Incidence of Postoperative Residual Neuromuscular Blockade - A Multicenter, Observational Study in Portugal

Study Protocol with Statistical Analysis Plan

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1. SYNOPSIS

Title	Incidence of Postoperative Residual Neuromuscular Blockade - A Multicenter, Observational Study in Portugal.
Study Design	Epidemiological multicenter, observational, prospective study.
Primary Objective	To determine the incidence of postoperative residual neuromuscular blockade - defined by a TOF ratio < 0.9 - at PACU arrival.
Secondary Objectives	To determine the incidence of severe postoperative residual neuromuscular blockade – defined by a TOF ratio < 0.7 at PACU arrival To evaluate the association of postoperative residual blockade and the use of reversal agents (neostigmine, sugammadex or none) To evaluate the association of postoperative residual blockade and the use of intra-operative monitoring of neuromuscular blockade
Target Population	Subjects aged at least 18 years old (n=360) admitted for different types of elective surgical procedures requiring general anesthesia with neuromuscular blocking agents.
Sample Size Calculation	Sample size was calculated according to the following assumptions: • Portuguese population to be submitted to surgery with general anesthesia in the next year is approximately 100.000 cases • incidence of patients that arrive at the PACU with objective evidence of incomplete neuromuscular recovery is 26% • Discontinuation rate of 20% Assuming a margin of error of 5% and a confidence interval of 95%, it is expected that approximately 360 patients are required to achieve primary endpoint
Statistical Analysis	Patients will be stratified as follows: patients with TOF ratio ≥ 0.9, patients with TOF ratio < 0.9, patients with TOF ratio < 0.7 Absolute and relative frequencies will be calculated for each category of TOF ratios. 95% confidence intervals will be estimated and presented. Statistical significance of the comparisons with TOF ratio <0.9 and TOF ratio <0.7 at PACU will be performed through Chi-square test or Fisher's Exact Test. In addition, relative risks and 95% CI for TOF ratio <0.7 and TOF ratio <0.9 at PACU will be performed for the comparisons.

A descriptive analysis will be performed for all demographic and clinical data.

1.1. *Study Flow Chart*

	Pre-surgery	**Post-surgery**	
Procedures	**At Anesthetic visit**	**Period 1** At PACU arrival	**Period 2** At hospital discharge
Written informed consent	**X**		
Inclusion/exclusion criteria	**X**	**X**	
Patient number		**X**	
Vital signs: arterial blood, pressure, heart rate, temperature and oxygen saturation		**X**	
Neuromuscular blockade assessment (TOF ratio measurements)		**X**	
Demographic data (gender, age, weight, height)		**X**	
Clinical history		**X**	
Co-morbidities		**X**	
Information about operating room		**X**	
Surgical diagnostic		**X**	
ASA status		**X**	
Medication: NMBA, NMBA reversal agents, volatile anesthetics, hypnotics, opioids		**X**	
Dates: discharge/death		**X**	
Adverse events			**X**
Final outcome: discharge/death			**X**

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3. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ASA	American Society of Anesthesiologists
CNPD	National Data Protection Committee
CRF	Case Report Form
CSR	Clinical Study Report
FAS	Full Analysis Set
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
NA, N/A	Not Applicable
NMB	Neuromuscular Blockade
NMBA	Neuromuscular Blocking Agent
OR	Operating Room
PACU	Post Anesthesia Care Unit
SAE	Serious Adverse Event
TOF	Train-of-four

4. RATIONALE

General anesthesia is usually achieved through the balance of three components: analgesic, hypnotic and neuromuscular blocking agents (NMBAs). NMBAs optimize surgical conditions and tracheal intubation. Nevertheless, one of the problems associated is the residual neuromuscular blockade, secondary to the remaining effect of these agents at a moment that complete reversal of their effect would be desirable.[1-3]

Residual neuromuscular blockade is frequently described in surgical patients at the post anesthesia care units (PACUs) when non-depolarizing NMBAs are administered in the operating room (OR).[4-9] Incidence values range from 16% to more than 70% with a definition of residual neuromuscular blockade in presence of train-of-four (TOF) ratio < 0.7-0.9.[9-12] The use of NMBAs of intermediate action, intraoperative neuromuscular monitoring and reversal of NMBAs have been described as factors that contribute to the reduction, but not the elimination, of residual neuromuscular blockade.[5,12-14]

Quantitative neuromuscular monitoring methods, such as acceleromyography, are the most reliable to assess neuromuscular blockade.8,15 Quantitative neuromuscular monitoring provides a more objective data on neuromuscular transmission and improves detection of residual neuromuscular blockade in comparison with visual or tactile evaluation of the TOF response.[8,16-18]

For many years, the standard criterion of adequate recovery of neuromuscular function was a TOF ratio of at least 0.7. However, evidences have been provided that considerable signs and symptoms of residual neuromuscular blockade may persist until a TOF ratio of 0.9. Therefore, presently, the criterion for adequate reversal of residual neuromuscular blockade is a TOF ratio ≥ 0.9 at the thumb adductor.[17,19-21]

Clinical consequences of residual neuromuscular blockade in PACUs have been documented since 1979.[22] Impaired airway protective reflexes and increased risk for aspiration, a reduced hypoxic ventilator response, pharyngeal dysfunction, hypoxemia, diplopia and unpleasant symptoms of muscle weakness are complications of residual neuromuscular blockade that may increase postoperative morbidity.[5,11,16,20,23-25]

A first study was conducted in eight Portuguese hospitals between July and November 2010 reported a global incidence of 26% of TOF ratio < 0.9 at arrival at the PACU highlighting the dimension of the problem in Portugal.[26]

Since 2010 neuromuscular blockade management had considerably changed. This previous study promoted a growing conscience of the real importance of residual blockade in our surgical patients and convinced us that changes must be done to improve these results. Clinical sessions on neuromuscular blockade management and monitoring were held in various Portuguese hospitals. At the same time, a novel neuromuscular reversal agent (sugammadex) was available and experience with this new drug has been increasing each year replacing in many cases the conventional anticholinesterasic drugs. Based on these two facts we propose to reassess the incidence of residual neuromuscular blockade six years after the first study keeping a similar study design to confirm the paradigm shift that we believe might have happened.

5. OBJECTIVES

5.1. *Primary Objective*

- To determine the incidence of postoperative residual neuromuscular blockade - defined by a TOF ratio < 0.9 - at PACU arrival.

5.2. *Secondary Objective*

- To determine the incidence of severe postoperative residual neuromuscular blockade – defined by a TOF ratio < 0.7 at PACU arrival

- To evaluate the association of postoperative residual blockade and the use of reversal agents (neostigmine, sugammadex or none)

- To evaluate the association of postoperative residual blockade and the use of intra-operative monitoring of neuromuscular blockade

5.3. *Exploratory Objective*

- To evaluate the association of postoperative residual blockade with co-morbidities and ASA status

6. INVESTIGATIONAL AND ANALYSIS PLAN

6.1. *Overall Study Design*

This is a multicenter, observational/non-interventional study involving adult patients undergoing different types of elective surgical procedures requiring general anesthesia with neuromuscular blocking agents.

The study will have two periods:

- Period 1 – Evaluation at PACU arrival.
- Period 2 - Collection of hospital patient discharge data.

A total of 360 patients will be included from approximately 10 centers in Portugal, where the PACU is adjacent to the Operating Room (OR). Each center should recruit between 30 and 40 patients.

6.2. *Beginning and End of the Study*

Each subject is considered to be enrolled in the study when the subject has provided written informed consent.

Enrolment will be stopped when approximately 360 patients are recruited.

A subject is considered to have completed the trial after all of the protocol specified activities are completed.

A subject is considered to have discontinued after he/she has withdrawn consent or has been discontinued under the conditions specified in Section 6.4.3.

Overall, study start is when the first site is initiated and study ends at database lock.

6.3. *Study Procedures*

During the routine preoperative anesthesia visit the patient will be asked to participate in the study. A description of the study will be provided to the patient by the investigator or qualified designee and any questions will be properly answered. If the patient agrees to participate in the study an informed consent form (ICF) will be signed.

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion. A copy of the signed and dated consent form should be given to the subject before participation in the study.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study.

All consented subjects will be given a unique patient number that will be used to identify the subject for all procedures. Each subject will be assigned only one patient number.

6.3.1. Period 1 - data collection at PACU arrival

Immediately after patient arrival in the PACU and as soon as clinically adequate (basic monitoring and oxygen therapy in place) the anesthesiologist assigned to the PACU (who was not involved in the anesthetic procedure) will collect demographic data (gender, age, weight, height), vital signs (heart rate, blood pressure, oxygen saturation and temperature). Neuromuscular blockade (TOF Ratio) will be measured. Clinical history, co-morbidities, surgical diagnosis, ASA classification and perioperative medication data (dosage and last administration time) will be collected as well.

As this is an observational study, intra-operative monitoring of neuromuscular blockade will not be mandatory by protocol and will be left at the discretion of the anesthesiologist as according to the clinical practice. Only information about whether this evaluation was performed or not, and if yes if it was used quantitative or qualitative methods, will be collected in the CRF.

Neuromuscular blockade evaluation

Neuromuscular blockade will be evaluated using a quantitative method. Three consecutive TOF stimulations will be applied. In case these 3 measures differ more than 20%, another

sequence of 3 consecutive TOF measurements will be considered. If after the 2nd sequence the 3 consecutive TOF measurements still differ more than 20% between the maximum and the minimum the patient will be excluded.

Residual neuromuscular blockade definition

Residual neuromuscular blockade will be defined by a TOF ratio < 0.9.

Patients will be stratified as follow:

TOF ratio ≥ 0.9 – Absence of Residual Neuromuscular Blockade

TOF ratio < 0.9 – Presence of Residual Neuromuscular Blockade

TOF ratio < 0.7 – Presence of severe Residual Neuromuscular Blockade

6.3.2. Period 2 - Discharge data collection

Hospital Patient Discharge Data will be collected for each subject. The occurrence of SAEs and AEs will be recorded as well as the final outcome.

6.3.3. Other considerations

This study will reflect real life clinical practice. The anesthetic technique in terms of drugs and type of monitoring used will be of entire responsibility of the anesthesiologist.

All study activities will be consistent with EU directive 2001/20/EC section for non-interventional studies :

- NMBAs and reversal agents' (as well as all drugs which will be used during the anesthesia) administration will be done in accordance with routine anesthesiology practice and labeling of these medicine products;
- No further interventional means, methods or procedures, are scheduled for subjects, which would otherwise not be applied;
- Furthermore, there will be no additional visits to the hospital or a mandatory visit schedule, deviating from daily clinical practice.

6.3.4. Study Schedule

The study schedule and activities are provided in the Study Flow Chart in Section 1.1.

6.4. *Target Population*

6.4.1. Subject Inclusion Criteria

To participate in this study subjects must meet the following criteria:

- 18 years of age or older;
- Informed consent signed;
- Admission for elective surgery;
- Administration of non-depolarizing NMBAs during surgery.

6.4.2. Subject Exclusion Criteria

Subjects will be excluded from this study if they do not fulfill the inclusion criteria or in case of:

- Admission for emergency surgery;
- Reoperation on the same hospital admission;
- More than 10 minutes elapsed between extubation and neuromuscular block monitoring at PACU.

6.4.3. Subject Discontinuation Criteria

A subject may discontinue the study at any time without having to state the reason. As this is an observational study, discontinuation from the study does not mean any change to the surgical, anesthesia or medical care procedures.

Additionally subject participation must be terminated during the study for any of the following reasons:

- Impossibility to obtain 3 measures of TOF ratio at PACU;

If a patient withdraws from the study for any reason before its completion, the reason and the date of withdrawal should be recorded on the CRF.

6.5. *Participating Centers*

The study will be carried out in public hospitals with a relevant number of surgeries with general anesthesia. Centers will also be selected based on the distance between OR and

PACU which should not exceed 10 min walking distance.

About 10 hospitals will be invited to participate in the study.

7. STATISTICAL ANALYSIS

7.1. *Sample size determination*

Sample size determination was calculated by assuming that the Portuguese population to be submitted to elective surgery with general anesthesia is approximately 100.000 cases/year.[26]

From the previous study of Esteves et al[26], the incidence of patients that arrive at the post anesthesia care unit with objective evidence of incomplete neuromuscular recovery was 26%.

When considering this incidence of 26%, a margin of error of 5% (acceptable maximum deviation) and a confidence interval of 95%, we obtained a minimum sample size of 295 patients (StatsDirect 3 Statistical Software).

Considering conservative estimation for the discontinuation rate of 20%, it is expected that approximately 360 patients are required to achieve the primary endpoint.

7.2. *Primary Endpoint*

- TOF ratio < 0.9 at PACU

7.3. *Secondary Endpoints*

- TOF ratio < 0.7 at PACU
- TOF ratio <0.9, TOF ratio <0.7 at PACU by reversal agents administered (neostigmine, sugammadex or none)
- TOF ratio <0.9, TOF ratio <0.7 at PACU by NMB monitoring used intraoperatively

7.4. *Exploratory Endpoints*

- TOF ratio <0.9, TOF ratio <0.7 at PACU by co-morbidities and ASA status

7.5. *Missing data*

Missing data will not be imputed.

7.6. *Interim Analyses*

Not applicable.

7.7. *Statistical and Analytical Methods*

7.6.1. Definition of Analysis Population

Full analysis set population (FAS) will include all treated patient if the patient meets the all criteria.

TOF result will be defined as the average of 3 measures. If the 3 measures have a difference above 20%, another sequence of 3 TOF measurements should be assessed.

7.6.2. Variables and Statistical Methods

Variables/Time Points of Interest

- Demographic/anthropometric information (i.e: age, sex, height and weight)
- Clinical history
- Co-morbidities
- Vital signs (i.e.temperature, oxygen saturation, heart rate and arterial blood pressure)
- ASA classification
- Surgical diagnostic
- Anesthesia duration (time)
- Perioperative medication, its' dosages and last administration time (used during surgical procedure, including neuromuscular blocker and reversal agents)
- Time between date of surgery and date of discharge
- TOF ratio at PACU
- Adverse events
- Assessment if NMB monitoring in the OR during surgery was performed
- Final outcome (discharge or death).

Statistical Methods

All subjects that meet the study criteria will be included in the statistical analysis. The TOF result is defined as the average of 3 measures as described in the study procedures.

A descriptive statistical analysis will be performed on all demographic and clinical data. Considering the continuous variables distributions, data will be presented as mean and standard deviation or as median, minimum and maximum, as appropriate. Categorical

variables will be presented as absolute and relative frequencies.

Patients will be stratified as follows:

- patients with TOF ratio ≥ 0.9
- patients with TOF ratio < 0.9
- patients with TOF ratio < 0.7.

Primary Variable

The primary variable of the study is the TOF ratio <0.9. Absolute and relative frequencies will be calculated. 95% confidence intervals will be estimated and presented.

Secondary Variables and Exploratory Variables

Comparisons will be performed between TOF ratio <0.9, TOF ratio <0.7 at PACU, and the following variables:

- the use of reversal agents (neostigmine, sugammadex or none)
- NMB monitoring used intraoperatively and type of monitoring used
- co-morbidities and ASA status

Statistical significance of the comparisons with TOF ratio <0.9 and TOF ratio <0.7 at PACU will be performed through Chi-square test or Fisher's Exact Test. In addition, relative risks and 95% CI for TOF ratio <0.7 and TOF ratio <0.9 at PACU will be performed for the comparisons. All tests will be performed considering a significance level of 0.05 (5%). Analysis will be performed using IBM SPSS Statistics.

8. PHARMACOVIGILANCE

This is a non-interventional study. No individual administration of any therapeutic or prophylactic agent is assigned in this protocol, and there are no additional procedures required as part of this protocol.

Reporting will be in compliance with the International Conference on Harmonization (ICH) definitions of adverse events (AEs) and serious adverse events (SAEs) (ICH Guideline E2A: Definitions and Standards for Expedited Reporting) procedures and any applicable local laws and regulations.

Only Serious Adverse Events will be collected and sent to the Sponsor within 24 hours of becoming aware of the event. Non-serious adverse events as well as any safety information that is clinically significant in the opinion of the investigator will be collected and recorded in the CRF.

Definitions

Adverse Event

In accordance with the ICH E2A guideline, an adverse event is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

Serious Adverse Event

In accordance with the ICH E2A guideline, a serious adverse event or reaction is any adverse drug, biologic, or device experience occurring at any dose that results in any of the following outcomes:

1. Death;
2. Life-threatening adverse study drug experience; "life-threatening" in the context of serious adverse event, refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe;
3. New or prolongation of an in-patient hospitalization;
4. Persistent or significant disability/incapacity; or
5. Congenital anomaly/birth defect.

In addition, an important medical event that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Severity

Where the determination of AE severity rests on medical judgment, the determination of severity must be made with the appropriate involvement of a medically qualified investigator.
The severity of AEs will be graded according to the following definitions:
Mild: awareness of sign, symptom, or event, but easily tolerated.
Moderate: discomfort enough to cause interference with usual activity and may warrant intervention.
Severe: incapacitating with inability to do normal daily living activities or significantly affects clinical status, and warrants intervention.

Causality

A causality assessment (attribution) must be performed and recorded for each SAE/non-serious AE in relationship to the use of the study drug or device. Causality will be determined by an investigator who is a qualified physician according to his/her best clinical judgment. Use the following criteria as guidance (not all criteria must be present to be indicative of causality to a product: There is evidence of exposure to a product; the temporal sequence of the AE onset relative to the administration of the product is reasonable; and the AE is more likely explained by the a determined product than by another cause.

9. ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Pharmacoepidemiology Practice; and all applicable local laws, rules and regulations relating to the conduct of the clinical study.

This project will be carried out in accordance with prevailing ethical principles:

- Subject's written agreement to participate
- Ethical Committee review (to safeguard subjects' interests, rights and privacy)
- Approval by applicable Hospital Administrations

9.1. *Ethical Conduct of the Study*

Prior to initiation of the study at any center, the study, including the protocol, informed

consent, and other study documents must be approved by an appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC) if this is a local requirement. Approval by the National Private Data Protection Committee (CNPD) will also be required.

The IRB/IEC must be constituted according to applicable regulatory requirements. As appropriate, amendments to the protocol must also be approved by the IRBs/IECs before implementation at the centers, unless warranted to eliminate an immediate hazard. The IRB/IEC approval should be obtained in writing, clearly identifying the study, the documents reviewed (including informed consent), and the date of the review. The study as described in the protocol (or amendment), informed consent, and other study documentation may be implemented only after all the necessary approvals have been obtained as applicable and the sponsor has confirmed that it is acceptable for the investigator to do so.
In the event that the IRB/IEC requires changes in the protocol, the sponsor shall be advised and must approve the changes prior to implementation. The investigator shall not modify the study described in the protocol once finalized and after approval by the IRB/IEC without the prior written approval of sponsor.

9.1.1. Subject Information and Consent

Since this is a non-interventional study, the consent needed from the patient is for the collection of his/her data that are or become available during routine care. Subjects will also be asked to consent that the information collected about their surgery and their health may be used for further analysis and publication.

The informed consent form (ICF) will stipulate that all applicable regulations to protect the privacy of his/her data will be respected. Only anonymous data and sample results will be collected. All subjects included must sign the ICF in the subject's native language before any information is collected for the study. The investigator will co-sign the ICF. The ICF must be approved (e.g., by an Ethics Committee) as per local regulatory requirements before study initiation.

The following will be applied to subject informed consent:

- The details of the protocol must be discussed with each potential subject, and written informed consent must be obtained for all subjects before any study-related procedure is performed;

- In obtaining informed consent, the information must be provided in language and terms understandable to the subject;
- The subject, or the subject's legal representative, must give written consent to participate in the study;
- The signed and dated consent form itself must be retained by the investigator as part of the study records;
- A copy of the signed and dated consent form must be given to the subject;
- The consent form must include all of the required elements of informed consent in accordance with ICH Guidelines E6 and local laws, which do apply for non-interventional trials;
- The consent form must be approved by the appropriate IRB/IEC and sponsor before study initiation at a study site;
- Any subsequent changes to the approved ICF must be reviewed and approved by the appropriate IRB/IEC and sponsor before implementation.

9.2. *Publications*

This study is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript.

For multicenter trials, subsequent to the multicenter publication, an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual study site data does not add value to complete multicenter results, due to statistical concerns. Limitations of single study site observations in a multicenter trial should always be described in such a manuscript. In such cases the Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this study 45 days prior to submission for publication/presentation.

Authorship credit should be in accordance with International Committee of Medical Journal Editors (ICMJE) guidelines criteria for authorship of Publications:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the article or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions

related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Authors must meet conditions 1, 2, 3 and 4. All significant contributions to study execution may also be taken into account to determine authorship, provided that contributions have also been made to all four of the preceding authorship criteria.
All significant collaborators at site level should be determined by the Principal Investigator at each site and should not exceed 6.
Appearance of the name of authors in the publications will follow the following order: the first author is the investigator sponsor, the second author is the person responsible for the data analysis and statistics, followed by the list of names of the principal investigators of the centers according to their contribution to the study, and the last author is the investigator coordinator.

9.3. *Study Documents and Records Retention*

During the study and after termination of the study the investigator must maintain copies of all documents and records relating to the conduct of the study. This documentation includes, but is not limited to, protocols, CRFs and other data collection forms, advertising for subject participation, adverse event reports, subject source data, correspondence with health authorities and IRBs/IECs, consent forms and investigator's *curriculum vitae*.

Subject files and other source data must be kept for the maximum period of time permitted by the hospital. The sponsor must be consulted if the investigator wishes to assign the files to someone else, remove them to another location, or is unable to retain them for the specified period.

All study documents shall be made available if required by relevant health authorities. The investigator should consult with the sponsor prior to discarding study and/or subject files.

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