Study title: **Neuromuscular monitoring and incidence of postoperative residual curarization: a prospective observational study (PORC trial)**

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Abstract

Neuromuscular blocking agents are commonly used in clinical anesthetic practice to facilitate tracheal intubation and allow muscle relaxation during surgical interventions.

An incomplete postoperative recovery of neuromuscular function (postoperative residual curarization – PORC) continues to represent a common problem in post-anesthesia care units (PACU), potentially exposing the patient to adverse respiratory events.

Anesthesiologist's subjective qualitative assessment of the patient's recovery of muscle strength before extubation based solely on clinical signs is not predictive of adequate neuromuscular recovery and an expert consensus statement in 2018 suggested that a quantitative and objective assessment of neuromuscular function using the train-of-four ratio (TOFR) acceleromyographic method at the level of the adductor muscle of the thumb represents the best way to minimize this risk after administration of a non-depolarizing neuromuscular blocker.

This monitoring system, introduced by Ali in the early 1970s, is based on the application of Newton's second law of motion (force=mass x acceleration). Since the mass of the thumb is constant, its acceleration is directly proportional to the force applied.

The acceleration measurement is performed by a piezoelectric sensor fixed at the thumb level which, when moving in response to 4 supramaximal 2 mA stimuli at 0.5 second intervals (2 Hz frequency) delivered by 2 surface electrodes positioned at the level of the distal portion of the forearm along the course of the ulnar nerve, produces an electrical signal in the sensor, proportional to the acceleration of the thumb.

This signal is digitized, processed and then the muscular response to the fourth stimulus is compared with that to that to the first stimulus, and displayed in real time on a monitor as a numerical value in a range of 0-100. Recovery of neuromuscular function is considered acceptable when a TOFR ≥ 0.9 is achieved.

In case of TOFR ≤ 0.9, reversal of the neuromuscular block is normally performed with drugs belonging to the class of acetylcholinesterase inhibitors or with sugammadex, a selective antagonist of rocuronium and vecuronium which acts by encapsulating the neuromuscular blocking molecule making it ineffective.

Recurrence of neuromuscular blockade may, however, occur primarily due to mechanisms of redistribution of the muscle relaxant or if insufficient doses of the reversal drug are administered.

Primary outcome of this prospective observational study is the evaluation of the incidence of residual curarization upon arrival in the PACU, defined as a TOFR≤0.9, assessed by acceleromyographic method in interventions in which non-depolarizing neuromuscular blockers with intermediate duration of action were administered at the time of tracheal intubation, and/or for maintaining a condition of myoresolution during surgery.

Secondary outcomes

- number of possible respiratory adverse events during the stay in the PACU and during the hospital stay.

- Estimation of a logistic regression model to define risk factors for residual curarization. Age of the patient, type of administered anesthesia (inhalational or intravenous), duration of anesthesia, repeated doses of neuromuscular blockers, the reversal of the neuromuscular blockade and the type of neuromuscular blocker used during the procedure will be considered as possible risk factors.

Respiratory adverse events will be defined as episodes of desaturation (SpO2 <92%) requiring oxygen supplementation or the finding of atelectasis, pneumonia or pleural effusion of non-cardiac origin found on thoracic imaging tests possibly performed during the hospital stay.

Background

Neuromuscular blocking agents are commonly used in clinical anesthetic practice to facilitate tracheal intubation and allow muscle relaxation during surgical interventions.

Anesthesiologist's subjective qualitative assessment of the patient's recovery of muscle strength before extubation is not predictive of adequate neuromuscular recovery even if many surveys conducted at an international level [1,2,3] demonstrate how this modality of evaluation is often used above all due to the not always widespread availability of tools for quantitative monitoring of neuromuscular blockade3.

An incomplete recovery of neuromuscular function at the end of surgery (Postoperative residual curarization – PORC) exposes the patient to potential adverse respiratory events and a Consensus Statement [4] of experts in 2018 suggested a quantitative and objective evaluation of neuromuscular function using the train acceleromyographic method -of-four ratio (TOFR) at the level of the adductor muscle of the thumb represents the best way to minimize this risk after administration of non-depolarizing neuromuscular agents.

This monitoring system, introduced by Ali in the early 1970s, present in every operating room of this hospital and routinely used in clinical anesthetic practice, is based on the application of Newton's second law of motion (force=mass x acceleration) .

Since the mass of the thumb is constant, its acceleration is directly proportional to the force applied.

The acceleration measurement is performed by a piezoelectric sensor fixed to the thumb which, when moving in response to the delivery of 4 2 mA stimuli at 0.5 second intervals (2 Hz frequency) by 2 surface electrodes positioned at the distal portion of the forearm, along the course of the ulnar nerve, produces an electrical signal in the sensor, proportional to the acceleration of the thumb [5].

This signal is digitized, processed, and the muscular response to the fourth stimulus is compared with that to the first stimulus, and displayed in real time on a monitor as a numerical value in a range of 0-100. Recovery of neuromuscular function is considered acceptable when a TOFR ≥ 0.9 is achieved [5,7,8].

In case of TOFR ≤ 0.9, reversal of the neuromuscular block is normally performed with drugs belonging to the class of acetylcholinesterase inhibitors (e.g. neostigmine 0.03-0.05 mg/kg, associated with an antimuscarinic agent such as atropine to counteract the cholinergic effects) or by sugammadex (2 or 4 mg/Kg), a selective antagonist of rocuronium and vecuronium which acts by encapsulating the neuromuscular blocking molecule making it ineffective.

Recurrence of neuromuscular blockade may, however, occur primarily due to mechanisms of redistribution of the muscle relaxant or if insufficient doses of the reversal drug are administered.

Study outcomes

Primary outcome

- evaluation of the incidence of postoperative residual curarization upon arrival in the PACU, defined as a TOFR≤0.9, by acceleromyographic method in interventions in which non-depolarizing neuromuscular blockers with intermediate duration of action were administered at the time of tracheal intubation and/or for maintaining a condition of myoresolution during surgery.

Secondary outcomes

- Number of any adverse respiratory events that occurred during the stay in the PACU and during the hospital stay. Respiratory adverse events will be defines as episodes of desaturation (SpO2<92%) requiring oxygen supplementation or the finding of atelectasis, pneumonia or pleural effusion of non-cardiac origin found on thoracic imaging tests possibly performed during the hospital stay;

- Estimation of a logistic regression model to define risk factors for residual curarization Will be considered as possible risk factors those reported in the literature : the patient's age, the duration of anesthesia, the type of anesthesia administered (inhalation or totally intravenous), the number of administrations and the total dose of neuromuscular blocker, reversal or not of the neuromuscular blockade, the antagonist drug and the type of neuromuscular blocker used during surgery [7].

Study endpoints

Primary endpoint

- incidence of postoperative residual curarization

Secondary endopoints

- number of possible respiratory adverse events during the stay in the PACU and during the hospital stay

- estimation of a logistic regression model to define the risk factors associated with residual curarization

Methods

Since this is an observational study, the anesthetic conduct will not be standardized - dose of neuromuscular blocker administered during surgery, possible administration of pharmacological antagonist, neuromuscular monitoring and the decision regarding the moment in which to proceed with extubation of the patient will be left to discretion of the treating anesthetist consistently with their clinical routine.

Upon arrival of the spontaneously breathing patient in the Post-Anesthesia Care Unit, a researcher will note from the anesthesia record the type of surgical intervention performed and the type of non-depolarizing neuromuscular blocker agent administered. The TOFR will then evaluated to detect any residual neuromuscular block using the acceleromyographic method at the level of the adductor thumb.

In analogy with other studies [9,10], 2 TOFR measurements will be performed 30 seconds apart. If the difference between the two measurements is ≤ 0.1, the average value will be considered for the purposes of the analysis. In case of a difference > 0.1, a third measurement will be taken and the average of the two closest results will be considered.

If a residual block is detected sugammadex will be administered (2 mg/kg in the case of at least 2 contraction responses to TOF stimulation or 4 mg/kg in the case of no contraction response) to restore normal neuromuscular function , assessed by subsequent TOFR measurement.

Furthermore, data relating to the patient's age, sex, BMI, comorbidities and the TOFR value before induction of anesthesia and that reported at the time of extubation will be recorded, reporting them on a specific form, if reported in the medical record.

The time of induction of general anesthesia and the end of surgery will also be noted; the type of neuromuscular blocker administered, the time of its administration and related dosage, as well as any drug (acetylcholinesterase inhibitor or sugammadex) with relative dosage, used as reversal agents.

Any adverse respiratory events that occurred during the stay in the PACU will also be reported before discharge to the ward and during the stay in the ward.

By respiratory adverse events we mean episodes of desaturation (SpO2<92%) requiring oxygen supplementation or the finding of atelectasis, pneumonia or pleural effusion of non-cardiac origin found on thoracic imaging tests possibly performed during the hospital stay.

The collected data will then be transcribed on a personal computer to a Microsoft ExcelTM spreadsheet for analysis.

Only the people identified as Data Managers in the aforementioned protocol will have access to the final database of the study. The personal computer used for the analyzes is the property of the Promoter and intended exclusively for research purposes conducted within the structure.

Study design and duration

Prospective, observational, single-center study, lasting 12 months from the time of approval by the Ethics Committee; involves the total enrollment of 90 patients.

Study population

Inclusion criteria

Adult patients aged ≥ 18 years, American Society of Anesthesiologists (ASA) physical status I-III, who have expressed written consent to participate in the study and who will undergo surgery under general anesthesia with the use of non-depolarizing neuromuscular blocking agents at intermediate duration of action, for the purposes of tracheal intubation and/or for maintaining a condition of myoresolution during surgery.

Exclusion criteria

Patients undergoing emergency surgery, who do not require the administration of non-depolarizing neuromuscular blockers, patients with neuromuscular pathologies, or who require postoperative monitoring in the Intensive Care Unit.

Sample size calculation

From the data obtained from a meta-analysis published in 2020 [11] conducted on 53 studies and a total of 12664 patients, 22 studies were selected (n=4268), with population, objectives and methodology similar to those under study. In these studies, regardless of whether or not an intraoperative monitoring system of neuromuscular function was adopted, the incidence of postoperative residual curarization (defined as a TOFR ≤ 0.9%) after the use of intermediate-acting neuromuscular blockers was detected in PACU with acceleromyographic method, it was 28%.

Assuming an equal incidence of 28% we estimated that the study requires a sample size of 78 patients to estimate the expected proportion with an absolute precision of 10% and a confidence level of 95% (https://www.calculator.net/sample-size-calculator.html?type=1&cl=95&ci=10&pp=28&ps=&x=Calculate).

Assuming a drop-out of 15%, the sample was increased to 90 patients.

Statistics

The sample will be described in its demographic, clinical and laboratory characteristics through descriptive statistics techniques. Continuous quantitative variables with normal distribution will be reported as mean and standard deviation; the variables distributed differently will be summarized with median and interquartile range. The normality of the distribution of the variables will be verified graphically using

histograms and with the Shapiro-Wilk test. Categorical variables and missing data will be presented as absolute value and percentage, n (%).

A logistic regression model will be estimated to define the risk factors associated with residual curarization. Those reported in the literature will be considered as possible risk factors: the patient's age, the duration of anesthesia, the type of anesthesia administered (inhalation or totally intravenous), the number of administrations and the total dose of neuromuscular blocker, the antagonization or not of the neuromuscular blockade, the antagonist drug and the type of neuromuscular blocker used during the operation.

All tests used will be 2-sided with an α significance level of 0.05.

All analyzes will be performed with the statistical software R version 4.1.2 (R Foundation for Statistical Computing, Austria).

References

1. Di Marco P, Della Rocca G, Iannuccelli F, Pompei L, Reale C, Pietropaoli P. Knowledge of residual curarization: an Italian survey. Acta AnesthesiolScand 2010; 54: 307-312. doi:10.1111/j.1399-6576.2009.02131.x

2. Batistaki C,VagdatliK, Tsiotou A,Papaioannou A, Pandazi A, Matsota P. A multicenter survey on the use of neuromuscular blockade in Greece. Does the real-world clinical practice indicate the necessity of guidelines? Journal of Anaesthesiology Clinical Pharmacology 2019. doi: 10.4103/joacp.JOACP_195_18

3. Naguib M, Kopman AF, Lien CA, Hunter JM, Lopez A, Brull SJ. A survey of current management of neuromuscular block in the United States and Europe. Anesth-Analg 2010;111:110-9

4. Ali HH, Utting JE, Gray C. Stimulus frequency in the detection of neuromuscular block in humans.

Br J Anaesth 1970;42:967–78

5. Naguib M, Brull SJ, Kopman AF, Hunter JM, Fülesdi B, Arkes HR, Elstein A, Todd MMT, Johnson KB. Consensus statement on perioperative use of neuromuscular monitoring.Anesth- Analg2018:127:71-80.

6. Miller RD, Ward TA. Monitoring and pharmacologic reversal of a nondepolarizing neuromuscolar blockade should be routine. Editorial Anesth-AnalgJuly 2010, Volume 111, Number 1.

7. Beaussier M, Boughaba MA.Residual neuromuscular blockade. Annales Françaises d'Anesthésie et de Réanimation 24 (2005) 1266-1274. doi:10.1016/j.annfar2005.06.006.

8. Naguib M, Kopman AF, Ensor JE. Neuromuscular monitoring and postoperative residual curarization: a meta-analysis. British Journal of Anesthesia 98 (3):302-16 (2007). doi:10.1093/bja/ael386.

9. Fortier LP, McLeen D, Turner K, de Médicis É, Warriner B, Jones PM, Chaput A, Pouliot JF, Galarneau A. The RECITE study: a Canadian prospective, multicenter study of the incidence and severity of residual neuromuscular blockade. AnestAnalg 2015; 121:366-372. doi: 10.1213/ANE.0000000000000757.

10. Butterly A, Bittner EA, George E, Sandberg WS, Eikermann M, Schmidt U. Postoperative residual curarization from intermediate-acting neuromuscular blocking agents delays recovery room discharge. Br J Anesth 2010; 105:304-3

11. Carvalho H, Verdonck M, Cools W, Geerts L, Forget P, Poelaert J. Forty years of neuromuscular monitoring and postoperative residual curarisation: a meta-analysis and evaluation of confidence in network meta-analysis. Br J Anesth 2020; 125 (4): 466-482. Doi: 10.1016/j.bja.2020.05.063