ORIGINAL

Residual neuromuscular block as a risk factor for critical respiratory events in the post anesthesia care unit

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KEYWORDS
Neuromuscular blockade;
Postoperative complications;
Anesthesia recovery period;
Recovery room

Abstract
Objective: Residual neuromuscular block is an important postoperative complication associated to the use of neuromuscular blocking drugs. The purpose of this study was to access the incidence of residual neuromuscular block in a post-anesthesia care unit and to evaluate its association with critical respiratory events.

Material and methods: Prospective cohort study was conducted in a Post Anesthetic Care Unit (PACU) for a period of 3 weeks. Two hundred two adult patients who submitted to scheduled non-cardiac and non-intracranial surgery were eligible to the study. The primary outcome variable was residual neuromuscular block after arrival to PACU that was defined as train-of-four ratio <1.0 and objectively quantified using acceleromyography. Demographic data, perioperative variables, lengths of hospital and recovery room stay and critical respiratory events were recorded. Inadequate emergence was classified in its different forms according to the Richmond agitation and sedation scale 1 min after admission to the recovery room.

Results: Residual neuromuscular block incidence in the post-anesthesia care unit was 29.7% (95% confidence interval: 23.4, 36.1). Patients with residual neuromuscular block had more frequently overall critical respiratory events (51% versus 16%, \(P < 0.001\)), airway obstruction (10% versus 2%, \(P = 0.029\)), mild-moderate hypoxemia (23% versus 4%, \(P < 0.001\)), severe hypoxemia (7% versus 1%, \(P = 0.033\)), respiratory failure (8% versus 1%, \(P = 0.031\)), inability to breathe deeply (38% versus 12%, \(P < 0.001\)) and muscular weakness (16% versus 1%, \(P < 0.001\)). Residual neuromuscular block was more common after high-risk surgery (53% versus 33%, \(P = 0.011\)) and was more often associated with post-operative hypoactive emergence as defined by the Richmond Agitation and Sedation Scale (21% versus 6%, \(P = 0.001\)).

Conclusions: This study suggests that residual neuromuscular block is common in the PACU and is associated with more frequent critical respiratory events.

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Residual neuromuscular block as a risk factor for critical respiratory events in post anesthesia care unit

PALABRAS CLAVE
Bloqueo neuromuscular residual; Complicaciones postoperatorias; Recuperación de anestesia; Unidad de Recuperación Postanestésica

El bloqueo neuromuscular residual como factor de riesgo para eventos críticos respiratorios en la Unidad de Recuperación Postanestésica

Resumen
Objetivo: El bloqueo neuromuscular residual es una importante complicación postoperatoria asociada al uso de fármacos bloqueantes neuromusculares. El objetivo de este estudio fue valorar la incidencia de bloqueo neuromuscular residual en una unidad de recuperación postanestésica (URPA) y evaluar su asociación con eventos respiratorios críticos.

Material y métodos: Estudio de cohortes, prospectivo realizado en una URPA durante un periodo de 3 semanas. Se incluyó a doscientos dos pacientes adultos sometidos a cirugía programada no cardíaca no-intracraneal. La variable de resultado principal fue la presencia de bloqueo neuromuscular residual después del ingreso en unidad de recuperación postanestésica definido como un cociente del tren de cuatro estímulos-TOF < 0.9 y objetivamente cuantificado usando aceleroradiografía. Se registraron datos demográficos, variables perioperatorias, tiempo de permanencia en la unidad, tiempo de estancia hospitalaria y complicaciones respiratorias. La recuperación inadecuada se clasificó de acuerdo con la escala de agitación y sedación de Richmond 10 minutos después del ingreso en la unidad.

Resultados: La incidencia de bloqueo neuromuscular residual en la URPA fue de 29.7% (Intervalo de Confianza 95%: 23.4 - 36.1). Los pacientes con bloqueo residual tuvieron eventos respiratorios críticos, considerados de forma global con mayor frecuencia (51% frente 16%, p < 0,001), obstrucción de vía aérea (10% frente 2%, p=0,029), hipoxemia leve-moderada (23% frente 4%, p < 0,001), hipoxemia grave (7% frente 1%, p=0,033), insuficiencia respiratoria (8% frente 1%, p=0,031), incapacidad para respirar profundamente (38% frente 12%, p < 0,01) y debilidad muscular (16% frente 1%, p < 0,001). El bloqueo neuromuscular residual fue más frecuente después de cirugía de alto riesgo (53% frente 33%, p=0,011) y se asociaba más a menudo con recuperación anestésica hipoactiva según lo definido por la escala de agitación y sedación de Richmond (21% frente 6%, p < 0,001).

Conclusiones: Este estudio sugiere que el bloqueo neuromuscular residual es común en la URPA y se asocia a mayor frecuencia de incidentes respiratorios críticos.

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Background

When neuromuscular blocking drugs (NMBD) are administered intraoperatively, residual neuromuscular Block (RNMB) is often observed in the Post Anesthesia Care Unit (PACU). Some studies have established an association between RNMB and increased postoperative morbidity and mortality, critical respiratory events (CRE), and longer PACU stays. Among nerve stimulation types, objective quantitative monitoring by means of acceleromyography is preferred in the clinical setting.

Since the studies of Eikermann et al. and Sundman et al. it became clear that partial neuromuscular transmission failure even to a degree insufficient to evoke respiratory symptoms markedly decreases upper airway function. These studies support the current recommendations of reaching a TOF ratio equal to or greater than 0.9 to ensure a safe muscle function recovery. Despite the use of short-acting NMBDs and pharmacological reversal of neuromuscular block, the incidence of RNMB on arrival to the PACU can be as high as 31-64%. Increases in the incidence of CRE at the PACU even in the presence of small degrees of RNMB have been reported. Many factors related to patients, surgical procedures and anesthetic management could be involved. Patient risk factors include advanced age, male sex, chronic obstructive pulmonary disease, diabetes and obesity. Surgery-related variables include abdominal or orthopedic, emergency and long duration surgery. Finally, anesthetic risk factors for CRE in the PACU include the use of general anesthesia, opioids and NMBD. Inadequate emergence from anesthesia can be classified into two subtypes: emergence delirium, characterized by agitation, restlessness and hyperactivity; and hypoactive emergence, characterized by a delayed recovery after anesthesia. Inadequate emergence after anesthesia is a frequent complication seen in PACU. Hypoactive emergence occurs less frequently than emergence delirium and is associated with a longer postoperative hospital stay.

The purpose of this study was to assess the incidence of RNMB in the PACU and to examine its association with the appearance of critical respiratory events (CRE).

Our hypothesis was that patients with RNMB had a higher incidence of CRE. We hypothesized that some perioperative characteristics could have an association with RNMB.

Methods

The Institutional Review Board and the Ethic Committee of Centro Hospitalar São João approved this study. Written informed consent was obtained from all participants. Centro Hospitalar S. João, Porto, is a 1124-bed tertiary hospital in a
major metropolitan area that serves 3,000,000 people. This prospective observational study was conducted in a 12-bed PACU between 8:00 AM and 8:00 PM, Monday–Friday, over a three-week period (from May 9th to May 27th, 2011).

Inclusion criteria were the ability of patient to provide written informed consent, admission to the PACU on spontaneous ventilation and intraoperative use of NMBD. Exclusion criteria were patient refusal, incapacity of providing informed consent, a score of <25 in the mini-mental state examination (MMSE),²⁰ age under 18 years, foreign nationality, known neuromuscular disease, urgent/emergent surgery and cardiac surgery, neurosurgery or other procedures that required therapeutic hypothermia.

Before surgery a small interview was conducted to obtain consent, to perform MMSE test and to collect the medical history.

The anesthesiologist in charge was blinded to patient involvement in the study. The anesthesiologist performed anesthesia and monitoring, but by following minimum departmental standards. NMBD were used for tracheal intubation, and additional boluses if needed. The use of neuromuscular monitoring, was at the discretion of the anesthesiologist and no written policy exists concerning its use. To ensure that the anesthesiologist remained blinded to their participation in the study, we did not attempt to observe the use or interpretation of TOF intraoperatively. At the conclusion of the surgical procedure the anesthesiologist was free to take the decision to reverse the NM with neostigmine. In our practice this drug is usually administered early (>15–20 min before tracheal extubation) and at a shallower depth of block.

Usually the patient is extubated at the operating room and transferred to the PACU. Criteria for extubation included sustained head lift or hand grip for more than 5 s, the ability to follow simple commands, a stable ventilatory pattern with an acceptable arterial oxygen saturation (SpO₂ >95%), and a TOF ratio of greater than 0.80. All subjects were administered 100% oxygen by facemask after tracheal extubation. The anesthesiologist is free to decide if oxygen was administered during the time between transfer to the cart and admission to the PACU.

Upon arrival on the PACU oxygen was applied to all subjects by either nasal cannula or face mask.

The RNMB was defined as TOF ≤0.9 and it was quantified at admission to the PACU using acceleromyography of the adductor pollicis muscle. The stimulation current was set to 50 mA. Three consecutive TOF measurements (separated by 15 s) were obtained, and the average of the 3 values was recorded. If a value differed from the others by more than 10%, an additional TOF measurement was obtained and the closest 3 ratios were averaged. Neuromuscular block was re-assessed hourly if TOFr ≤0.9.

The time when the patient showed TOFr >0.9 was recorded and the attending anesthesiologist was contacted and informed.

The initial TOF ratios were measured before any therapeutic intervention in the PACU. A standardized data collection sheet was completed for each patient.

We record patient age, weight, height, body mass index (BMI), American Society of Anesthesiologists physical status (ASA-PS). The Revised Cardiac Risk Index (RCRI) was calculated using the classification system reported by Lee et al.²¹ that scores high risk surgery (i.e., intraperitoneal, intrathoracic, or suprainguinal vascular) and clinical risk factors (history of ischemic heart disease, history of compensated or prior heart failure, history of cerebrovascular disease, diabetes mellitus, and renal insufficiency). Intraoperative details recorded included type of anesthesia, surgical procedure, duration of anesthesia, duration of surgery, intraoperative fluids, NMBD, time in which last dose of the NMBD was injected and neuromuscular block reversal drug used. Patients’ tympanic temperature, blood pressure, heart rate, peripheral oxygen saturation and mean TOF ratio were recorded on admission to the PACU. The length of PACU stay and occurrence of CRE were also recorded.

Each CRE was defined on the data collection sheet using the following criteria used by Murphy et al.²:

1. upper airway obstruction requiring an intervention (jaw thrust, oral or nasal airway);
2. mild-moderate hypoxemia oxygen saturations (SpO₂) of 93–90%);
3. severe hypoxemia (SpO₂ <90%);
4. signs of respiratory distress or impending ventilator failure (respiratory rate >20 breaths per minute, accessory muscle use, tracheal tug);
5. inability to breathe deeply when requested;
6. symptoms of respiratory or upper airway muscle weakness (difficulty breathing, swallowing or speaking);
7. patient requiring reintubation in the PACU; and
8. clinical evidence or suspicion of pulmonary aspiration after tracheal extubation (gastric contents observed in the oropharynx and hypoxemia).

PACU nurses were instructed to review this checklist on each patient after PACU admission and to contact the investigator if a CRE was observed. In that situation investigator examined the patient to confirm that the patient met at least one of the criteria for a CRE.

Inadequate emergence was classified according to the Richmond agitation and sedation scale (RASS) 10 min after admission to the PACU. The Richmond Agitation-Sedation Scale (RASS) has demonstrated excellent interrater reliability and criterion, construct, and face validity.²²,²³

Emergence delirium was defined as a RASS score ≥+1, and hypoactive emergence was defined as a RASS score ≤−2 (18). PACU discharge times were recorded by PACU nurses.

Our power analysis (power 80% and alpha error = 0.005) was guided by the study of Murphy on RNMB and adverse respiratory events.²⁴ We expected an incidence of RNMB of 30%, and we calculated that 60 patients with and 140 without RNMB would provide a power greater than 80% to detect differences in the proportions of CRE (expected incidence 12%) or to detect a difference greater than 29% in the worst case.

Statistical analysis

Descriptive analysis of variables was used to summarize data. Ordinal and continuous data found not to follow a normal distribution, based on the Kolmogorov–Smirnov test for normality of the underlying population, are presented as median and interquartile range. Normally distributed data
are presented as mean and standard deviation (SD). An univariate analysis was performed to identify determinants for RNMB using the Mann–Whitney U test to compare continuous variables and Chi-square or Fisher’s exact test to compare proportions between two groups of subjects. Differences were considered statistically significant when $P < 0.05$. Data was analyzed using SPSS software for Windows Version 19.0 (SPSS Inc., Chicago, IL, USA).

**Results**

From the 357 patients consecutively admitted in the PACU during the study period, a total of 202 patients were studied. Gastrointestinal surgery accounted for 49% of cases, plastic and reconstructive surgery for 15%, gynecologic surgery and orthopedics each, 10%, urology 8%, vascular 4%, head and neck surgery to 3% and otorhinolaryngology to 1%.

Other perioperative characteristics are summarized in Tables 1 and 2.

Seventeen patients were excluded: 7 patients were admitted in a surgical intensive care unit, 3 patients did not provide informed consent or had a Mini Mental Status Examination $< 25$, 3 patients were not operated, one was less than 18 years old, one did not speak Portuguese, one refused to participate and one patient was not assessed due to the impossibility to perform TOF measurements as planned (patient had plaster on both arms).

Patients and the perioperative characteristics are summarized in Tables 1 and 2.

The CRE are showed on Table 3.

On arrival in the PACU, 61 patients (29.7%; 95% confidence interval: 23.4, 36.1) were found to have RNMB.

There were no differences in the incidence of RNMB according to type of NMBD used and to the type of anesthesia (combined versus general anesthesia). Median administration of crystalloids was 1000 ml for both groups and there were no differences in the amounts of fluids and blood products administered.

Time from last dose of NMBD injection to arrival in PACU was shorter in patients with RNMB (median 63 min versus 90 min, $P = 0.012$). Neostigmine was administered to 98% of patients with RNMB and to 81% of patients with TOF $> 0.9$ (Table 2). RNMB was also significantly more common after high-risk surgery (53% versus 33%, $P = 0.011$). Patients with RNMB had a higher incidence of CRE when compared to patients without (51% versus 16%, $P < 0.001$). This also applies to each CRE considered independently (Table 3). The length of stay in the PACU and in the hospital was not different between groups.

**Discussion**

In our work thirty percent of patients exhibited RNMB after surgery, on arrival to our PACU.

RNMB was more common after high-risk surgery because these patients might have been submitted to a different anesthetic management, eventually with a closer monitoring or because their surgery was long lasting.
Table 2  Anesthesia related characteristics of patients with (TOFm <90) and without (TOFm ≥90) neuromuscular residual block.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (N = 202)</th>
<th>TOFm &lt;90 (n = 61)</th>
<th>TOFm ≥90 (n = 141)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type anesthesia, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.501(b)</td>
</tr>
<tr>
<td>General anesthesia</td>
<td>181 (90)</td>
<td>56 (92)</td>
<td>125 (89)</td>
<td></td>
</tr>
<tr>
<td>Combined anesthesia</td>
<td>21 (10)</td>
<td>5 (8)</td>
<td>16 (11)</td>
<td></td>
</tr>
<tr>
<td>NMDB, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.363(b)</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>53</td>
<td>18 (30)</td>
<td>35 (25)</td>
<td></td>
</tr>
<tr>
<td>Vecuronium</td>
<td>1</td>
<td>0</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>144</td>
<td>43 (70)</td>
<td>101 (72)</td>
<td></td>
</tr>
<tr>
<td>Atracurium</td>
<td>4</td>
<td>0</td>
<td>4 (3)</td>
<td></td>
</tr>
<tr>
<td>Time(min) last NMBD to PACU, median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients given suxamethonium, n (%)</td>
<td>30 (15)</td>
<td>13 (22)</td>
<td>17 (12)</td>
<td>0.059(a)</td>
</tr>
<tr>
<td>TOFm (%)</td>
<td>174 (86)</td>
<td>59 (98)</td>
<td>115 (81)</td>
<td>0.005(b)</td>
</tr>
<tr>
<td>TOFm &lt;90</td>
<td>90 ± 15</td>
<td>75 (62-84)</td>
<td>97 (95-99)</td>
<td>&lt;0.001(c)</td>
</tr>
<tr>
<td>TOFm &lt;80</td>
<td>30.2</td>
<td>30.2</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>TOFm &lt;70</td>
<td>18.3</td>
<td>18.3</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>TOFm &lt;60</td>
<td>12.4</td>
<td>12.4</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Duration of surgery (min), median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-operative hypoaetive (RASS≤2), n (%)</td>
<td>21 (10)</td>
<td>13 (21)</td>
<td>8 (6)</td>
<td>0.001(a)</td>
</tr>
<tr>
<td>Temperature at PACU (°C), median (IQR)</td>
<td>35.2 (34.8-35.5)</td>
<td>35.2 (34.8-35.5)</td>
<td>35.2 (34.8-35.8)</td>
<td>0.463(c)</td>
</tr>
<tr>
<td>SpO2 at PACU admission, median(IQR)</td>
<td>96 (95-98)</td>
<td>97 (95-99)</td>
<td>96 (95-98)</td>
<td>0.148(c)</td>
</tr>
<tr>
<td>Length of PACU stay (days), median (IQR)</td>
<td>100 (74-136)</td>
<td>100 (74-136)</td>
<td>100 (73-140)</td>
<td>0.901(c)</td>
</tr>
<tr>
<td>Length of Hospital stay (days), median (IQR)</td>
<td>5 (2-7)</td>
<td>5 (2-7)</td>
<td>4 (2-7)</td>
<td>0.422(c)</td>
</tr>
</tbody>
</table>

(a) Pearson’s chi-squared test, (b) Fisher’s exact test, (c) Mann–Whitney U test.
NMDB, neuromuscular blocking drug; PACU, post-anesthesia care unit; TOFm, train-of-four ratio mean; RASS, Richmond agitation-sedation scale; SpO2, oxygen saturation.

Table 3  Incidence of critical respiratory events in patients with (TOFm <90) and without (TOFm ≥90) neuromuscular residual block in the post-anesthesia care unit.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 202)</th>
<th>Total % (95%CI)</th>
<th>TOFm &lt;90 (n = 61)</th>
<th>TOFm ≥90 (n = 141)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical respiratory events</td>
<td>51</td>
<td>26.2 (20.1-32.4)</td>
<td>31 (51)</td>
<td>22 (16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Upper airway obstruction</td>
<td>9</td>
<td>4.5 (1.6-7.3)</td>
<td>6 (10)</td>
<td>3 (2)</td>
<td>0.029</td>
</tr>
<tr>
<td>Mild-moderate hypoxia</td>
<td>20</td>
<td>9.9 (5.8-14.1)</td>
<td>14 (23)</td>
<td>6 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe hypoxia</td>
<td>5</td>
<td>2.5 (0.3-4.6)</td>
<td>4 (7)</td>
<td>1 (1)</td>
<td>0.033</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>7</td>
<td>3.5 (0.9-6.0)</td>
<td>5 (8)</td>
<td>2 (1)</td>
<td>0.331</td>
</tr>
<tr>
<td>Inability to breathe deeply</td>
<td>40</td>
<td>19.8 (14.3-25.3)</td>
<td>23 (38)</td>
<td>17 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Upper airway muscle weakness</td>
<td>11</td>
<td>5.5 (2.3-8.6)</td>
<td>10 (16)</td>
<td>1 (1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are number (percentage) of patients. TOFm, train-of-four ratio mean.

Many European hospitals have reported the practice of not administering NMDB reversal agents, however there is currently enough evidence to not recommend this practice. In our hospital it is common practice to use reversal agents in all patients as standard of care. This may account for the clinically RNMB incidence of 30% observed. Many factors contribute to the RNMB incidence of 30% observed. This includes demographical variables such as history of chronic obstructive lung disease, the type and duration of surgery, major abdominal and thoracic surgery and use of long lasting NMDB. The encapsulation of rocuronium by sugammadex could have an impact in decreasing the rate of RNMB and in CRE. Preliminary evidence indicates that sugammadex is not associated with RNMB in the PACU.

The incidence of CRE in this study was 26%. Patients with RNMB presented a higher incidence of CRE compared to patients with adequate neuromuscular recovery. This can be explained by the many risk factors for CRE as already stated. Interestingly, the percentage of patients receiving neostigmine was higher in the RNMB group than in the group with adequate neuromuscular recovery. Although most of the anesthesiologists routinely administered a reversal drug, some might have used subjective criteria. Patients who received neostigmine were probably already at a higher
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Risk of developing RNMB (due to a shorter time interval since the last dose of NMBD and the end of surgery, or a more profound than suspected neuromuscular block). On the other hand, patients with a longer time interval since the last dose of NMBD and the end of surgery may have not received neostigmine. This might have led to the administration of the reversal drug more frequently in patients who were bound to have RNMB anyway. Two other associations were found. First, the patients who underwent high-risk surgery presented a higher incidence of RNMB in the PACU. Second, patients with RNMB were more hypoactive in the PACU. Abdominal surgery is a risk factor associated with hypoactive emergence. In this way, abdominal surgery might be linked to the association found between high-risk surgery and the incidence of RNMB and also with the fact that patients with RNMB were more prone to develop hypoactive emergence.

The consequences of the RNMB delaying PACU discharge are difficult to evaluate and depend on individual institutional factors including staffing models, PACU size and availability of ward beds. Although a recent study suggested that RNMB delayed recovery room discharge, no difference was detected in our study. We reported a manifested short stay in the PACU for all patients that may be explained by the existence of intermediate level surgical units where the patients were discharged. This partially may explain the fact that there were no differences in PACU length of stay.

Regarding RNMB, there were also no differences in hospital stay, duration of anaesthesia and duration of surgery.

Our study has several limitations. First, the definitions of CRE had some subjective criteria and this may have influenced the diagnosis. Second, we did not monitor the status of NM in the operating room neither the use of other medication provided during surgery which may have influenced on respiratory function after surgery. This fact could have influenced the effect of neostigmine. Acceleromyographic monitoring was shown to reduce the risk of RNMB and CRE in the PACU but the evidence of its benefit is not as obvious when reversal agents are used routinely.

Third, the sample size was limited and can have sampling bias. One cannot exclude that other non-measured factors may have acted as confounders in this study. Fourth, acceleromyography is a quantitative method but there are technical and operator-related issues that must be taken into account. Therefore, some interpersonal variability and random error cannot be excluded. To minimize this, TOF-measurement training took place prior to the data collection. It must also be recognized that even high stimulating currents such as the 50 mA used may not be supramaximal in some patients. Blinding of investigators for TOF values and observation of CRE were not done and this may have influenced the results; also the initial observation of TOF values may have introduced a bias in the identification of patients with CRE.

Finally, in this study the incidence of hypothermia was high. Although it appears that the efficacy of neostigmine as an antagonist neuromuscular block is not altered by hypothermia, lower temperatures may have increased the duration of action and time for spontaneous recovery from neuromuscular blockade.

In conclusion RNMB was common in the PACU. RNMB was more common after high-risk surgery and was associated with a shorter time interval between the last dose of NMBD and admission to the PACU. RNMB was associated with a higher incidence of post-operative CRE and hypoactive emergence.

Conflict of interest

All the authors state they have no conflict of interests.

Acknowledgements

The authors state that they are responsible for the research that they have designed and carried out.

They also state that the research reported in the paper was undertaken in compliance with the Helsinki Declaration and the International Principles governing research on animals.

The authors state that the research is compliant with the “Responsabilidades éticas” published by Revista Española de Anestesiología y Reanimación.

They state that they are responsible for the research that they have designed and carried out; that they have participated in drafting and revising the manuscript submitted, whose contents they approve.

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