigmine and 5.3% with sugammadex ($P = .114$). In patients with intraoperative neuromuscular blockade (NMB) monitoring, RNMB incidence was 5% (95% CI, 2%–8%), which varied significantly according to the type of monitoring ($P = .018$). Incidence of adverse events was 3.3% (2 severe and 10 moderate).

Conclusions: The reported overall incidence of 5.5% is numerically lower than results from similar observational studies. An appropriate pharmacological neuromuscular reversal strategy, guided by quantitative neuromuscular monitoring, has the potential to achieve even better results, converting RNMB from an unusual to a very rare or even inexistent event.

Keywords: general anesthesia, neuromuscular blocking agents, neuromuscular reversal agents, neuromuscular monitoring, residual neuromuscular blockade

Introduction

General anesthesia is usually achieved through the balance of three components: analgesic, hypnotic, and neuromuscular blocking agents (NMBAs). Although NMBAs optimize surgical conditions and facilitate tracheal intubation, their use might be associated with residual neuromuscular blockade (RNMB). This RNMB is secondary to the remaining effect of these agents at a moment in which complete effect reversal would be desirable.[1-7] The reported incidence of RNMB varies between 16% to more than 70%, depending on the used definition (train-of-four [TOF] ratio <0.7 or <0.9), type of NMBA, type of reversal agent, and timing of measurements.[5] The use of NMBAs of intermediate duration, intraoperative NMB monitoring, and neuromuscular blockade pharmacological reversal seem to contribute to decrease, but not eliminate, RNMB.[3,8,9]

For several years, the standard criterion for adequate neuromuscular function recovery was a TOF ratio ≥0.7. However, evidence has shown that non-negligible RNMB signs and symptoms may persist up to a TOF ratio of 0.9. Therefore, the most currently accepted criterion for adequate RNMB reversal is a TOF ratio ≥0.9 at the thumb adductor.[5]

Clinical consequences of RNMB in the postanesthesia care unit (PACU) include impaired airway protective reflexes, pharyngeal dysfunction, and reduced hypoxic ventilatory response that may contribute to an increase in postoperative complications, namely increased oxygen desaturation, airway obstruction, reintubation, and pneumonia.[10,11]

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An initial study from our group, conducted between July and November 2010 in eight Portuguese hospitals to assess the incidence of postoperative RNMB, reported a global TOF ratio <0.9 incidence of 26% at PACU arrival.[12] This study raised awareness on the relevance of residual blockade in Portuguese surgical patients and emphasized the need to make changes to improve results. Therefore, clinical sessions on RNMB management and monitoring were held in various Portuguese hospitals. Simultaneously, sugammadex was introduced in clinical practice, gradually replacing the conventional reversal strategy with anticholinesterasic drugs.

The aim of this study was to assess neuromuscular blockade management in Portugal, by investigating RNMB incidence 8 years after the initial study.

Methods

Study design

This is a multicenter, prospective, observational study of adult patients undergoing different types of elective surgical procedures requiring general anesthesia with nondepolarizing NMBAs, between July 2018 and July 2019, conducted at 10 public Portuguese hospitals.

This study comprised two periods: (1) an initial evaluation at PACU arrival and (2) a subsequent collection of patient data at hospital discharge.

Each participating hospital was required to have their PACU adjacent to the operating rooms so that the transfer time between the operating room and PACU did not exceed 10 minutes.

Endpoints

The primary endpoint was the proportion of patients arriving at PACU with a TOF ratio <0.9. Secondary endpoints were (1) the proportion of patients arriving at PACU with a TOF ratio <0.7; (2) association between administration of NMBA during anesthesia and a TOF ratio <0.9 at PACU; (3) association between intraoperative NMB monitoring and a TOF ratio <0.9 at PACU. The association between comorbidities and the American Society of Anesthesiologists (ASA) physical status and a TOF ratio <0.9 at PACU were exploratory endpoints.

Inclusion and exclusion criteria

Inclusion criteria were as follows: patients aged 18 years or older admitted for elective surgery, having received nondepolarizing NMBAs during surgery, and being able and willing to provide written informed consent. Exclusion criteria were as follows: having been reoperated on the same hospital admission or if more than 10 minutes had elapsed since tracheal extubation until NMB monitoring at PACU.

Type of anesthesia and intraoperative monitoring

Type of anesthesia and intraoperative monitoring were left at the attending anesthesiologist discretion.

On PACU arrival and immediately after establishment of vital sign monitoring, two electrodes were placed over the ulnar nerve and three consecutive 40 mA TOF stimulations (four pulses of 0.2 ms duration at a 2 Hz frequency) were applied with 15-second intervals. Evoked thumb responses were measured by using the TOFscan acceleromyography monitor (IDMED, France). RNMB was defined by the average of three consecutive evoked response measurements. If measurements differed more than 20%, an additional sequence of three measurements was performed. Patients were excluded if a variation greater than 20% was registered in this second measurement sequence.

Variables

Following these procedures, patient data were collected, including demographics (sex, age, weight, and height), vital signs at PACU arrival (heart rate, blood pressure, oxygen saturation, and tympanic temperature), clinical history, comorbidities (according to International Classification of Diseases-9), surgical diagnosis, ASA classification, and relevant perioperative medication (total dosage and administration time). Adverse events, according to the International Conference on Harmonization definition of adverse events, during PACU stay and hospital discharge or death, were also recorded.

This study was registered at ClinicalTrials.gov (NCT03417804).

Ethics

This study was conducted according to the tenets of the Declaration of Helsinki in its latest version (Brazil 2013). Ethical approval for this study (2017.156-133-DEFI/125-CES) was provided by the Ethics Committee of the promoting hospital, on December 20, 2017. All participants signed a written informed consent.

Statistical analysis

Assuming an expected incidence of patients arriving at PACU with objective evidence of incomplete neuromuscular recovery of 26%,[12] a 5% error margin, a 95% confidence interval (95% CI), and a conservative discontinuation rate of 20%, a sample size of 360 patients was estimated to be required to complete the study (StatsDirect 3 Statistical Software).

Two groups were considered for statistical analyses: patients without RNMB criteria (TOF ratio ≥0.9) and patients with RNMB criteria (TOF ratio <0.9).

Categorical variables were expressed as frequencies (percentage) and continuous variables as median and interquartile range (IQR). The χ^2 test or the Fisher exact test was used for between group comparisons. Statistical significance was set at $P<.05$. Data were analyzed with SPSS Statistics (IBM SPSS version 25.0) software.

Results

Attrition rate

A total of 385 patients were recruited for the study. Nineteen (4.9%) of those were excluded because of the following reasons: not meeting inclusion criteria (n = 2), having elapsed more than 10 minutes between tracheal extubation and NMB monitoring at PACU (n = 6), not having a valid TOF ratio measurement at PACU (second TOF ratio measurement sequence with >20% difference [n = 4] or unobtainable TOF ratio measurement because of technical issues [n = 1]), or having missing NMB data in clinical records (n = 6). A final sample of 366 patients undergoing elective surgery was included in the study, representing an attrition rate of 4.9%.

Baseline characteristics

Of the 366 patients included in the study, 159 (43.4%) were male patients. The global median age was 59 years (IQR 22), and the median body mass index was 26.50 (IQR 6.93).

Table 1.

Baseline patient characteristics and at PACU arrival.

	Median (IQR) or Number (%)
Baseline	
Sex—female	207 (56.6%)
Age (years)	59 (22)
Weight (kg)	72 (21)
Height (m)	1.65 (0.13)
Body mass index	26.50 (6.93)
ASA physical status	
I	37 (10.1%)
II	214 (58.5%)
III	112 (30.6%)
IV	3 (0.8%)
At PACU arrival	
Temperature (°c)	35.9 (0.8)
Heart rate (bpm)	75 (22)
Systolic blood pressure (mmHg)	130 (27.5)
Diastolic blood pressure (mmHg)	74 (19)
O_2 saturation (%)	98 (3)

ASA, American Society of Anesthesiologists; IQR, interquartile range; PACU, Postanesthesia Care Unit.

A total of 37 patients (10.1%) were included in ASA physical status I, 214 (58.5%) in ASA II, 112 (30.6%) in ASA III, and 3 (0.8%) in ASA IV (Table 1). The most frequent comorbidities were endocrine/metabolic/immunological disorders in 55.5% of cases, circulatory system conditions in 50.8%, neoplasms in 32.8%, respiratory system disorders in 26%, digestive system disorders in 19.1%, genitourinary system disorders in 17.2%, mental disorders in 14.8%, nervous system disorders in 10.1%, blood and blood-forming organ disorders in 6%, and musculoskeletal/connective tissue disorders in 5.7%. All other comorbidities had an incidence below 2.5%.

Patient characteristics at PACU arrival

At PACU arrival, median body temperature was 35.9 C° (IQR 0.8), median heart rate was 75 (IQR 22) beats per minute, median systolic blood pressure was 130 (IQR 27.5) mmHg, median diastolic blood pressure was 74 (IQR 19) mmHg, and median O_2 saturation was 98% (IQR 3%) (Table 1). Thirty-three patients (9%) required a second TOF ratio assessment sequence at PACU. Twenty patients displayed a TOF ratio <0.9 on PACU arrival, representing an RNMB incidence of 5.5% (95% CI, 3.1%–7.8%). Of those, only two patients displayed a TOF ratio less than 0.7, placing the incidence of severe RNMB at 0.5% (95% CI, 0.4%–2.5%).

Table 2.

Intraoperative data of used drugs.

	Number (%)
Neuromuscular blocking agents (n = 366)	
Rocuronium	364 (99.5)
Cisatracurium	2 (0.5)
Succinylcholine	7 (1.9)
Reversal agents (n = 366)	
Sugammadex	340 (92.9)
Neostigmine	12 (3.3)
No reversal	14 (3.8)
Other agents used during surgery (n = 366)	
Propofol	323 (88.3)
Fentanyl	321 (87.7)
Sevoflurane	101 (27.6)
Desflurane	95 (26.6)
Remifentanil	55 (15.0)
Midazolam	52 (14.2)
Morphine	42 (11.5)
Others (<5%)	76 (20.8)
Neuromuscular blockade monitoring (n = 365)	
Yes	195 (53.4)
Quantitative monitoring	153 (78.5)
Qualitative monitoring	39 (20.0)
Missing	3 (1.5)

Intraoperative drug data

Intraoperative drug data are summarized in Table 2. The most widely used NMBA was rocuronium (n = 364, 99.5%), with cisatracurium used in only two (0.5%) patients. Succinylcholine was used in 7 patients (1.9%), 6 of which had also received rocuronium and one cisatracurium. A total of 352 patients (96.2%) received a reversal agent, 340 (96.6%) of which sugammadex and 12 (3.4%) neostigmine. A total of 195 patients (53.3%) had intraoperative NMB monitoring, 153 (78.5%) of which quantitative monitoring and 39 (20.0%) qualitative monitoring. For three patients, information on the type of monitoring was missing. Doses of NMBA and NMB reversal agents are shown in Table 3.

RNMB incidence and association with other parameters

RNMB incidence in patients not receiving reversal agents was 0%. In patients receiving reversal agents, RNMB incidence was 16.7% in patients receiving neostigmine (2/12) and 5.3% in those receiving sugammadex (18/340), but this difference was not statistically significant (P = .114; Fig. 1). Regarding the occurrence of RNMB according to neuromuscular blocker, the two patients receiving cisatracurium did not present RNMB.

RNMB incidence in patients with intraoperative NMB monitoring was 5% (95% CI, 2%–8%), while in patients without NMB monitoring was 6% (95% CI, 2%–9%), with no significant differences (χ^2 test P = .752).

In patients having intraoperative monitoring, a statistically significant difference was found in RNMB incidence according to type of monitoring (Fisher exact test P = .018; Fig. 2). Figure 3 summarizes RNMB occurrence according to ASA physical status of patients. Figure 4 summarizes the RNMB occurrence when comparing patients with ASA physical status below IV and IV.

For comorbidity analysis, only comorbidities with an incidence higher than 10% were considered. Differences in RNMB incidence were not statistically significant in any of the considered comorbid categories (Fig. 5).

Table 3.

Total doses of neuromuscular blocking agents and reversal agents used.

	Dose (mg), Median (IQR)
Neuromuscular blocking agents	
Rocuronium	60 (40)
Cisatracurium	10 and 30
Succinylcholine	80 (40)
Reversal agents	
Sugammadex	200 (50)
Neostigmine	2.5 (0.5)

IQR, interquartile range.

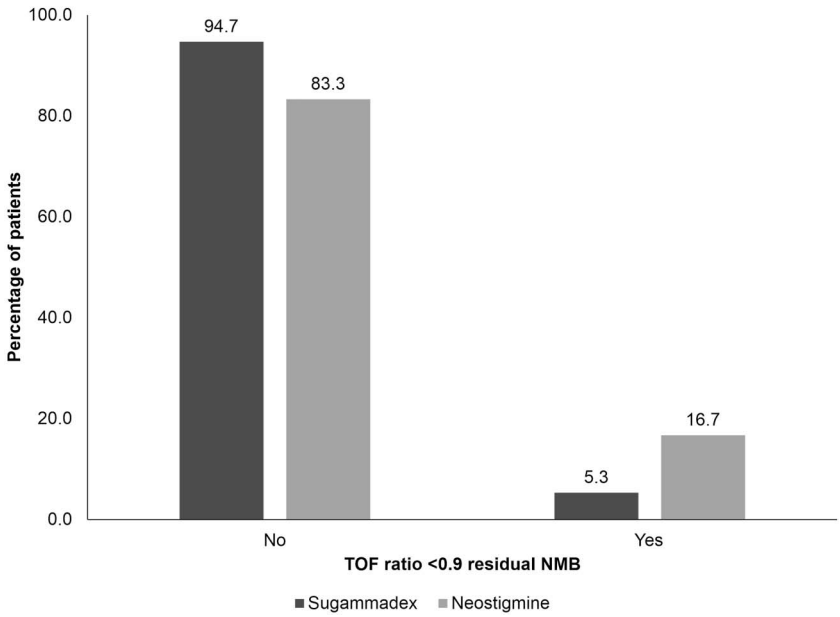

Figure 1. Presence of residual neuromuscular blockade (RNMB) according to reversal agent. Fisher exact test not significant ($P = .114$). TOF, train-of-four.

Hospital stay

The median length of hospital stay after surgery was 2 days (IQR 4).

Adverse events

The reported incidence of adverse events was 3.3%, which were classified as severe in two cases and moderate in ten. Severe adverse events included one case of severe RNMB associated with dyspnea, which was treated with sugammadex, and one case of pulmonary thromboembolism. The remaining adverse events consisted of hypoxemia and one case of sore throat. All adverse events requiring additional treatment were completely resolved.

Discussion

This study found an incidence of RNMB (TOF ratio <0.9) of 5.5% and of severe RNMB (TOF ratio <0.7) of 0.5% at PACU arrival, which is numerically lower than the results from similar observational studies reporting an incidence of RNMB between 10.8% and 45.2% and of severe RNMB between 3.6% and 28.2% in the same setting.[13-17] These discrepancies are possibly

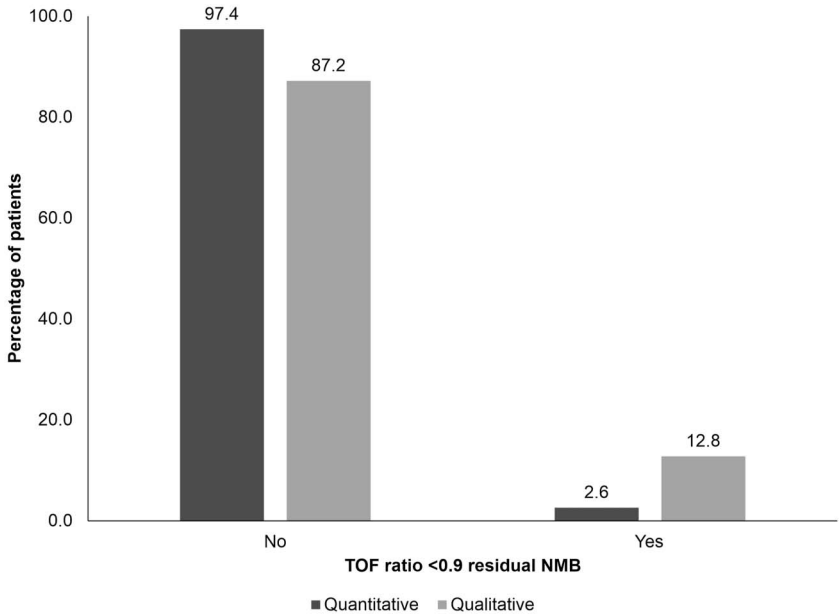

Figure 2. Presence of residual neuromuscular blockade (RNMB) in patients with intraoperative NMB monitoring according to type of monitoring. Fisher exact test significant ($P = .018$). TOF, train-of-four.

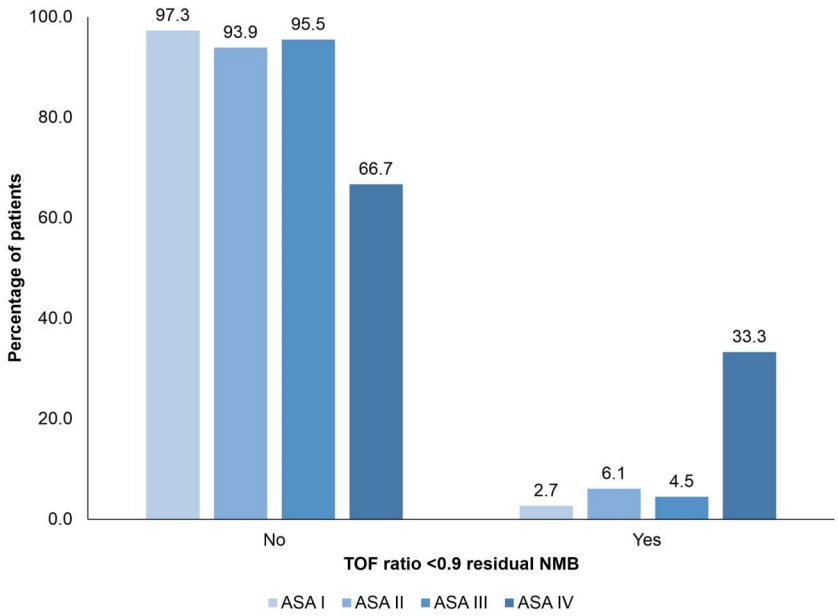

Figure 3. Presence of residual neuromuscular blockade (RNMB) according to ASA physical status. χ^2 not significant ($P = .143$). TOF, train-of-four.

because of differences in the proportion of patients receiving NMB reversal agents, type of reversal agent administered (sugammadex or neostigmine), and use of quantitative neuromuscular monitoring, among other factors influencing RNMB incidence.[9]

Regarding intraoperative neuromuscular monitoring, this study showed that 53.3% of patients were monitored, 78.5% of which quantitatively. Although quantitative monitoring is the recommendation of the current guidelines,[9,18] these numbers compare favorably with others from similar studies reporting a very low frequency of neuromuscular quantitative monitoring in these patients.[13-17] In fact, the most reliable methods to assess neuromuscular blockade are quantitative neuromuscular monitoring methods, such as acceleromyography, because they provide more objective data on neuromuscular transmission and improve RNMB detection compared with visual or tactile TOF response evaluation.[19-22]

Contrarily to a previous study,[14] no statistically significant association was found between the type of reversal agent (sugammadex or neostigmine) and RNMB incidence. Nevertheless, it is interesting to note that RNMB occurred even in patients reversed with sugammadex, confirming what was previously suggested by other authors that this agent is not always 100% effective in preventing RNMB,[14,23,24] probably because of the

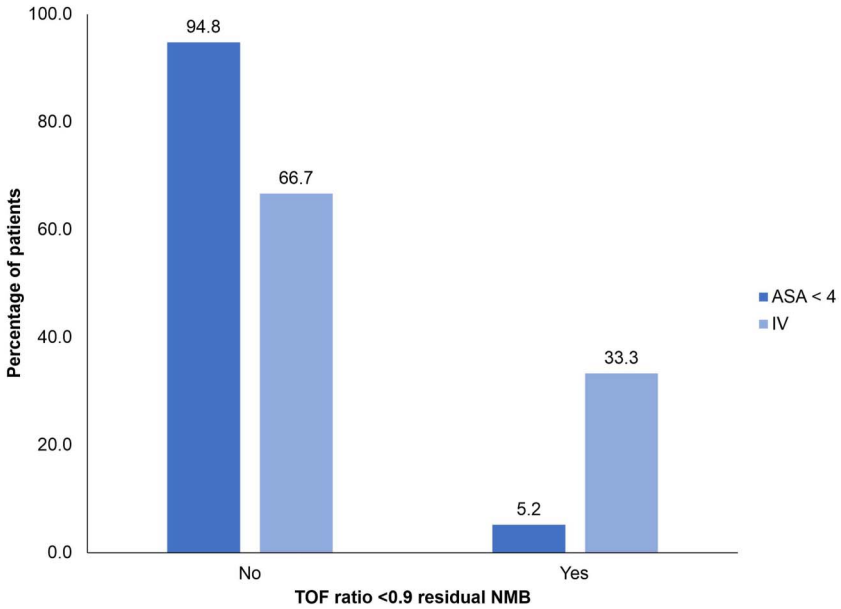

Figure 4. Presence of residual neuromuscular blockade (RNMB) according to ASA physical status IV. Fisher exact test not significant ($P = .156$). TOF, train-of-four.

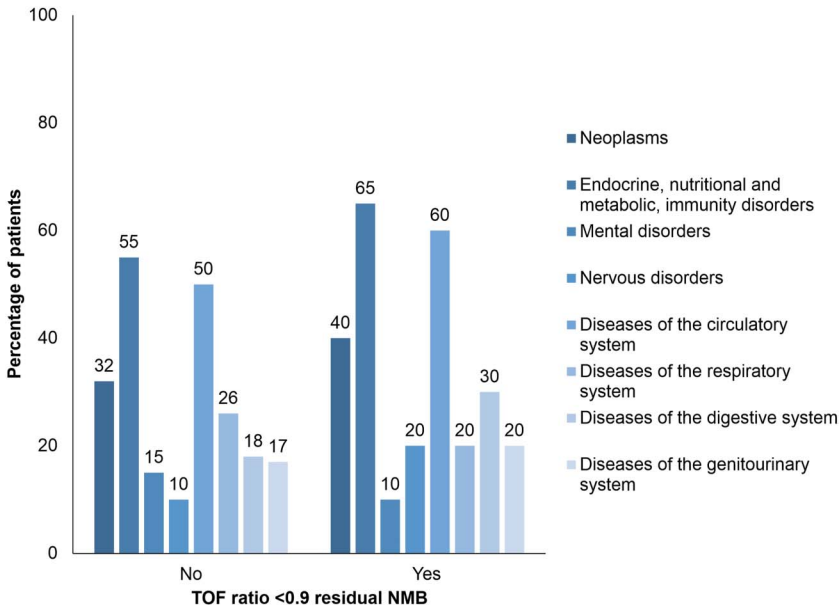

Figure 5. Presence of residual neuromuscular blockade (RNMB) for each comorbidity category. χ^2 or Fisher exact test not significant in any of the comorbidity categories (neoplasms $P = .480$; endocrine disorders $P = .378$; mental disorders $P = .750$; nervous disorders $P = .131$; diseases of the circulatory system $P = .398$; diseases of the respiratory system $P = .532$; diseases of the digestive system $P = .239$; diseases of the genitourinary system $P = .760$). TOF, train-of-four.

administration of an insufficient dose for the depth of neuromuscular blockade at the time of reversal.

In addition, no significant association was found between intraoperative neuromuscular monitoring (quantitative and qualitative) and RNMB. However, when quantitative and qualitative monitoring were compared, a statistically significant association was found between quantitative monitoring and lower RNMB incidence, which is in accordance with current recommendations and a recently published meta-analysis[9,25] but is not a consistent finding among studies. While in the study by Fortier et al qualitative monitoring was also found to be related to RNMB incidence,[16] the study by Saager et al suggested otherwise.[26] Errando et al also reported an association between neuromuscular monitoring and RNMB incidence, but the type of monitoring was not specified.[15]

Regarding exploratory endpoints, no statistically significant association was found between ASA status or comorbidities and RNMB, similarly to the study by Fortier et al.[16]

Eight years after our first study of RNMB incidence at PACU in Portuguese public hospitals,[12] the scenario seems to have changed in Portugal. In the present multicenter study, intended to depict the daily clinical practice, RNMB incidence was numerically lower than the reported in the initial study (5.5% versus 26%), and the anesthetic practice concerning intraoperative NMB also seem to have changed.[12] Notwithstanding the lack of a formal comparison, in this study, rocuronium was clearly the nondepolarizing NMBA of choice, used in 99.5% of patients compared with 44.2% of patients 8 years ago. In addition, the frequency of administration of NMB reversal agents, which was 66.6% in our previous study, was 96.2% in this study. The choice of the reversal agent also seems to have changed: In 2010, sugammadex was administered in 3.0% of patients receiving reversal agents while in this study, it was administered in 92.6% of patients. Neostigmine was administered in 97.0% and 3.4% of patients, respectively. Given these data, it seems that the awareness efforts that were conducted in Portugal regarding RNMB risks contributed to the present results. An adequate pharmacological neuromuscular reversal strategy guided by quantitative neuromuscular monitoring in all patients might achieve even better results, converting RNMB from an unusual to a very rare or even inexistent event.

TOF-Watch SX is used in most RNMB studies. Owing to the interruption in TOF-Watch production in July 2016, an alternative portable monitor had to be adopted, primarily because the same type of monitor should be used in all 10 participating centers. After testing some of the commercially available neuromuscular blockade quantitative monitors, TOFscan was chosen. Although this monitor has no calibration capabilities, research similar to this study is usually performed without calibration, using a set amperage of 30–40 mA, which is easily tolerated by patients. On the other hand, this device has a 3D accelerometer and the sensor is incorporated on a rubber U-shaped adapter that facilitates positioning. A first study comparing TOF-Watch SX and TOFscan concluded that, despite poor results for onset and early recovery phases, good agreement was obtained for later recovery to TOFr 90%.[27] A 2018 study by Murphy G et al confirmed good agreement between TOF-Watch SX with calibration and preload application and uncalibrated TOFscan throughout all stages of neuromuscular recovery.[28]

This study has strengths and limitations. Concerning strengths, this was a properly sized study, potential regional differences were addressed through recruitment of hospitals from north, center, and south regions of Portugal, and the authors intended to portray a picture of the incidence of RNMB in Portugal 8 years after first questioning this topic. Regarding limitations, this study was based on a convenience sample, not a random one. Owing to its observational nature, it was not possible to standardize practices between centers. Consequently, the time frame between extubation and TOF measurement may be different between patients and centers, and this may have influenced RNMB incidence, particularly regarding sugammadex reversal because 2 or 3 minutes can make a substantial difference in TOF ratio. Finally, the attending anesthesiologist was not blinded to inclusion of patients in the study, which could be a source of bias.

Conclusion

Rocuronium was shown to be the almost exclusive NMBA administered in the conditions of the study. The same was shown for the reversal agent sugammadex, administered in 96.6% of patients who were administered a reversal agent. Intraoperative NMB monitoring was used in 53.3% of patients. The reported incidence of 5.5% of RNMB in this study is numerically lower than the results from similar observational results.

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Conflicts of interest

S. Esteves, F. Abelha, H. Machado, N. Fernandes, and V. Pinho-Oliveira received consultant and lecture fees from MSD Portugal. The remaining authors have no conflicts of interest.

Previous presentation

Incidence of postoperative residual neuromuscular blockade—A multicenter, observational study in Portugal (INSPIRE 2)—presented at Euroanaesthesia 2020 (virtual congress). Incidência de bloqueio neuromuscular residual pós-operatório—um estudo observacional multicêntrico em Portugal (INSPIRE2)—apresentado no Congresso da Sociedade Portuguesa de Anestesiologia 2021 (congresso híbrido).

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