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Deep Neuromuscular Blockade Monitoring and Control

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ABSTRACT

Deep neuromuscular blockade is important in surgeries where patients' complete immobility is essential, providing optimal intubation and surgical conditions. Despite that, there is still some uncertainty in anesthesia practice on how to regulate and ensure the stable maintenance of this level of muscle relaxation. This research aims to overcome this limitation by investigating the relationship between rocuronium use and the neuromuscular blockade effect, in order to support the design and development of an advanced closed-loop system to control and maintain the deep neuromuscular blockade during the surgical procedures.

To complete the proposed objective, the projects' methodology included a comprehensive study of the literature regarding the current techniques and limitations of the approaches used in anesthesia. In addition, a questionnaire was conducted to a group of anesthesiologists, as well as complementary studies regarding the neuromuscular monitors' technical requirements. From the gathered information, it was possible to define blockade monitoring and drug infusion proceedings to be included in the design of a clinical study. These technical methods were implemented in a LabVIEW interface to ensure an advanced and reliable data acquisition and visualization of the patient's neuromuscular status in real-time.

Results of the clinical study allowed to assess the difference between the measurements of two of the most used neuromuscular blockade monitors, in which the TOFscan® exhibited higher sensitivity than TOF-Watch® SX. In addition, from the data gathered, the study of the rocuronium pharmacokinetic-pharmacodynamic relationship during deep neuromuscular blockade was addressed, providing an acceptable estimation of the individuals' post-tetanic count effect. The findings of this clinical investigation were crucial for developing a control approach integrated into an upgrade of the previously developed interface, named RelaxAn.

This novel system uses the monitoring feedback to guide the infusion of rocuronium, providing a means of individualizing and optimizing the maintenance of deep neuromuscular blockade in surgeries. Experimental testing of the RelaxAn performance showed promising results by providing an accurate way to maintain the desired neuromuscular block degree, benefiting the patient's immobility and care conditions. Additionally, this system presents an advanced solution for the professionals, that contributes to the reduction of an important concern during general anesthesia.

Since currently there is no equivalent system commercially available, RelaxAn presents unique features that can provide a new and improved solution of advanced patient-specific maintenance of a deep neuromuscular blockade during surgeries, and benefit the anesthesiology practice worldwide.

RESUMO

O bloqueio neuromuscular profundo é importante em cirurgias onde é necessária a total imobilidade do paciente, facultando condições ideais de intubação e cirúrgicas. No entanto, ainda existe alguma incerteza na prática anestésica relativamente à forma de regular e garantir a manutenção estável deste nível de relaxamento muscular. A presente tese pretende colmatar esta limitação, através da investigação da relação entre o consumo de rocurónio e o seu efeito ao nível do bloqueio neuromuscular, que contribuirá para o projeto e desenvolvimento de um sistema avançado em malha-fechada, cuja função é controlar a manutenção do bloqueio neuromuscular profundo durante os procedimentos cirúrgicos.

A fim de completar o objetivo proposto, a metodologia adotada para a execução deste projeto incluiu um estudo abrangente da literatura acerca das técnicas e limitações das abordagens atualmente usadas na anestesia. Além disso, foi realizado um questionário a anestesiologistas, bem como outros estudos complementares relativos aos requisitos técnicos dos monitores neuromusculares. A partir das informações recolhidas, foi possível definir as especificações da monitorização e da infusão de rocurónio a serem incluídas na conceção de um estudo clínico. Os métodos técnicos então definidos foram implementados numa interface em LabVIEW, para garantir a aquisição e visualização dos dados referentes ao bloqueio neuromuscular do paciente de forma avançada, confiável e em tempo real.

Os resultados do estudo clínico permitiram avaliar a diferença entre as medições de dois dos monitores de bloqueio neuromuscular mais utilizados na anestesia, em que o TOFscan® exibiu maior sensibilidade que o TOF-Watch® SX. Além disso, a partir dos dados recolhidos, foi possível investigar a relação farmacocinética-farmacodinâmica do rocurónio durante o bloqueio neuromuscular profundo, que permitiu estimar de forma aceitável o efeito das contagens pós-tetânicas dos indivíduos. Os resultados deste estudo foram cruciais para o desenvolvimento de um algoritmo de controlo, que foi integrado numa versão atualizada da interface e denominado RelaxAn.

Este novo sistema utiliza o feedback da monitorização para guiar a infusão de rocurónio, de forma a personalizar e otimizar a manutenção do bloqueio neuromuscular profundo durante as cirurgias. Os testes experimentais ao desempenho do RelaxAn indicaram resultados promissores, não só no que diz respeito à precisão na manutenção do nível de bloqueio neuromuscular desejado, potenciando as condições de imobilidade e de cuidados do doente. Adicionalmente, este sistema providencia uma solução avançada para os profissionais, que lhes permite ter menos uma preocupação durante a anestesia geral.

Como atualmente não existe um sistema equivalente comercialmente disponível, o RelaxAn apresenta características únicas, sendo capaz de providenciar uma solução nova e avançada para a manutenção individualizada do bloqueio neuromuscular profundo durante procedimentos cirúrgicos, e beneficiar a prática clínica de anestesiologia em todo o mundo.

To Guilherme.

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ACRONYMS AND SYMBOLS

Acronyms and abbreviations

ACh	Acetylcholine
AMG	Acceleromyography
ASA	American Society of Anesthesiologists
AUC	Area Under the Curve
BIS	Bispectral index
BMI	Body Mass Index
CAL	Calibration
CHUP	Centro Hospitalar e Universitário do Porto
CI	Confidence Interval
CNS	Central Nervous System
DBS	Double-burst stimulation
EMG	Electromyography
FCT	Fundação para a Ciência e a Tecnologia
FDA	Food and Drug Administration
FEUP	Faculty of Engineering of University of Porto
FFM	Fat-free mass
GCP	Good Clinical Practice
HW	Haes-Wierda PK model
IAP	Intra-abdominal pressure
IBW	Ideal Body Weight
ICU	Intensive Care Unit
INEGI	Instituto de Ciência e Inovação em Engenharia Mecânica e Engenharia Industrial
IOP	Intra Ocular Pressure

KMG	Kinemyography
LBW	Lean Body Weight
MDAPE	Median absolute performance error
MDPE	Median performance error
MESO	Medical Solutions
MIMO	Multiple-input multiple-output
MISO	Multiple-input single-output
MMG	Mechanomyography
NCT	Clinical Trial Number
NMB	Neuromuscular Blockade
NMBA	Neuromuscular Blockade Agents
NRS	Numeric rating scale
OCR	Optical character recognition
PCA	Principle Component Analysis
PCB	Printed Circuit Board
PD	Pharmacodynamics
PE	Performance error
PID	Proportional, integral, and derivative model
PK	Pharmacokinetic
PMG	Phonomyography
PORC	Postoperative respiratory complications
PTC	Post-tetanic count
PTP	Post-tetanic potentiation
SC	Surgical conditions
SPA	Sociedade Portuguesa de Anestesia
SRS	Surgical Rating Scale
ST	Single twitch

SW	Saldien-Wierda PK model
TBW	True Body Weight
TCI	Target-controlled infusion
TET	Tetanic stimulation
TOF	Train-of-Four

Symbols

ED_{95}	Effective dose to inhibit muscle contraction by 95 %
Ti	Twitch count *i*
Ce	Effect-site concentration
Ci	Concentration in compartment *i*
Cp	Plasmatic concentration
Ce_{50}	Effect-site concentration to elicit 50 % of maximum drug effect
γ	Hill coefficient
E_0	Baseline effect
E_{max}	Maximal effect
u	Rocuronium infusion rate
k_{e0}	Rate constant between central and effect compartment
k_{ij}	Rate constant for equilibration between compartments *i* and *j*
V_i	Distribution volume of compartment *i*
AUC_{PTC}	Area under the curve of the Post-tetanic count measurement
PE_{PTC}	Predicted effect of the PTC response
PTC_i^{avg}	Average estimation of the PD parameters to estimate PTC effect for PK model *i*
PTC_i^{ind}	Individual estimation of the PD parameters to estimate PTC effect for PK model *i*
PTC_{Target}	Target post-tetanic count response
Kc	Proportional gain of the controller
Ti	Integral time of the controller

Td	Derivative time of the controller

1 INTRODUCTION

General anesthesia is usually characterized by three main components that result from drug administration: hypnosis (unconsciousness and memory loss), analgesia (pain relief), and immobility, also known as the neuromuscular blockade (NMB), which is the focus of this work.

The use of muscle relaxants, such as rocuronium, provides important benefits for patient care in surgical procedures, allowing for good tracheal intubation and ensure patients' immobility [1–3]. Total immobility is especially important in meticulous surgical procedures (*e.g.*, laparoscopic surgeries) where hazardous coughing or spontaneous movements can jeopardize patient care. As such, to enhance the surgical conditions by guaranteeing complete immobility of the patient, including abdominal musculature and diaphragm, deep neuromuscular blockade is often used [4–7].

Consensus and recommendations have endorsed monitoring the NMB to evaluate the degree of neuromuscular transmission when neuromuscular blocking agents (NMBA) are administered [8–11]. Currently, this is the only method available to objectively measure the level of neuromuscular block, providing necessary information for drug titration, ensuring optimal surgical conditions, and preventing residual paralysis and potential morbidity at recovery [7, 12]. Despite the benefits in the management of NMB perioperatively, NMB monitoring is still not a standard procedure, and anesthesiologists frequently do not use it when administering NMB agents [13]. The absence of a reliable objective method to regulate the neuromuscular function is the main reason for the professionals to discards their routine use. This issue is the basis of motivation to justify the current research project.

1.1 MOTIVATION

This research project addresses a study of the monitoring and control for the maintenance of deep neuromuscular blockade during general anesthesia. Many studies have investigated and characterized

muscle relaxation based on the assessment of the effect, namely focusing on the regulation of moderate levels of NMB [14–19]. Few pieces of research have tried to explore the combination of adequate monitoring with the administration of NMB drugs for deep NMB during surgical procedures, therefore being an area that suffers from lack of investigation.

The main goal of this project comprised the study and development of an advanced closed-loop control system to guide the administration of an NMBA, based on the monitoring response, to promote a stable, safe, and accurate deep neuromuscular blockade for surgical patients. This innovative technology intends to provide a pioneer and improved means to accurately personalize the maintenance of deep NMB for each patient, providing a very unique and attractive solution to anesthesiology worldwide. As a result, the proposed research question is: “How effective is the control of deep neuromuscular blockade through a closed-loop system?”

1.2 METHODOLOGY FRAMEWORK

This study was executed under the doctoral program in Engineering Design and Advanced Manufacturing - Leaders for Technological Industries (EDAM–LTI) from MIT Portugal, supported by a FCT grant with the reference PD/BD/114378/2016. The proposed research was conducted at Faculdade de Engenharia da Universidade do Porto (FEUP) in collaboration with the anesthesiology research department of Centro Hospitalar e Universitário do Porto (CHUP, Hospital de Santo Antonio). The supervision and support of the research project were accomplished by Professor Joaquim Mendes (Ph.D., FEUP), Pedro Amorim (MD expert in anesthesiology at CHUP), and Professor Catarina S. Nunes (Ph.D., CHUP, Universidade Aberta).

The CHUP anesthesiology department is a national reference for neuromuscular block anesthesia and research. This is clearly evidenced in the many R&D and clinical trials performed by this team over the past 15 years. In addition, there is a rigorous daily clinical practice in the administration of NMB relaxants, antagonists and monitoring; therefore, being a reference in anesthesiology and important support for the completion of the current project, which comprises an unestablished field of research. Therefore, to limit the variability and assess the suitability of this study, the procedures and technical protocols of CHUP routine clinical practice were maintained and grounded in the NMB standards already established in the field.

To complete a system to control and regulate deep NMB considering a closed-loop control technique, a comprehensive rationale of what NMB comprises and the referring specifications of the methodologies used in routine clinical practice were initially explored. Based on the assessment of the current technologies and principles of the anesthesia practice, to accomplish this research project,

three main aspects needed to be carefully addressed: the drug administration, the monitoring, and the feedback methodologies (Figure 1.1).

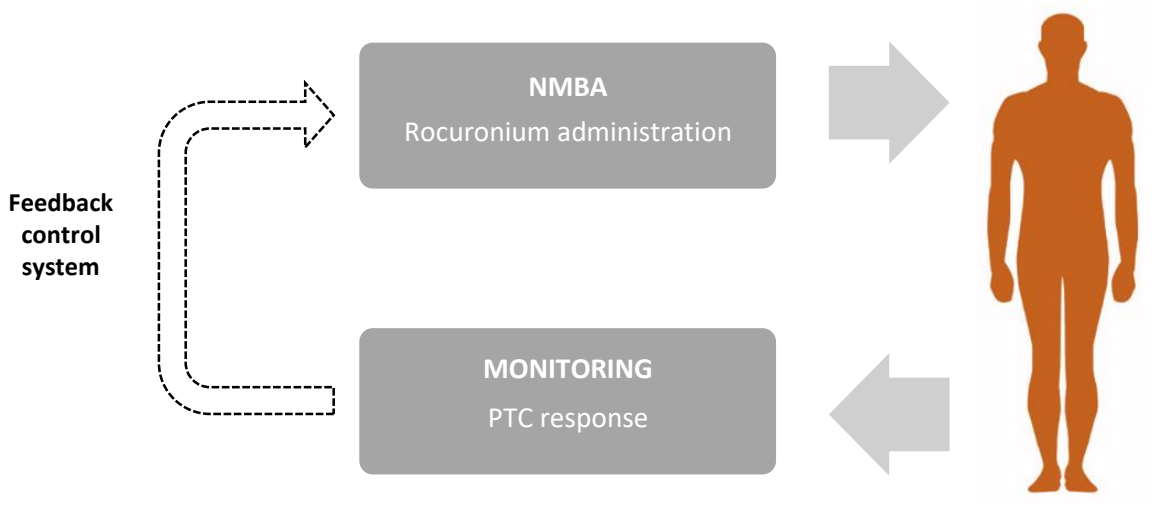


Figure 1.1 - Illustration of the methodological features included in the work proposal for the deep NMB control and maintenance.

First, regarding the muscle relaxants administration, there is great variability in everyday clinical practice when NMB drugs are used. Frequently, the administration of NMBA is based on the producers' dosage recommendations, relying on the experience of trained professionals to individualize the dosage administered, which can vary according to different criteria (*e.g.*, patient features, duration of surgery, method of sedation, possible interaction with other drugs). Rocuronium stood out as an ideal NMBA for this study due to its advantages as a non-depolarizing drug agent: fast onset, dose-dependent duration of action, lack of known side effects, no active metabolites nor toxins, and independent elimination [20]. Moreover, the introduction and rising availability of sugammadex in the operating room, that allows to perform a safe and effective reversal due to the strong binding capacity with rocuronium, additionally supports the use of these valuable drug agents in this research [12, 21–24].

Regarding the NMB monitoring, among the different techniques used to monitor the neuromuscular blockade quantitatively, acceleromyography is widely used and has been proven to be one of the most accurate and reliable methods in evaluating the neuromuscular response. It functions by measuring the evoked response via an acceleration sensor at the thumb, after stimulation of the ulnar nerve. For deeper levels of NMB, the Post-Tetanic Count (PTC) stimuli are used to assess the neuromuscular function [12]. As mentioned before, to ensure complete immobility of the patient, very little or no neuromuscular response is desired [4–7]. Although there is no consensus on the NMB degree classification, for this study, the target range for the deep neuromuscular blockade to assure these conditions was set to 1-2 PTC responses.

Ultimately, in agreement with the focus of this research on the achievement of an improved solution to ensure the stable maintenance of the desired deep NMB degree during surgical procedures, it is essential to combine the rocuronium delivery and the NMB monitoring. To do so, one fundamental step is to describe the drug administration over time and relate it with the corresponding PTC effect. Coupling this information with a monitoring feedback control system integrated into a closed-loop approach was suggested to individualize and optimize the performance of the proposed solution and accomplish the project's goal. Closed-loop controllers use the monitoring feedback to adjust the output of a dynamic system and minimize the deviation between the signal and the desired target; therefore, providing an advantageous means to regulate the NMB in the human body.

A set of objectives were delineated in the work plan to complete this research project, and are listed below:

- Study the background and current methods for the maintenance of deep NMB;
- Explore the features of the proposed system for the anesthesiology field;
- Define and select main requirements and specifications for a study protocol;
- Establish and test a protocol for individualization of rocuronium dosing and monitoring of NMB response;
- Develop an interface to accurately evaluate the deep NMB during surgeries;
- Analyze the gathered data and develop an advisory solution for managing deep NMB;
- Integrate the solution with a compliant NMB drug delivery method in a closed-loop system prototype;
- Test and validation of the developed system;
- Description of the technology, the operating regulations, and the potential market.

1.3 RELEVANCE AND CONTRIBUTIONS

From the overall project, the benefits and limitations of this research can be highlighted. The core contribution of this work is to emphasize the importance of performing deep neuromuscular blockade in surgery. Moreover, achieving a functional closed-loop system brings an advanced patient-specific NMB assessment and regulation tool for the anesthesiology clinical practice around the world. Currently, no such system is commercially available, allowing to introduce a new and unique solution to the medical field.

Some limitations must be considered in terms of the functional characteristics and inherent features of the systems' components that support this field of research. In other words, the NMB paradigm is sustained on longstanding studies that established the standards or principles of conduct adopted by

the anesthesiologists for monitoring the patient's muscle relaxation degree. The neuromuscular transmission, blockade, and monitoring present a wide range of variables that need to be well defined to promote an appropriate neuromuscular evaluation and patient-specific blockade. These include the theoretical extent of the neuromuscular transmission and blockade, the monitoring feature considerations, the accuracy of pharmacokinetics and pharmacodynamics of the rocuronium infusion approach, the individual's specific metabolic action on NMB drugs, among many others.

Despite these obstacles, the success of the proposed technology, that combines the NMBA drug infusion and monitoring feedback in a closed-loop approach integrated into a single and unique system, has the capacity to critically improve the management of NMB in everyday clinical practice. A deep NMB controller system can provide essential advances not only for patient immobility during surgeries but also in terms of time and cost that the inadequate administration of anesthetic drugs entails. That is, in addition to the stable maintenance of the NMB degree during general anesthesia, it has the potential to provide important benefits relative to the lower consumption of NMBA and other anesthetics, reduce the incidence of hypotension, improve the control of depth of hypnosis and avoid the overuse of sugammadex (to repair eventual overdose of NMBA). Ultimately, issues such as over administration of expensive drugs and prolonged stay in the recovery room can carry disadvantages in terms of costs, schedules, and patient care.

1.4 CONFERENCE AND JOURNAL PUBLICATIONS

This section provides a brief description of the academic publications written during this Ph.D. research. The work done allowed to accomplish three conference presentations, which resulted in a book chapter and two proceedings publications, and also, two systematic review studies. More recently, three new articles have been submitted for journal publication, and are currently under review. Furthermore, an application for provisional intellectual property has been submitted.

CONFERENCE PROCEEDINGS

M. Couto, C. S. Nunes, S. Esteves, P. Amorim, J. Mendes, "TOF-Watch NMB Monitoring Misleading Display Output During Moderate Neuromuscular Blockade", abstract presented at the XV Mediterranean Conference on Medical and Biological Engineering and Computing – MEDICON 2019 in Coimbra, Portugal, September 2019, J. Henriques et al. (Eds.): MEDICON 2019, IFMBE Proceedings Springer, vol. 76. pp.768-775, 2020. DOI:10.1007/978-3-030-31635-8_91

M. Couto, R. Correia, C. Nunes, S. Esteves, P. Amorim, J. Mendes, "Neuromuscular blockade monitoring during cranial or spinal surgeries may contain a high percentage of errors that may affect

adequate maintenance and reversal", abstract presented at the SNACC 47th Annual Meeting in Phoenix, USA, September 2019, Journal of Neurosurgical Anesthesiology, vol.31, no. 4, pp. 495, 2019.

C. Nunes, M. Couto, R. Correia, S. Esteves, P. Amorim, J. Mendes, "Train-of-four Possible Monitoring Errors During Standard Neuromuscular Blockade", abstract presented at the Anesthesiology annual meeting, Orlando, USA, November 2019.

JOURNAL PUBLICATIONS

M. Couto, C. Nunes, S. Vide, P. Amorim, and J. Mendes, "Rocuronium Continuous Infusion for Profound Neuromuscular Blockade." Clin. Neuropharmacol., vol. 42, no. 6, pp. 203–210, 2019. DOI: 10.1097/WNF.0000000000000366. Impact Factor 2019-2020: 1.430

M. Couto, J.G. Couto, C. Nunes, S. Vide, P. Amorim, and J. Mendes, "Systematic review on rocuronium continuous infusion for deep neuromuscular blockade.", Curr Clin Pharmacol., vol 14, 2019. DOI: 10.2174/1574884714666191120144331. Impact Factor 2019-2020: 1.190

JOURNAL SUBMISSIONS UNDER REVIEW

M. Couto, S. Vide, C. Nunes, J. Mendes, P. Amorim, and S. Esteves, "Comparison of the TOF-Watch® SX and the TOFscan® monitoring during profound neuromuscular blockade.", in Anesthesia & Analgesia.

M. Couto, S. Vide, S. Esteves, C. Nunes, P. Amorim, and J. Mendes, "Comparison of two PK-PD models of rocuronium during profound neuromuscular blockade: analysis of estimated and measured PTC effect.", in British Journal of Anaesthesia.

S. Vide, A. Ferreira, M. Kreuzer, M. Couto, M. Agustí, A. Chen, S. Jaramillo, G. Schneider, P. García, P. Amorim, I. Trocóniz, M. Larson, P. Gambús, "Cortical, brainstem and autonomic responses to nociception under total intravenous anesthesia with propofol and remifentanil", (co-authorship) in Anesthesia & Analgesia.

PATENT APPLICATION SUBMITTED

"Deep neuromuscular blockade control for general anesthesia" Provisional intellectual property application, in U. Porto Inovação.

1.5 THESIS OUTLINE

The outline of this thesis is presented below, which provides a binding version across the contents and contributions of the research conducted. This thesis is divided into six main chapters, as follows:

Chapter 1 - INTRODUCTION. In the present chapter, a brief background statement and motivation of the work are included, as well as an overview of the investigation scope on the monitoring and control for deep NMB. Then, a methodology framework was included to justify the approach being pursued in the execution of the work. The research objectives are presented, followed by a brief description of the main contributions of the project. At last, a list of the academic publications accomplished in the completion of this project is summarized.

Chapter 2 - LITERATURE REVIEW. In this chapter, background information on the anesthesia practice is included, describing the fundamental aspects of the muscle relaxation approaches and NMB monitoring techniques used in clinical practice. Furthermore, a systematic review and meta-analysis were conducted for studies applying continuous infusion pared with NMB monitoring for the maintenance of profound NMB (0-2 PTC). This study was mirrored, and another review was completed to assess the approaches of rocuronium administration and NMB monitoring regarding the different layers of the deep NMB level (0-10, 0-5, and 1-2 PTC).

Chapter 3 – STUDY DESIGN AND METHODS. In line with the literature review performed before, this chapter is dedicated to understanding the requirements and technical specifications for the design of a clinical study and, further on, for the development of the system to control deep NMB. Subsequently, the materials and methods defined for the clinical investigation were implemented in a computational interface for data acquisition.

Chapter 4 – CLINICAL STUDY RESULTS. In this chapter, the results of the clinical study are described and analyzed. From the data gathered, it was performed a study comparing the NMB measurements of the two main acceleromyography-based NMB monitors, the TOF-Watch® SX and the TOFscan®. Furthermore, a study regarding the rocuronium pharmacokinetics and pharmacodynamics relationship in estimating the post-tetanic count effect for the maintenance of deep NMB was also addressed.

Chapter 5 – CLOSED-LOOP CONTROLLER FOR DEEP NMB. An advisory system is designed and developed to individually control the deep NMB, adding feedback information regarding the patient's monitoring response in a closed-loop approach. Preliminary tests were conducted to assess the system's performance, and the referring results are reported. The proposed technology and its future optimization steps are included, as well as a brief description of the market analysis and the regulatory requirements.

Chapter 6 – CONCLUSIONS AND FUTURE WORK. This chapter has the purpose of presenting the overall conclusions of this research project, emphasizing the main contributions of the work. Also, the implications of the findings and the recommendations for future investigation are summarized.

2 LITERATURE REVIEW

To ground the development of the research conducted, it is important to understand and include the theoretical and methodological concepts and standards of anesthesiology, namely the knowledge and guidelines regarding neuromuscular blockade.

The anesthesia practice background for NMB and monitoring methods were reviewed and described, presenting the current information related to the fundamental aspects of the neuromuscular transmission and its assessment. Additionally, to understand and define the specifications and requirements of a system able to combine monitoring and personalized NMBA administration, it was conducted a review of the current studies using continuous infusion of rocuronium for deep NMB.

2.1 BACKGROUND

Anesthesia is a unique field of medical practice that has significantly contributed to major advances in health care. This specialty concerns the total perioperative care of patients by safely supporting and regulating their vital functions throughout surgical procedures.

Over the last decades, many advances have been introduced with extraordinary contributions to patient care. Although the scope of anesthesiology practice involves several areas, in the context of this research, a brief review of the background on the general anesthesia practice and the neuromuscular blockade is described next.

2.1.1 ANESTHESIA PRACTICE AND NEUROMUSCULAR RELAXATION

The development of surgical anesthesia is considered one of the most important discoveries of modern surgery. Anesthesiologists are actively involved in the clinical care of many ambulatory surgery facilities, operating rooms, intensive care units, and respiratory therapy departments. They

are responsible for ensuring patient safety by monitoring and control of the vital signals such as cardiovascular, respiratory, neurological, body temperature, among others; to which the neuromuscular transmission is no exception.

During surgery, there are three primary outcomes expected from anesthesia drug administration: the hypnotic, the analgesic, and the immobility effects. The focus of this work is related to the immobility component, which is regulated by muscle relaxants. Introduced in 1942, curare was the first agent used that greatly facilitated tracheal intubation and muscle relaxation in surgical operations. Other neuromuscular blockers were subsequently studied and used. More recently, other agents were introduced in the field that more closely resemble an ideal neuromuscular blockade: vecuronium, atracurium, cis-atracurium, and rocuronium.

The main objectives of appropriate neuromuscular relaxation are to provide the best conditions for patient's intubation and extubation and, later on, guarantee the immobilization and muscle relaxation during the surgical procedure for an easier/lenient muscle incision/operation [25, 26]. This is of paramount importance in ensuring safer conditions for patient care, especially crucial in meticulous procedures such as aneurisms, epigastric/abdominal, ophthalmic, and airways surgeries.

2.1.1.1 Neuromuscular transmission and blockade

The central nervous system (CNS) comprises the brain and the spinal cord, in which the primary component is the neuron. The typical structure of a neuron consists of a cell body, dendrites, and an axon. The neuron network communication occurs due to the electrically excitable properties of this cell. This polarization/depolarization interchange in the cell membrane generates the stimulation action potential, conducting an electrical impulse from one or more dendrites through the axon that carries the impulse away from the cell body, up until it reaches the muscle fibers [27].

The phenomenon called neuromuscular transmission, or muscle contraction, results from the chemical transmission of the electrical impulse between the motor neuron and a muscle cell at the neuromuscular junction. The junction consists of three distinct parts: the distal motor nerve ending, also known as the presynaptic part; the synaptic cleft (20-nm gap); and the postsynaptic, which is a part of the muscle fiber membrane (Figure 2.1). The neuromuscular transmission occurs when the action potential at the nerve depolarizes the terminal, generating an influx of calcium ions through voltage-gated calcium channels into the nerve cytoplasm allowing the neurotransmitter molecules, named acetylcholine (ACh) that are synthesized and stored in vesicles, to be instantaneously released by the nerve terminal into the synaptic gap. The ACh molecules diffuse across the synaptic cleft to the

post-synaptic site to bind with nicotinic cholinergic receptors on a specialized portion of the muscle membrane, called the motor end-plate.

Each neuromuscular junction contains approximately 5 million ACh receptors; however, activation of only about 500 000 receptors is required for normal muscle contraction. Acetylcholine is the neurotransmitter for the entire parasympathetic nervous system, parts of the sympathetic nervous system, some neurons in the CNS, and somatic nerves innervating skeletal muscle [25, 26].

As one of the main goals of anesthesia is to ensure the loss of ability to move the muscles, the neuromuscular transmission can be regulated via administration of muscle relaxants, resulting in the neuromuscular blockade.

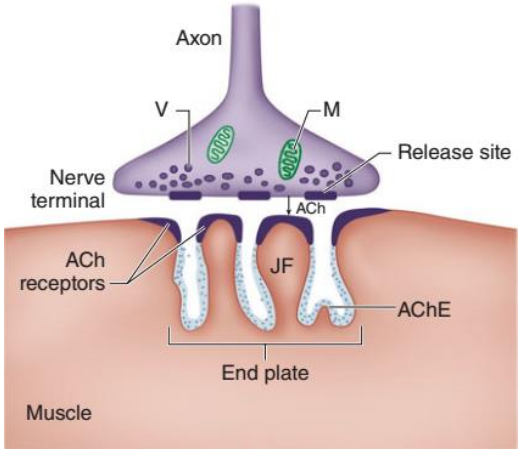


Figure 2.1 - The neuromuscular junction. V - transmitter vesicle; M - mitochondrion; Ach - acetylcholine; AChE - acetylcholinesterase; JF- junctional folds [25].

There are several mechanisms of NMB that may interfere with the function of the ACh, by restricting the normal functioning of the ACh receptor binding site or the normal receptor channel functioning. These may include inhaled or injected anesthetic agents. Nonetheless, muscle relaxants can be distinguished in two main types: depolarizing and non-depolarizing.

Depolarizing muscle relaxants act as ACh receptor agonists. The most common depolarizing NMB is succinylcholine that has a rapid onset (30–60 s) and short duration of action (< 10 min). Succinylcholine consists of two joined ACh molecules that readily bind to ACh receptors. The end-plate cannot repolarize if the depolarizing muscle relaxant continues to bind to ACh receptors; this is called phase I block. After a period, prolonged end-plate depolarization can cause changes in the ACh receptor that result in a phase II block, which clinically resembles non-depolarizing muscle relaxants. Since depolarizing NMBAs cause continuous depolarization of the endplate, a quick change from excitation and muscle contraction to blockade of the neuromuscular transmission, can be observed.

Alternatively, non-depolarizing muscle relaxants function as competitive antagonists. Act by competing with acetylcholine for the receptors binding sites, thereby blocking neuromuscular

transmission. This type of NMBA can be differentiated in short, intermediate, and long action times. In contrast to depolarizing muscle relaxants, there is a wide selection of non-depolarizing muscle relaxants. As mentioned, rocuronium will be the non-depolarizing NMBA used during the course of this work. Rocuronium is less powerful than most non-depolarizing neuromuscular relaxants, designed to provide a rapid onset of action (60–90 s) and effective induction. Rocuronium undergoes hepatic metabolism (10-20 %) and is excreted primarily by biliary elimination (50-70 %) and slightly though the urine (10-25 %) [25, 28].

Rocuronium dosage

Current dose recommendations on the use of NMBA are well established and guarantee the immobilization, procedure facilitation, prevention of secondary complications and invasive ventilation, which can vary according to each patient's clinical context and physiological/pathological status. Nonetheless, there is considerable variability among patients in response to muscle relaxants, and there are several pharmacological variables that can influence the blockade, such as temperature, acid-base balance, electrolyte abnormalities, age, weight, drug interactions, liver or renal diseases, among others. Also, one main consideration in administrating NMBA is that muscle groups vary in their sensitivity to blocking onset and intensity, due to the differences in blood flow, distance from the central circulation, different fiber types, or even the muscle relaxant itself. In general, the diaphragm, jaw, larynx, and facial muscles respond to and recover from muscle relaxation sooner than the distal muscles such as the thumb, which is the most commonly monitored site [25].

Dosage reference (mg/kg) is based on the ED_{95} of the drug. This refers to the median dose required to produce 95 % of the therapeutic effect. For rocuronium, the ED_{95} corresponds to 0.3 mg/kg, which derived from studies based upon the reduction of the response to twitch stimuli. In general anesthesia, the standard approach based on the manufactures' recommendation, considers an induction dose of two ED_{95} (0.6 mg/kg), usually administered for quick intubation. The maximum blockade is normally achieved within 3 minutes and can last 14 to 85 minutes [29, 30]. Larger intubating doses decrease the time of onset; however, it also exacerbates side effects and prolongs the duration of blockade action, which may lead to difficulty in completely reversing the blockade and consequent increase the incidence of postoperative pulmonary complications, known as the residual blockade.

Dosing guidelines are generally based on true body weight (TBW). However, NMBA act at the muscular terminals obstructing the neuromuscular transmission, therefore the adaptation of drug dosages to obese patients, with body mass index (BMI) over 25 kg/m^2, is a subject of major concern. Overweight people have larger absolute lean body masses, as well as fat masses and a decreased proportion of

muscle mass and body water; therefore, administration of a drug based on a TBW metric may result in overdose and longer duration of the NMB [31, 32].

In the last decade, several studies have been conducted comparing pharmacokinetic parameters when dosing is based on ideal body mass versus TBW [31, 33–38]. The authors of these trials recommended against the use of TBW and consistently suggested using ideal body weight (IBW) for weight-based dosing of NMBAs. IBW is a surrogate for lean body weight (LBW) or fat-free mass (FFM), defined as a combination of body cell mass, extracellular water, and non-fat connective tissue to assess the difference between muscle and fat weights. Thus, guidelines for sustained NMB suggest not to use TBW and instead consider a consistent weight when calculating NMBA doses for obese patients [3].

Several authors have used different formulas to calculate the IBW [39–41]. Despite being an important measure in clinical practice, there is no consensus as to what IBW really represents or how to calculate it. Ideal body weight has no robust physiologic basis, and there is no single weight that is ideal for any patient of a given height. However, there is a general agreement between the IBW equations developed and some simplified approaches that allow easy calculation in the operating room [41–43]. Current, the *Sociedade Portuguesa de Anestesiologia* (SPA) guidelines of management of NMBA administration in obese patients, states that hydrophilic drugs dosing, such as rocuronium, should be based on:

$$Dose_{men}(\text{mg}) = 1.2 \times (Height(cm) - 100) \quad \text{Eq. 1}$$

$$Dose_{women}(\text{mg}) = 1.2 \times (Height(cm) - 105) \quad \text{Eq. 2}$$

These include only the patient's height as a variable to determine the dose. One interesting method applied for the calculation of body weight in obese patients, when using rocuronium for muscle relaxation, was introduced by Janmahasatian S. [39]. The equations for estimating lean body weight are sex-specific and incorporate both, TBW (kg) and BMI (kg/m^2), showing better predictive performance and more accuracy in estimating reasonable dosages for normal weight and moderate obese patients as well:

$$BMI\ (kg/m^2) = \frac{TBW\ (kg)}{Height\ (m)^2} \quad \text{Eq. 3}$$

$$FFM_{male}\ (\text{mg}) = \frac{9270 \times TBW(kg)}{(6680 + 216 \times BMI(kg/m^2))} \quad \text{Eq. 4}$$

$$FFM_{female}\ (\text{mg}) = \frac{9270 \times TBW(kg)}{(8780 + 244 \times BMI(kg/m^2)} \quad \text{Eq. 5}$$

This rationale is also reasonable for reversal drugs; however, current recommendations suggest that TBW should continue to be used to ensure a safe and effective reversal [44].

2.1.1.2 Pharmacokinetics and Pharmacodynamics

Clinical pharmacology is very closely connected to the anesthesiology practice. The extent of the effect of the anesthetics depends on the pharmacokinetics (PK) and pharmacodynamics (PD) of the drugs used and the duration of administration. Based on these concepts, several PKPD models for optimal control of anesthesia were studied over the last decades to describe the drug effect in relation to the dose over time [25, 45].

Pharmacokinetics defines the relationship of the drug dosing and patient characteristics (e.g weight, height, age, and sex) to assess the drug concentrations in blood and the effect-site tissues over time, thus representing the processes of drug metabolism and excretion. Four linked processes must be considered to describe how the drugs used in anesthesia act: absorption, distribution, biotransformation, and elimination. While PK describes what the body does to the drug, PD describes what the drug does to the body. Thus, pharmacodynamics relates the plasma concentration with the pharmacologic effect and involves two main concepts: potency and efficacy [25, 46].

Two or three-compartment models are usually adequate to analyze how the volumes and clearances of the drug distribute into the different organs and body compartments, with acceptable precision (see Figure 2.2) [47, 48].

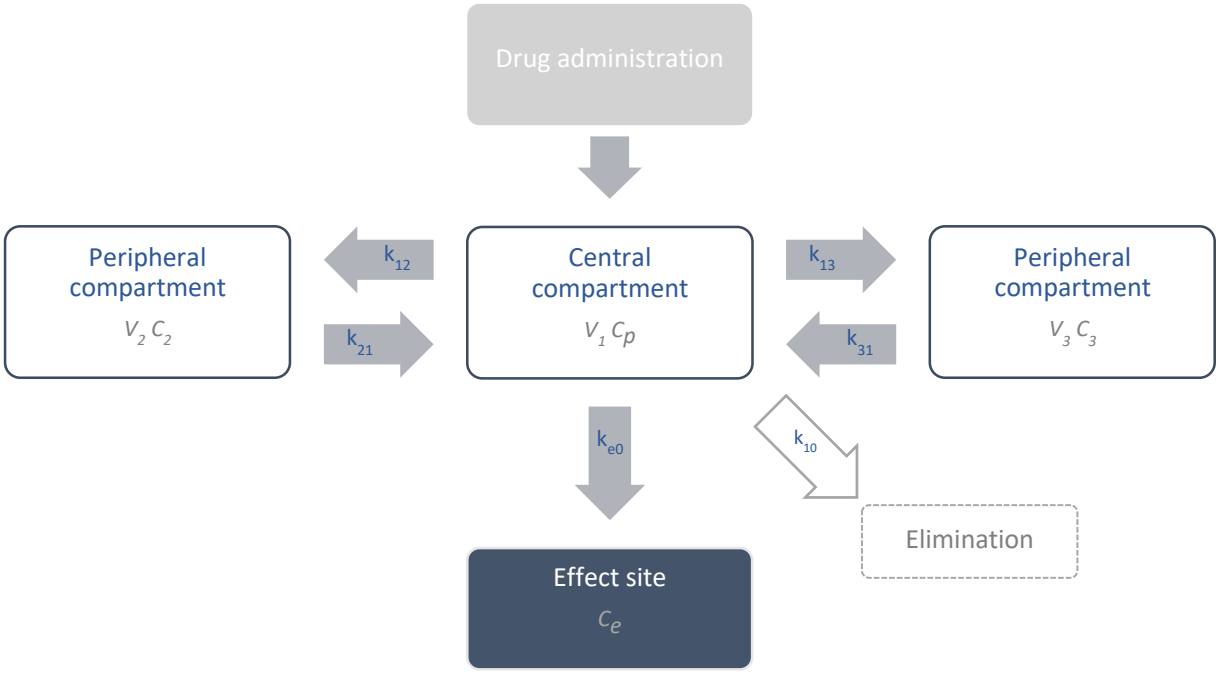


Figure 2.2 - Three-compartment model based on the Sheiner L. PK model that includes the effect compartment. The effect-site is assumed to have a negligible volume and synchronized effects [25, 49]. C_i is the drug concentration in compartment i; V_i is the drug volume in compartment i; k_{ij} is the coefficient that describes drug movement from compartment i to j.

Most compartment models divide the body into three entities (central, peripheral slow, and peripheral rapid) that can be described by definite volumes and concentrations of the drug. The relationship

between compartments, known as drug kinetics, is used to describe the drug distribution. This allows to determine the drug concentration in plasma and highly perfused organs and, after that, the tissue concentration by considering inter-compartment rate constants (k_{ij} describes drug movement from compartments *i* to *j*), as well as the drug elimination process, which is achieved through the central compartment (defined by k_{10}). The relationship between plasma and the effect-site concentration of the drug is modeled by a first-order process, described by the equilibration rate constant of the drug, called k_{e0} (rate constant between central and effect compartments) [25, 50]. The equation that relates effect-site concentration (*Ce*) to plasma concentration (*Cp*) is:

$$\frac{dC_e}{d_t} = k_{e0} \times (C_p - C_e) \quad \text{Eq. 6}$$

The PD modeling techniques provide an estimate of the lag time between plasma concentrations and the observed effect [45]. The relationship between *Ce* and each effect can be assessed in most cases by a sigmoidal model described by Hill A. (see Figure 2.3). This model characterizes the effect based on the effect-site concentration associated with specific curve parameters such as a drug concentration to elicit 50 % of maximum drug effect (Ce_{50}) and the dynamic steepness of the sigmoid curve that represents the slope of the concentration-effect relationship (γ). The standard equation for this relationship is known as Hill equation [51]:

$$Effect = E_0 + (E_{max} - E_0) \times \left(\frac{Ce^{\gamma}}{C_{50}{}^{\gamma} + Ce^{\gamma}}\right) \quad \text{Eq. 7}$$

where E_0 is the baseline effect, E_{max} is the maximal effect with respect to E_0 [45, 52, 53].

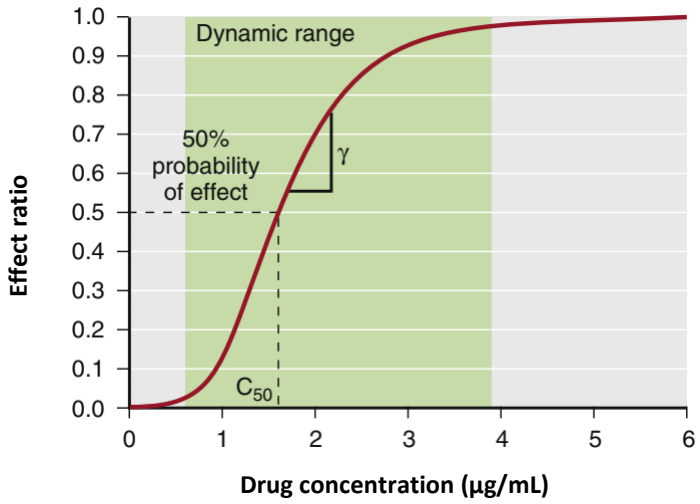


Figure 2.3 – Illustration of a pharmacodynamic model for the concentration-effect sigmoid relationship [25].

Most PK-PD models developed to date are data-driven, being based on observations to create the mathematical models. Thus, anesthesiologists can take into account the drug and patient characteristics coupled with a PK model, observe the effect outcome and accordingly adjust the specific parameters to establish a relationship with the PD parameters [45, 54].

A PK-PD model allows the prediction of an effect-site concentration for a given dose, as well as estimate the required dose to be given to achieve a certain, predefined target plasma or effect-site concentration by adjusting the administration rate over time. The PK-PD modeling approach has been widely applied in target-controlled infusion (TCI) systems, namely to optimize intravenous drug administration during anesthesia for hypnosis and analgesia, by integrating it in computer-controlled infusion pumps. Current systems include information from covariate factors such as age, weight, height, and/or sex so that the size of the parameters of the model adapts to the characteristics of the patient, decreasing variability in the expected response. TCI systems have shown evidence of accurately delivering a drug to the desired concentration and improved patient care [45, 55].

Controlling predicted concentrations is not a clinical goal but instead, control and maintain the therapeutic effect by titrating drug administration and thus avoiding under or overdosing [53, 56]. Therefore, there is great potential in applying TCI with automatic closed-loop administration of drugs to ensure the drug effect is achieved in a stable manner, and NMBAs are no exception. The first published work about muscle relaxants, establishing the relationship between PK and PD, was performed using vecuronium [49, 57]. Subsequently, numerous computer control strategies for NMB drugs have been reported; however, a major hurdle in the design of adequate feedback controllers for physiological systems is the variability of the response among individuals to the same drug [58]. Thus, intra and inter-individual variability of the patient's effect must be taken into account for optimal and personalized application of PK-PD models for NMBAs, allowing to attune the drug delivery and achieve the desired NMB degree. Nonetheless, no such system has been commercially introduced for clinical use yet.

2.1.1.3 Neuromuscular blockade reversal

The incomplete curarization of neuromuscular blockade is associated with reports of post-surgical residual paralysis and morbidity. Thus, careful evaluation and reversal of the NMB are recommended when muscle relaxants are administered. The reversal depends on gradual diffusion, redistribution, metabolism, and excretion from the body of the NMBA (spontaneous reversal). This process can be assisted by the administration of specific reversal agents.

Cholinesterase inhibitors (or anticholinesterase) indirectly increase the amount of acetylcholine available to compete with the non-depolarizing agents and re-establish normal neuromuscular transmission. Neostigmine, which provides covalent bonding to acetylcholinesterase, has been extensively used to revert the effect of non-depolarizing blockers. However, it has the side effect of slowing the heart rate; therefore, it is often used together with atropine to revert the stimulation effect of the parasympathetic nervous system.

Alternatively, specific reversal agents, such as cyclodextrins and cysteine, which have superior ability to reverse neuromuscular blockade, are increasingly being used in routine clinical practice. Sugammadex is a recent selective relaxant-binding agent that exerts the reversal effect by forming tight complexes in a 1:1 ratio with steroidal non-depolarizing agents, such as rocuronium. Its cyclodextrin structure permits a hydrophobic interaction with the NMB drug, resulting in a rocuronium–sugammadex complex that terminates the NMB action and restrains the drug in extracellular fluid, where it cannot bind with nicotinic acetylcholine receptors. Sugammadex produces a rapid, safe, and effective reversal and is essentially eliminated unchanged via the kidneys [25, 26].

As far as the reversal agent's administration goes, the time required to fully curarize a non-depolarizing block depends on several factors, which include: the selected reversal drug and dose that was given, the muscle relaxant being antagonized, and the degree of the blockade before administration. Therefore, careful evaluation is recommended to avoid post-surgical residual paralysis and respiratory complications [59, 60]. A dose of 4 mg/kg is recommended for reversal of the NMB that reaches a deep degree of blockade (1-2 PTC) and 2 mg/kg if there is a spontaneous recovery (at least 2 TOF counts).

2.1.2 NMB MONITORING

NMB monitoring is the only means available to provide necessary information regarding the degree of muscle relaxation. When NMBAs are used, there are several moments during the course of the general anesthesia that the neuromuscular assessment is essential: tracheal intubation, incision, ongoing immobilization during surgical procedures, and NMB reversal [8–11].

Even though it is possible to perform tracheal intubation without the use of NMBAs, when these are administered, the intubation quality is greatly improved, showing results of fewer postoperative airway injury and vocal cord damage [3, 61]. Besides that, it allows to ensure optimal conditions at key stages of the surgery, and one of the most critical times to monitor neuromuscular function is the end of surgery for the diagnosis of residual paralysis. Residual NMB is clinically significant and can persist, leading to serious postoperative respiratory complications (PORC), such as atelectasis or pneumonia, and an increase in morbidity and mortality. Considering the multitude of aspects influencing the duration and magnitude of NMB, PORC cannot be ruled out based only on subjective clinical criteria or reversal agent administration. Therefore, it is important to objectively monitor the degree of NMB during and after anesthesia to reduce the incidence of postoperative complications and improve patient care [10, 62].

Several studies have stressed the importance of perioperative NMB monitoring to objectively measure the degree of neuromuscular transmission [8–11]. France is the only known country where monitoring is mandatory whenever an NMB drug is administered. Despite the evidence, survey studies indicate the routine use of NMB monitors when muscle relaxants are administered ranges from 9 to 58 % of the procedures (taking into account surveys conducted in Denmark [63], Germany [64], United Kingdom [65], New Zealand [66], Middle-East [67] and Greece [68]). The incidence of PORC has been ranging between 3.5 to 88 % [67, 69–72] (26 % just in Portugal [59]), and 20 to 40 % of patients arrive at the intensive care unit (ICU) with evidence of residual block [71, 73]. The NMB monitoring is discarded even more when the surgery does not require deep levels of NMB, and with the introduction of sugammadex, anesthesiologists tend to rely on the reversal agents' action alone. Nevertheless, despite the 60 % decrease, the incidence of PORC remains as high as 9.4 % [62, 74, 75]. The main reasons for the reports of sparse use of NMB monitoring in routine clinical practice are the low availability of monitoring equipment, ergonomic installation concerns, the absence of an ideal and reliable device, and the lack of clarity in anesthetic guidelines and standards [10, 61, 65]. In addition, much of this is related to old beliefs that monitoring is unnecessary to provide clinical benefit to the patient, and that the monitoring installation takes up too much time and is too cumbersome to use. Furthermore, reversal administration is often based on clinical signs and time from the last NMBA dose, a practice that is supported by no evidence [62, 74, 76].

2.1.2.1 Peripheral nerve stimulation

In patients under anesthesia, conventional clinical tests can be used to assess muscle power directly and to estimate neuromuscular function indirectly (*e.g.*, muscle tone, feel of the anesthesia bag as an indirect measure of pulmonary compliance, tidal volume, inspiratory force). However, all these tests are influenced by factors other than the degree of NMB, whenever more precise information regarding the extent of neuromuscular function is needed, peripheral nerve stimulation is ideal. This is the most used method to assess neuromuscular transmission, which consists of the evaluation of the muscle evoked response after its motor nerve stimulation [25, 61].

In neuromuscular function monitoring, there are two types of peripheral motor nerve stimulation: the magnetic stimulation, which is more comfortable and less painful, but provides a difficult supramaximal stimulation of a peripheral motor nerve and requires heavy and bulky equipment; and the electrical stimulation of the motor nerve, which is the more frequently used technique [25].

In assessing muscle activity, nerve stimulation amplitude is a key factor. After one electrical nerve stimulation, the neuromuscular junction reacts following an "all or nothing principle", which means that after stimulation, depending on whether it exceeds the threshold potential, the muscle fiber

response may or not occur. However, if this action potential happens, it will be at a maximal strength response. The total number of neuromuscular junctions activated determinates the extent of muscle contraction. Also, the muscle force is directly proportional to the intensity of the stimulus, which increases when the electrical current is augmented until it is sufficiently intense to activate all axons. Thus, the affected muscle achieves the maximum strength, reaching a plateau. The muscular response does not increase beyond this point, even if a much higher current is applied (Figure 2.4) [10, 77]. The supramaximal intensity is set approximately 10-20 % higher than the required current to depolarize all fibers in a particular nerve bundle, which varies according to the stimulated nerve and the individual response of each patient. Limit currents of 50-60 mA are commonly implemented to ensure the reliable activation of the maximal muscle response [10]. Additionally, the stimulators are often constant current type, with the output voltage varying automatically as skin impedance changes over time (up to a maximum of 300 V) [78].

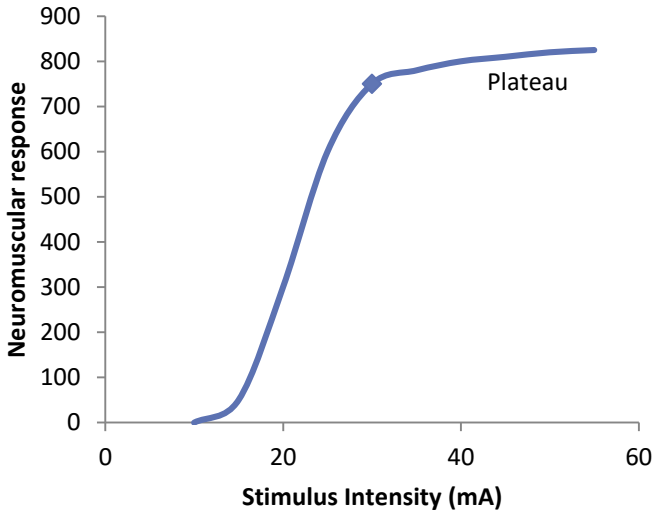


Figure 2.4 - Neuromuscular response increases with the increase of the stimulation current until it reaches a plateau (supramaximal stimulation threshold at approximately 30 mA) [10].

To assess the extent of neuromuscular blockade and provide a baseline for its evaluation, the use of supramaximal stimulation is crucial to actively stimulate as many muscle fibers as possible and enforce the maximal muscle response. After the NMBA administration, the stimulatory response decrease depends exclusively on the degree of neuromuscular blockade, reflecting the range of muscle fibers blocked. It must be taken into account that many other external factors can affect the electrical stimulation and muscular response, for instance: other drug-induced changes, skin temperature, and impedance, and/or movements at the monitoring site [10].

Stimulation patterns

The electrical stimulation consists of the use of electrodes to conduct the current at ideal stimulation sites and evoke the response of the nerves in specific relevant muscle groups. For assessing the neuromuscular function, various patterns of stimulation were studied and developed over the years.

In 1947, Chou T. [79] was a pioneer in assessing the muscle response by applying a discharged stimulation to achieve maximal contraction in the phrenic diaphragm nerve of a rat that received curare-like drugs. Some years later, the first nerve stimulation was introduced as a diagnostic tool for prolonged apnea after the use of NMBA [10, 79].

In 1971 Ali H. [81] published the first application of a peripheral nerve stimulation pattern for assessing the neuromuscular function, the train-of-four (TOF), which remained one of the most useful methods for about 50 years. However, this method had limited application in the evaluation of the deep degree of NMB [10]. As a result, the high-frequency tetanic stimulus was introduced, which allowed to assess the neuromuscular transmission based on the post-tetanic potentiation (PTP). From PTP, Viby-Mogensen J. introduced the Post-tetanic count (PTC) and the double-burst stimulation (DBS) [81, 82].

Following these developments, the most modern nerve stimulators permit for the anesthesiologists to apply different stimulation patterns and, thereafter, assess the neuromuscular blockade degree in crucial phases of the surgical procedure (*e.g.*, intubation, incision, recovery) [10].

Single-Twitch stimulation (ST)

In single-twitch electrical stimulation, a supramaximal square wave pulse is applied to a peripheral motor nerve, at frequencies ranging from 1.0 Hz (one stimulus every second) to 0.1 Hz (one stimulus every 10 seconds), lasting at least 0.2 ms (see Figure 2.5). The response to single-twitch stimulation is sometimes assessed during the induction of anesthesia [25, 61].

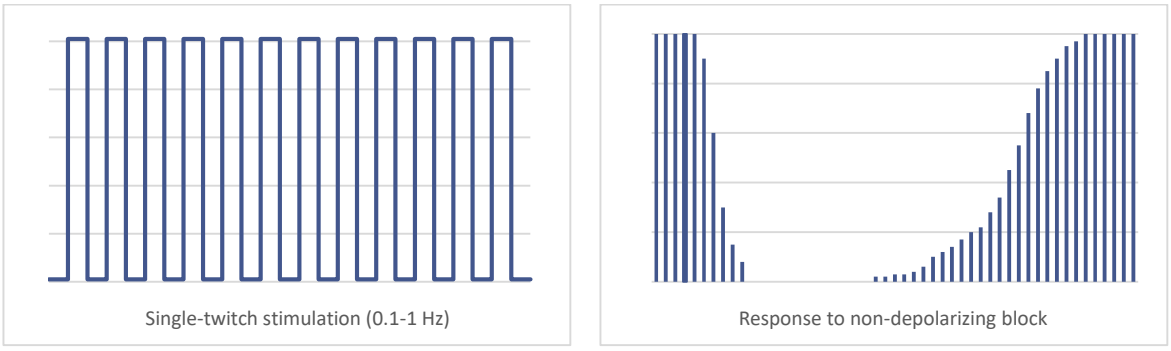


Figure 2.5 – a) Single-twitch square wave stimulation and b) the depression and recovery of the evoked muscle response when a non-depolarizing neuromuscular blocking drug is administered [10].

The muscular response to the single-twitch stimuli is rather limited since it can only be assessed by comparing it to a baseline value recorded before the administration of NMBA. Thus, after

administering a non-depolarizing neuromuscular blocker, the ST response decreases as a result of the inhibited muscle contraction [10, 77].

Train-Of-Four stimulation (TOF)

Train-of-four consists of four square pulses stimuli of 0.2 ms duration given every 0.5 seconds (2 Hz). This nerve stimulation pattern is based on the concept that ACh is depleted by successive stimulations. The TOF stimulus is a standard method throughout relevant phases of neuromuscular blockade: onset of action, intraoperative monitoring of the moderate blockade, and neuromuscular recovery. Since after a stimulus there is no release of additional ACh, the response to each of the four twitches is individually detected with the same intensity, showing the muscle fatigue or fade in the train of responses. This provides the basis for the NMB evaluation. To avoid misleading interpretations, measuring two successive TOF series must be separated with a minimum interval of 10 seconds, allowing for the neuromuscular end-plate to recover.

Train-of-four monitoring has been recommended to measure neuromuscular relaxation and recovery, especially when non-depolarizing NMBA are used. The fourth twitch (*T4*) is the first to show the fade effect, followed by the remaining responses until all disappear. This corresponds to TOF = 0 and is determined as the best time for intubation.

As the process is reversed, the nerve responses unfold in the opposite order of disappearance (*T1* appears first and *T4* last), and the NMB recovery starts. The number of detected responses after TOF stimulation is called TOF-count. In turn, the proportion that results from dividing the amplitude of the fourth twitch response by the amplitude of the first twitch response is defined as TOF-ratio (*T4*/*T1*) (Figure 2.6) [10].

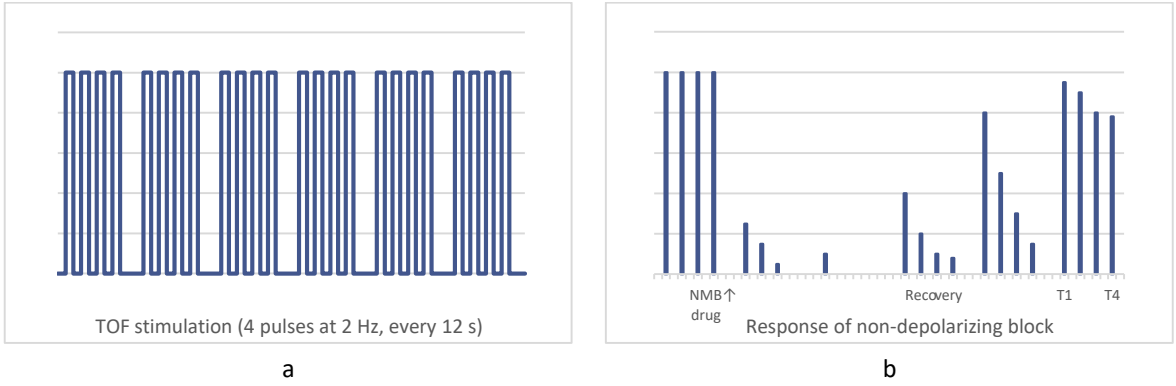


Figure 2.6 – a) Train-of-four (TOF) stimulation and b) the evoked muscle responses after administration of non-depolarizing neuromuscular blocking drugs (represented by the arrow) [10].

In the control response (before the administration of the NMB drug), all four responses are expected to measure the same (TOF-ratio of 100 %). Following the non-depolarizing NMBA administration, the TOF-ratio decreases, showing the fade effect [10]. TOF-ratios between 15-25 % usually indicates

adequate surgical relaxation. On the other hand, TOF-ratio > 90 % have been proven to guarantee sufficient NMB recovery for safe tracheal extubation [25, 61, 77]. More recent studies propose considering TOF-ratio > 95 % before extubation to significantly reduce the risk of PORC [62].

Tetanic Stimulation (TET)

The application of TET stimulation was proposed as a possible way to deliver more accurate information about the degree of NMB and predict residual paralysis. Commonly, the tetanic stimulation discharges a 50 Hz frequency stimulation sustained for 5 seconds. During the TET burst, the stimulatory response blend together, and the observed response is a single strong continuous muscle contraction. If the recovery of a non-depolarizing blockade is incomplete, after the tetanic stimulus, an increase in muscle contraction is clear and is followed by an evident fade (see Figure 2.7).

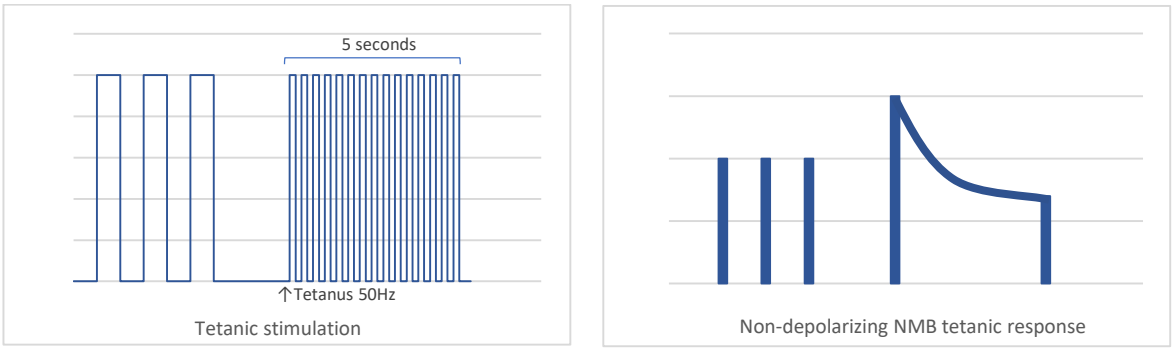


Figure 2.7 – a) Following ST, the Tetanic stimulation of 5 seconds (50 Hz), and b) the evoked response during moderate block after injection of non-depolarizing NMB drugs, showing the fade in the response [10].

The occurrence of fade after TET stimulation is usually pre-synaptic; thus, large amounts of acetylcholine are released in the motor end-plate. After exhausting the immediately available stores, the ACh at disposal is reduced, and the equilibrium between mobilization and synthesis is achieved, known as post-tetanic potentiation (PTP) [25]. The degree and duration of PTP depends on the degree of NMB, usually disappearing within 60 seconds after the tetanic stimulation ceases. Moreover, this stimulation is extremely painful and directly proportional to the applied frequency. Therefore, the use of TET is restricted to anesthetized patients, being used mainly as a component of post-tetanic assessment [10, 25].

Post-tetanic Count stimulation (PTC)

In pursue of a more powerful technique to monitor the degree of NMB, by combining tetanic and ST stimuli patterns, the post-tetanic count stimulation pattern was introduced. In common practice, PTC applies the tetanic pulse of 50 Hz sustained for 5 seconds, followed by a stop of 3 second, then a 10-20 single twitch of 1 Hz each (one twitch per second). Grounded on the PTP phenomenon, the ratio overturn of acetylcholine molecules generated by the TET stimuli and by the NMBA drugs, permits to

discern muscle contractions for a brief duration. As a result, the tetanic stimuli is not included in the response assessment; instead, an enhanced response to subsequent single twitch stimulations is observed, allowing to evaluate the post-tetanic counts (see Figure 2.8) [10, 25, 77, 83].

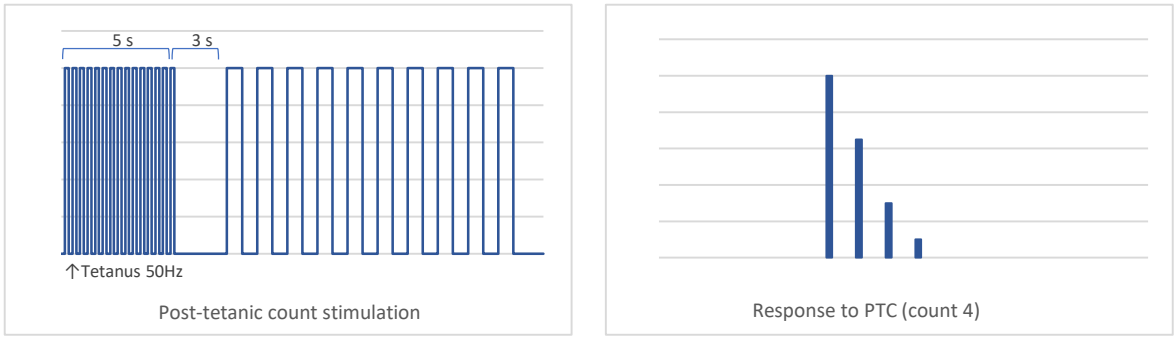


Figure 2.8 – a) Post-tetanic count stimulation and b) evoked response (*e.g.*, 4 responses counted) [10].

To evaluate two successive PTC stimulations, the interval between assessments must be at least 3 minutes and, ideally, not more than 6 minutes. Otherwise, due to the occurrence of PTP, the response of the second subsequent PTC can be underestimated, and the NMB can be inaccurately assessed [25].

Double-Burst Stimulation (DBS)

Double-burst stimulation was introduced to tackle the subjective NMB evaluation of TOF stimulation. DBS facilitates the manual detection of fade when in the TOF response cannot be identified with sufficient accuracy to exclude residual curarization (namely distinguish TOF-ratios of 90 %). It consists of two short-duration bursts of tetanic stimulation separated by a 750 ms interval, with a 0.2 ms duration of each square pulse in the burst (equivalent to a 50 Hz stimulation, each stimulus separated by 20 ms). DBS stimulation has two modes, the most commonly used is $DBS_{3,3}$, which applies three impulses in each of the two bursts, while in the $DBS_{3,2}$, the first burst has three impulses and two in the second burst (see Figure 2.9) [10, 83].

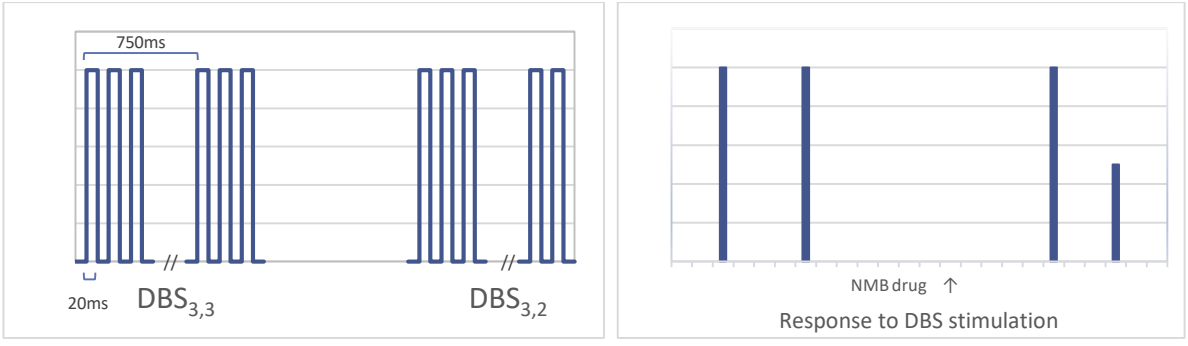


Figure 2.9 - Double-burst stimulation: $DBS_{3,3}$ with three impulses in each of two tetanic bursts, and $DBS_{3,2}$ with three impulses in the first and two impulses on the second burst - and of the evoked muscle responses [10].

The DBS ratio is the amplitude of the second response to stimulation divided by the amplitude of the first, which, in a partially paralyzed muscle, quantifies the fade of DBS response [25, 61].

Stimuli application

Single-twitch has no clinical relevance as a sole stimulation pattern. Nowadays, its use is only as a component of combined stimulation modes and/or for investigation purposes. In turn, TOF stimulation provides important information, namely TOF-count and TOF-ratio, for the assessment of the onset of action, intraoperative state, and neuromuscular recovery after the administration of NMB drugs. Moreover, TOF stimulation has some advantages over DBS and tetanic stimulation, as it is less painful and does not generally influence subsequent monitoring, it can be used continuously. On the other hand, for subjective assessment of the intensity of blockade in the recovery phase, DBS is more suitable than TOF (namely TOF-ratios up to 60-90 %) [85].

The introduction of tetanic stimulus and application of PTC is crucial to monitor deeper neuromuscular blockade, namely after the use of NMB drugs, where there is no response to TOF. This is especially important to reliably ensure patients' immobility, prevent diaphragmatic and/or laryngeal reactions, and avoid coughing or bucking that can compromise surgical conditions [86]. Additionally, PTC stimuli deliver decisive information on the neuromuscular relaxation degree that can be beneficial to avoid overdosage of NMB drugs and cumulative effects, as well as to estimate the time to TOF recovery after the dissipation of the blockade [77]. Moreover, in the NMB recovery, the PTC method is important to quantify the level of the block and provide insight into the required dosage of reversal agents, such as sugammadex [73, 74].

Monitoring sites

There are multiple options for selecting the site and method of neuromuscular monitoring (see Figure 2.10). Since muscles react differently with respect to onset, recovery, and the peak effect of NMB, the choice of monitoring site must consider some aspects in order to provide ideal assessment and adequate relaxation. First, the choice of site depends on the patient’s position and must be accessibility during surgery and/or should consider monitoring muscles of interest to the surgical site (*e.g.*, retinal eye surgery, neurosurgery) [77, 86].

One of the sites commonly used to quantified NMB is the muscles around the eye (orbicularis oculi and corrugator supercilii), which accurately reflect the response of refined laryngeal muscles or the diaphragm [88]. The adductor pollicis muscle (in the hand) correlates well when more peripheral muscles are adequate to be monitored (*e.g.*, upper airway and upper esophageal muscle) [61, 88]. Similarly, when the adductor pollicis is unavailable, an alternative monitoring site is the big toe (tibial nerve), which can be easily and safely accessed [87]. Very rarely, another transcutaneous stimulation that might be applied for monitoring larynx/diaphragms is the phrenic nerve [61, 86].

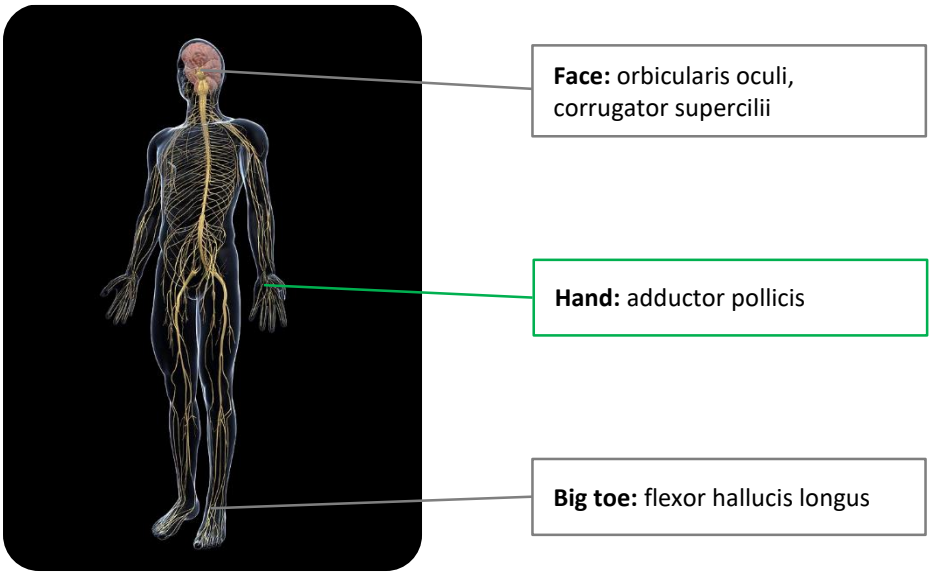


Figure 2.10 - Common monitoring sites for NMB degree assessment.

The most commonly used monitoring technique to assess and classify the degree of NMB is based on the measurement of the adductor pollicis evoked response after ulnar nerve stimulation [26, 61, 89]. Although its assessment does not fully represent the state of relaxation of the entire body or the laryngeal/diaphragm muscles, it provides an insightful reference for dose adjustments and adequate NMB recovery (*e.g.*, TOF-ratio > 90 % indicates sufficient recovery of NMB for awakening the patient, ensuring safe tracheal extubation conditions). Throughout this work, the assessment at the adductor pollicis was considered as reliable to monitor the NMB, and was included in the study setup design further on described in chapter 3.

Electrodes for stimulation

The electrical impulses are transmitted from the stimulator to the nerve by means of a surface or needle electrodes. Usually, disposable pre-gelled silver or silver chloride surface electrodes are used, having a small conducting area (approximately 7 to 11 mm in diameter) to ensure sufficient current that can reach the underlying nerve. When a supramaximal response cannot be obtained with surface electrodes, needle electrodes can be used in a few exceptional cases. These are placed subcutaneously to avoid direct injury to the nerve [10, 25].

Before placement of the electrodes, the skin site should always be properly cleaned, dried, and shaved, preferably rubbed with an abrasive scrub. For accurate neuromuscular monitoring, the electrodes should be placed over the path of the nerve. The negative (black) electrode is placed distally and closest to the muscle terminus, and the positive electrode (red/white) is placed 2-4 cm proximally (see Figure 2.11) [61]. The expected response is the adductor pollicis adduction, producing a movement not only of the thumb but also of every other finger.

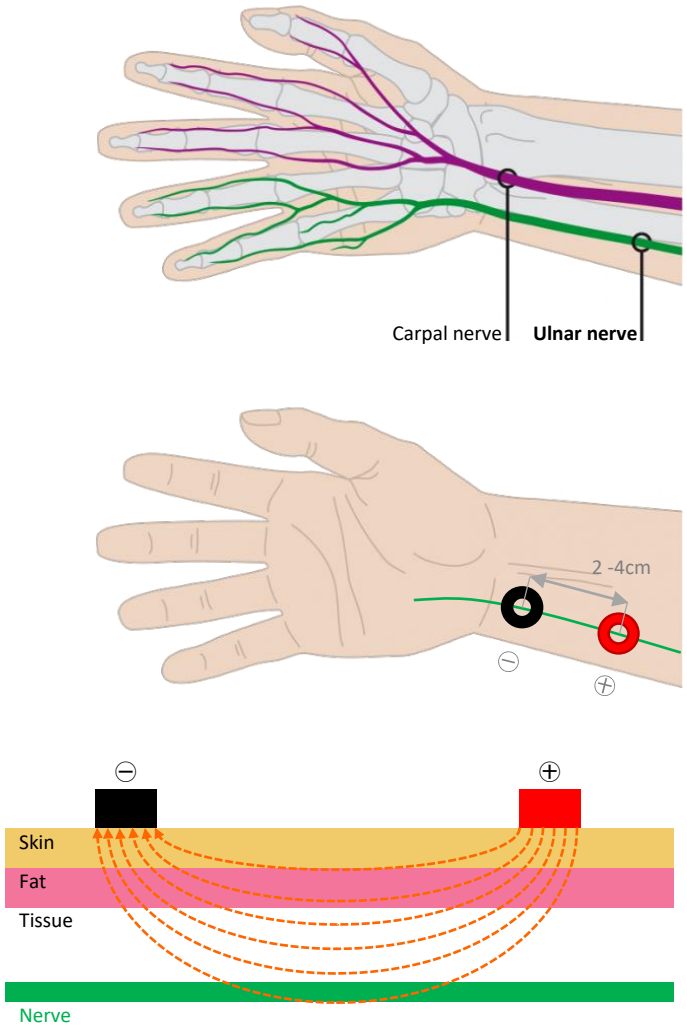


Figure 2.11 - Electrode disposal at the adductor pollicis muscle for the stimulation of the ulnar nerve [10].

Phases and classification of the NMB

Monitoring the NMB requires a set of considerations to obtain reliable results. It must take into account the surgical procedure requirements together with the muscle relaxation level intended (see Figure 2.12 and Table 2.1). In routine practice, the non-depolarizing NMB induced immediately after the administration of the intubation dose (*e.g.*, 2xED_{95}) is monitored and characterized in:

1. Onset phase - depression of the TOF response after the initial bolus;
2. Intense block - immediately followed by no evoked response to both TOF and PTC stimulations;
3. Deep block - comprises the phase from the first response to PTC up to the first response to TOF;
4. Moderate block - is defined as the period between the recovery of the first (*T1*) and the fourth (*T4*) TOF twitches;
5. Recovery phase - after all four responses to TOF are detected, and the TOF-ratio is computed [77].

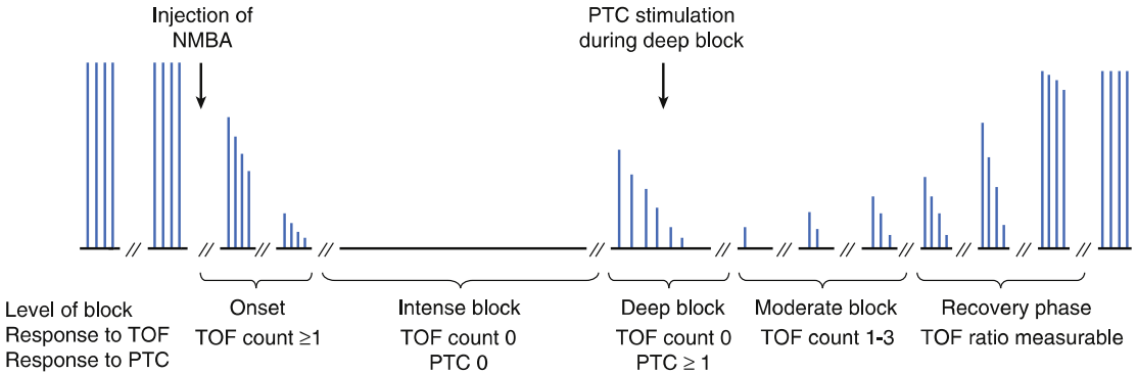


Figure 2.12 - Degrees of non-depolarizing neuromuscular blockade according to the responses to different stimuli [25].

Table 2.1 - Applicability of the different stimuli for the response assessment at different stages of block [10, 91].

Stimulation pattern	**Applicability**			
	Onset of action	**Deep blockade**	**Moderate blockade**	**Recovery**
Single twitch	No	No	No	No
TOF	Yes	No	Yes	Yes
Tetanus	No	No	No	Conditionally
PTC	Conditionally	Yes	No	No
$DBS_{3,3}$	Conditionally	Yes	No	Conditionally

From this NMB classification, the concept of "deep block" comprises a wider monitoring range, that allowed for a large variability in the methodologies of the investigation studies conducted over the years, which adopted different layers of the deep NMB degree scope (*e.g.*, 0-1, 0-2, 0-5, 0-10 or 1-2 PTC, further explored in section 2.2). In 2018, Naguib M. [8] proposed a consensus on perioperative use of neuromuscular monitoring, stratifying the neuromuscular block spectrum in 1-5 levels. Although this classification may be sufficient for the majority of surgical purposes, soon after, Biro P. [92] suggested a new classification for the NMB depth, in which the deep and narrow segment of post-tetanic counts values ranging from 1 to 3 responses are additionally distinguished. This classification of the neuromuscular block levels was differentiated and is listed below on Table 2.2:

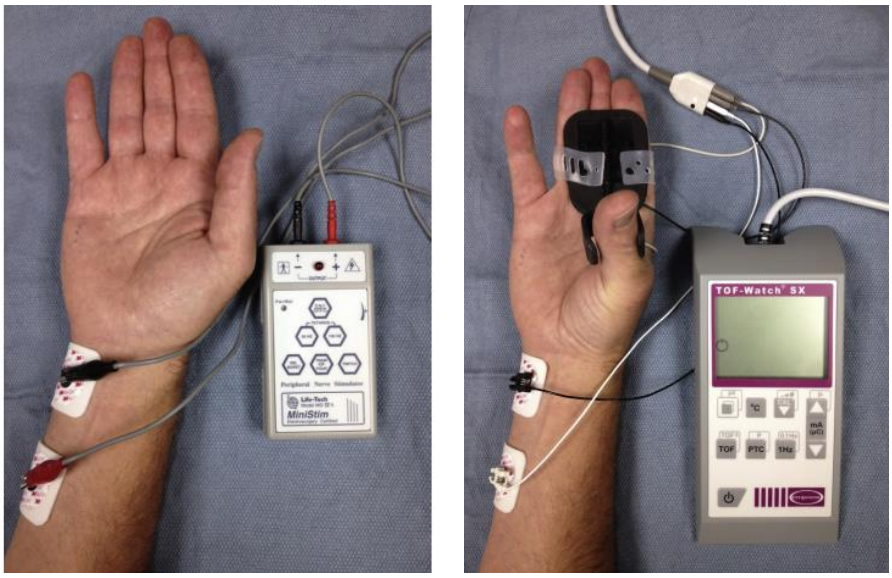
Table 2.2 - Modified classification of the depth of block [92].

Level of block	**Depth of block**	**NMB monitoring at the adductor pollicis**
Level 7	Complete block	PTC = 0
Level 6	Profound block	1 ≤ PTC ≤ 3
Level 5	Deep block	TOF = 0, PTC ≥ 4
Level 4	Moderate block	1 < TOF-count < 3
Level 3	Shallow block	TOF-ratio < 40 %
Level 2	Minimal block	40 % < TOF-ratio < 90 %
Level 1	Acceptable recovery	TOF-ratio > 90 %

As mentioned, to guarantee the complete immobility of the patient throughout the procedure, very little or no neuromuscular response is required, previously characterized and defined in the context of this work by 1-2 PTC responses, which falls within the category of the profound block [4–6, 92]. This was published and acknowledged in the late stage of the development of this project. Despite the nomenclature disarray, the objectives of the project are well-grounded and established for the development of the work, thus throughout this thesis, “deep NMB” refers to the 1-2 PTC measurement range.

2.1.2.2 NMB evaluation techniques

Over the years, several techniques have been used to evaluate the neuromuscular response by induced stimulation. Two main approaches can be distinguished: qualitative and quantitative neuromuscular monitoring (see Figure 2.13).



a b

Figure 2.13 - Ulnar nerve stimulation with a) qualitative method, where the response is subjectively assessed solely via visual/tactile evaluation; b) quantitative method, with sensorial evaluation recorded at the thumb, proportional to the muscle contraction [61].

Qualitative evaluation

The qualitative neuromuscular monitoring is based on a subjective assessment of the degree of relaxation after an electrical stimulus to a peripheral nerve. This clinical evaluation relies on the patient’s ability to perform certain tests (*e.g.*, hand-grip, eyebrow response), or via the tactile and visual muscle response assessment.

In routine general anesthesia, this technique is applied to evaluate the NMB recovery following curarization from anesthesia; however, it depends on several aspects, namely the degree of consciousness and cooperation of the patient [61]. There are three stimulation patterns to assess

residual blockade under qualitative monitoring: TOF, tetanic, and DBS. The occurrence of fade under these stimulations indicates incomplete neuromuscular recovery. Given the subjective interpretation of the response and the limited accuracy of the tests, it is difficult to rule out residual paralysis with certainty regardless of the stimulation pattern applied, therefore remaining an imprecise monitoring method [25, 61].

Quantitative evaluation

Quantitative assessment of an evoked neuromuscular response is an advance innovation in the measurement of the degree of muscle response. These NMB monitors are instruments that permit to accurately assess the muscle transmission and detect the residual paralysis that might occur. Five main techniques were developed to quantify the NMB: mechanomyography, kinemyography, phonomyography, electromyography, and acceleromyography (see Figure 2.14).

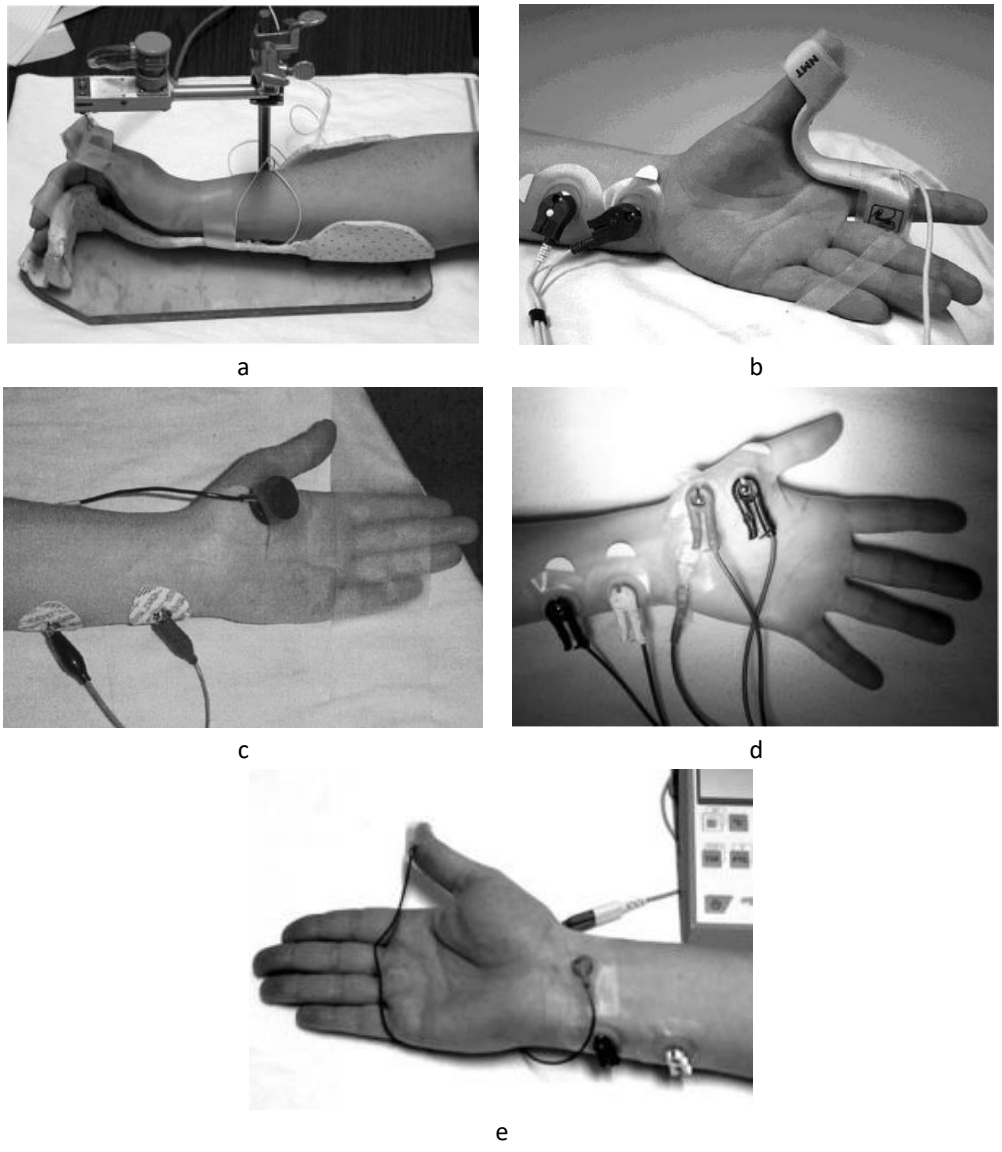


Figure 2.14 – Adductor pollicis monitoring setup for a) mechanomyography [61, 93]; b) kinemyography [95] c) phonomyography [61, 96]; d) electromyography [61]; and e) acceleromyography [61, 94].

Mechanomyography (MMG)

This neuromuscular monitoring method assesses the actual contraction force, being the basic method to monitor the degree of relaxation of a given muscle. Mechanomyography methods are not easy to apply in the clinical setting, requiring stringent preparations and meticulous control of hand positioning and a pre-load [61].

Kinemyography (KMG)

Kinemyography is based on the measuring of movement of the thumb by employing a piezoelectric transducer in a molded plastic device that faces the contour of the outstretched thumb and index/middle finger. KMG accuracy depends on the careful hand positioning to avoid artifacts [61].

Phonomyography (PMG)

Phonomyography is based on the emitted sound waves yield when muscles contract. This sound waves of very low frequencies (90 % of the signal spectrum is < 50 Hz) can be detected using special sensitive microphones, at the surface of the skin. PMG can be used non-invasively in every muscle of interest by ensuring the microphone attachment during the recording of the signal [61].

Electromyography (EMG)

Electromyography is used to evaluate the power of the action potential after evoked stimulation of a motor nerve. EMG can assess most monitoring sites, showing a good correlation in evaluating the effects of NMBAs at the diaphragm. It shows some restrictions in smaller muscles, such as the corrugator supercilii or orbicularis oculi muscles, due to the difficulty of measuring small action potentials. Furthermore, other EMG limitations relate to the inability to return to reference levels, failure to descend completely in fully relaxed muscles, and interference with other electronic devices [61].

Acceleromyography (AMG)

Acceleromyography is one of the most used technologies, providing one of the most accurate and reliable methods to detect the neuromuscular response. It is mainly used to measure the adductor pollicis muscle evoked response after the ulnar nerve stimulation via an acceleration sensor at the thumb. The AMG application to measure other muscles is limited due to the difficulty of distinguishing the movement [26, 61, 89].

From the different evaluation techniques, EMG and AMG are the most used technologies to objectively measure NMB in routine clinical settings. AMG has been proven to accurately evaluate the stimulation response in the different stages of the NMB, reducing the number of incomplete NMB recovery and post-operative complications reports [61]. There has been a recent rise in commercially

available EMG-based monitors, which have the advantage of not relying on the thumb movement and have shown promising results in the evaluation of the NMB [97].

2.1.3 MONITORING DEVICES

2.1.3.1 Nerve stimulator requirements

A nerve stimulator delivers stimuli to electrodes and must meet the optimal standards for clinical use. Ideally, a nerve stimulator should admit the following properties:

- The waveform signal must be monophasic and rectangular;
- It should provide the different modes of stimulation (ST, TOF, TET, PTC, and DBS), satisfying the requirements associated with each mode. Additionally, the device must have the option to change stimulus parameters such as frequency, current, and duration of stimuli;
- It must deliver a constant current;
- For safety reasons, the nerve stimulator should not generate currents higher than 80 mA;
- It must be battery operated and include a battery level check;
- It should have polarity indicators for electrodes;
- It must allow a quantitative measurement of the evoked responses;
- If the unit cannot deliver the specified stimuli or evaluation, an alarm should be displayed;
- It must present a user-friendly interface [12, 97, 98].

Many commercially available stimulators require a skin temperature assessment. This measurement is important for monitors that usually are able to deliver 25-50 mA only when skin resistance ranges from 0 to 2.5 kΩ. However, in low temperatures, skin resistance may increase up to 5 kΩ, which may cause the current delivered to the nerve to fall below the supramaximal level, leading to a decrease in the stimulation response and underestimation of the NMB degree [12]. Additionally, the monitors must have a computer communication link to allow the recording of the data.

2.1.3.2 NMB monitor market

The first commercially available stimulators relied on the qualitative method of evaluation. Over the years, several stimulation monitors were introduced for clinical practice. Nowadays, the use of quantitative NMB monitors is highly recommended [13, 99]. The quantitative neuromuscular monitoring provides one of the most reliable, effective, and reproducible techniques to evaluate the degree of NMB during surgeries [101]. These monitors are indicated to optimize the time of intubation, guide the degree of NMB, and prevent residual paralysis followed by safe extubation [13].

After the introduction of these monitors, studies reported a decrease in residual paralysis incidence from 62 % to 3 % [87].

Commonly, operation rooms with an integrated system for ventilation, vital signs monitoring, and breathing system, such as GE Datex Ohmeda Aisys (GE Healthcare, USA), can provide NMB assessment during the surgery. It consists of a neuromuscular transmission module (MechanoSensor; Datex-Ohmeda) based on the KMG evaluation of the NMB [102].

The TOF-cuff monitor (RGB Medical Devices, Madrid, Spain) couples the assessment of blood pressure and NMB monitoring. The stimulation is performed at the brachial plexus (humeral level) and records the evoked changes in pressure. Although it shows a promising assessment of the NMB, TOF-Cuff has risen some doubt in excluding residual paralysis [103].

Recently, two EMG based neuromuscular monitors have been developed and have become available in the market: TwitchView (Blink Device Company, Seattle, USA) and TetraGraph (Senzime, Uppsala, Sweden). There is very little literature regarding these devices, yet the studies available report good reliability and ease of use [103, 104].

AMG-based monitors have been widely used in everyday clinical practice. The individual and portable AMG devices that stand out are the following: TOF-Watch® SX® (Organon, USA); Stimpod NMS 450X (Xavant Technology Ltd., Pretoria, South Africa); and TOFscan® (IDMED, Marseille, France).

The monitoring devices available at CHUP for inclusion in this research are TOF-Watch® SX and TOFscan®. The operating principles of these devices are equivalent, and, when measuring NMB at the adductor pollicis, both apply a preload to increase precision by returning the thumb to the baseline position.

Organon has developed three models - TOF-Watch®, TOF-Watch® S, and TOF-Watch® SX – that comply with worldwide registration certified requirements; however, these are no longer manufactured. TOF-Watch® SX is the only device approved for research trials that monitor the neuromuscular blockade [106]. Using TOF-Watch® SX, a calibration should be performed before the administration of the NMBA, to detect supramaximal stimulating current and adjust the *T1* (single twitch) baseline response to 100 %. Also, the sensor consists of a single axis accelerometer that measures movements in the perpendicular direction only. This may raise questions regarding the accuracy of the measurement due to the complex movement of the thumb after stimulation of the ulnar nerve. The stimuli result in isotonic contractions of the adductor pollicis that are often in three dimensions by involving three joints [106, 107]. In contrast, TOFscan® is a more recent device available in the market that includes a three-dimensional accelerometer, allowing to measure the complete movement of the thumb accurately. This monitor dismisses the necessity for calibration, allowing for the current intensity to

be adjusted by the user [13]. In chapter 4.1, the comparison of TOF-Watch® SX and TOFscan® monitoring during deep neuromuscular blockade is studied and described.

2.2 ROCURONIUM CONTINUOUS INFUSION AND MONITORING METHODS FOR DEEP NMB

Deeper levels of the neuromuscular blockade are used to ensure improved surgical conditions and the use of continuous infusion of NMBAs stands out as the most appropriate technique, by benefiting the constant dose-effect relationship throughout the procedure and, thereafter, the blockade stability. Together with appropriate NMB monitoring, it is possible to guide the dosage requirements and improve the maintenance of the desired muscle relaxation, as well as help prevent residual paralysis at the neuromuscular recovery [12, 26, 108].

Rocuronium stands out as one of the most used drugs in general anesthesia, favoring the continuous maintenance of the NMB level due to its dose-based duration characteristic. In common practice, for an effective induction, 2xED_{95} of rocuronium are administered, producing response depression and rapid onset of action that allow for appropriate intubation conditions. However, its half-life duration is often insufficient for surgical procedures with longer duration (> 60 min) [14, 20, 29, 109, 110]. Nevertheless, rocuronium administration should be balanced according to the desired level of NMB, avoiding light dosage that may allow patients movement/coughing, as well as overdose, that can prolong and delay the NMB effect [112]. Often, to maintain muscle relaxation in prolonged procedures, several boluses are administered, resulting in a fluctuating blockade. A drawback of this approach is related to the complexity in ascertaining the NMBA demand, even when relying on NMB monitoring, due to the difficulty in anticipating the exact length of the procedure and each individual's effect duration [113].

Some investigations have compared intermittent boluses to continuous infusion of rocuronium [113–117]. Although no studies directly aiming for the deep NMB levels were found, it is reasonable to claim that continuous infusion presents inherent advantages in terms of improving the maintenance of neuromuscular blockade degree. Infusion pumps can provide a valuable solution for the ongoing administration of drugs, allowing for a balanced and stable NMB degree and to improve anesthesia quality. An update on the clinical practice guidelines for sustained NMB supporting the use of continuous infusion of NMBAs was recently published [3, 118]. This approach usually comprises an initial bolus for a quick onset, followed by the intubation and, after achieving the desired NMB level, the infusion is started and adjusted throughout the procedure. To maintain a constant effect, the rate of delivery of the drug should be equivalent to the rate of clearance from the plasma. The

recommendations for rocuronium infusion at steady-state block in standard anesthesia can range from 0.24-0.96 mg/kg/h (mean 0.6 mg/kg/h) [113, 119–121]. Rocuronium has been administered via continuous infusion, considering computer-based pharmacokinetics models paired with target-control infusion systems, as well as closed-loop feedback control systems [119, 122–124]. However, research is lacking in the development of an adequate solution for deeper NMB levels.

From the literature, it can be concluded that there is a wide variability when continuous administration of rocuronium to maintain deeper NMB levels is applied. A systematic review with a meta-analysis was conducted, evaluating the rocuronium demand, surgical conditions scores, and time of recovery after standard sugammadex dose. The reviewed studies applied continuous infusion pared with NMB monitoring for the maintenance of 0-2 PTC. Additionally, this review method was repeated for the investigation of rocuronium administration and NMB monitoring approaches regarding the different layers of NMB depth (0-10, 0-5, and 1-2 PTC). The accomplished work was published and is described next.

2.2.1 MODERATE versus DEEP NMB (0-2 PTC)

Recently, Bruintjes M. [7] conducted a systematic review and meta-analysis regarding the influence of moderate and deep NMB during laparoscopic surgeries, concluding that deep NMB improves the surgical space conditions (mean difference of 0.65 on a scale 1-5, 95 % confidence interval (CI): 0.47–0.83) and reduces post-operative pain. Nevertheless, the optimal approach for continuous administration of rocuronium to maintain deeper NMB levels remains unclear. This subsection aims to explore the current approaches for rocuronium infusion and the monitoring specifications that permit an improved and stable NMB when the target range of 0-2 PTC is desired.

2.2.1.1 Systematic search methodology

This review was registered as CRD42018106626 in PROSPERO and conducted based on PRISMA guidelines (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018106626).

The scope of the search included publications worldwide till February 28th, 2019, independently of language or publication status. PICO statement addresses studies with human adult participants, classified as ASA I-IV (American Society of Anesthesiologists class), undergoing a surgical procedure that used rocuronium through continuous infusion aiming for a neuromuscular blockade target of 0-2 PTC, as the intervention. Moderate NMB, conventional therapies of rocuronium administration (*e.g.*, via periodic boluses), and reversal methodologies were the basis of comparison. Randomized clinical trials, controlled trials, and cohort studies were eligible for inclusion. Studies that include pediatric or animal participants, or using other NMBA to maintain deep NMB were excluded. Primary outcomes

were the rocuronium consumption, surgical conditions, and time of reversal after 4 mg/kg of sugammadex. Secondary results include methodological features of rocuronium administration and NMB monitoring.

Data sources selection and extraction

The databases included PubMed, ISI Web of Science, Cochrane Library, and Google Scholar search engine, and the bibliographies of the included studies were evaluated for additional relevant references (snowballing). The search strategy of references is detailed in Appendix 8.1.1.

From the search results, the duplicate removal was conducted combining EndNote (X8; Clarivate Analytics, USA) and secondary manual scan. Then, titles and abstracts were screened for relevance to the topic. Next, the examination of the full texts was conducted, scanning discrepancies and redundancies. Studies fitting criteria were included in this review (details in Appendix 8.1.2).

The extraction of data was conducted independently, including the essential features of the studies (Author, year, NCT, ASA class, weight, BMI, participants) and details of the interventions. These details included the parameters of rocuronium administration (induction dosage, start infusion rate, rocuronium adjustment principles), monitoring specifics (device, PTC target and time interval between evaluations), and duration of the procedure. Results regarding the administered rocuronium for maintaining 0-2 PTC, surgical conditions, and time to recover after sugammadex were also included.

The data was extracted if the mean, standard deviation (SD), and the number of patients (N) were reported or could be estimated. Unadjusted values were calculated and normalized. For studies reporting median and range values, mean and SD calculations were based on the formulas presented by Hozo S. et al. [126] and Higgins J. and Green S. [127]. Parametrization of surgical condition scales was also conducted for equipotent comparisons of the results (5-point scale). Moreover, if the information on rocuronium used was not directly provided, the assessment of the total amount of drug administered to maintain the NMB target was calculated and standardize for analysis (stipulated as the administered rocuronium per weight per hour). The time interval of the NMB monitoring, total procedure, and recovery durations, were measured in minutes. Additionally, authors were contacted for a follow up on absent data.

The risk of bias assessment was performed for each study design, considering the Cochrane Collaboration tool [127].

Data analysis

OpenMetaAnalyst version 10.10 (Center for Evidence based Medicine, Brown University, USA) was used to conduct meta-analyses and calculate the effect size, expressed as means difference with 95 %

CI if data were available from a minimum of three studies. The difference in means was computed using the random-effects model. Heterogeneity was analyzed and reported as the I^2-test, considering over 50 % statistically significant heterogeneity. To investigate findings robustness, a sensitivity analysis was performed examining: 1) studies with the lowest risk of other bias, 2) studies with 1-2 PTC target, 3) studies with a shorter interval of PTC measurements (≤ 15 minutes). To explore possible causes of heterogeneity and the influence of certain variables, subgroup analysis could be included if necessary data was available. Moreover, if at least ten comparisons were accessible, publication bias examination through subgroup analysis and asymmetry of the funnel plot was considered.

2.2.1.2 Results and meta-analysis of the systematic review

Initially, the duplicate and redundancy screen resulted in a total of 151 admissible references. From first-hand title/abstract analysis, 23 publications were eligible for full-text review. By the time of the search, three clinical trials had still not reported results (NCT02454504, NCT01539044, and NCT02320734). A total of eight pieces of research met PICO criteria and were eligible for applicability (Figure 2.15), resulting in a total of 483 participants. The exclusion justifications of remaining articles are presented in Appendix 8.1.3, stressing the unadjusted target of NMB degree as the most common reason. The characteristics of the included studies are briefly summarized in Table 2.3 (detailed in Appendix 8.1.4). Although authors were contacted for a follow-up, they were unable to provide additional information.

All included records are randomized trials published in English between 2012 and 2019, reporting the maintenance of an NMB with PTC < 2 through the infusion of rocuronium. Seven studies compared moderate with deep NMB, and one study evaluated the reversal effect, comparing sugammadex with neostigmine. At induction, the intubation dose differed between 0.3 and 1 mg/kg, and initial infusion records show a variance of rate between 0.3 and 0.9 mg/kg/h. Regarding the NMB monitoring, the reported time interval between consecutive stimuli measurements ranged from 3 to 15 minutes. The applied level of NMB target was 1 to 2 PTC (75 %) or 0 to 1 PTC (25 %). The different ranges of PTC target adopted can generate different dose adjustments and different amounts of rocuronium required. The measurement of 0 PTC responses, which can be caused by overdosing, is inadvisable because it cancels the tracking of NMB and limits the measurement below it, blinding anesthesiologists to the cumulative effect and the expected time to recover positive values.

From the inclusive outcome measurements for meta-analysis: six studies reported the surgical space conditions (75 %); seven presented the amount of rocuronium required during the procedure in which only three quantified the data for both moderate/deep groups (38 %); two studies presented results on reversal time after standard sugammadex dose of 4 mg/kg (25 %).

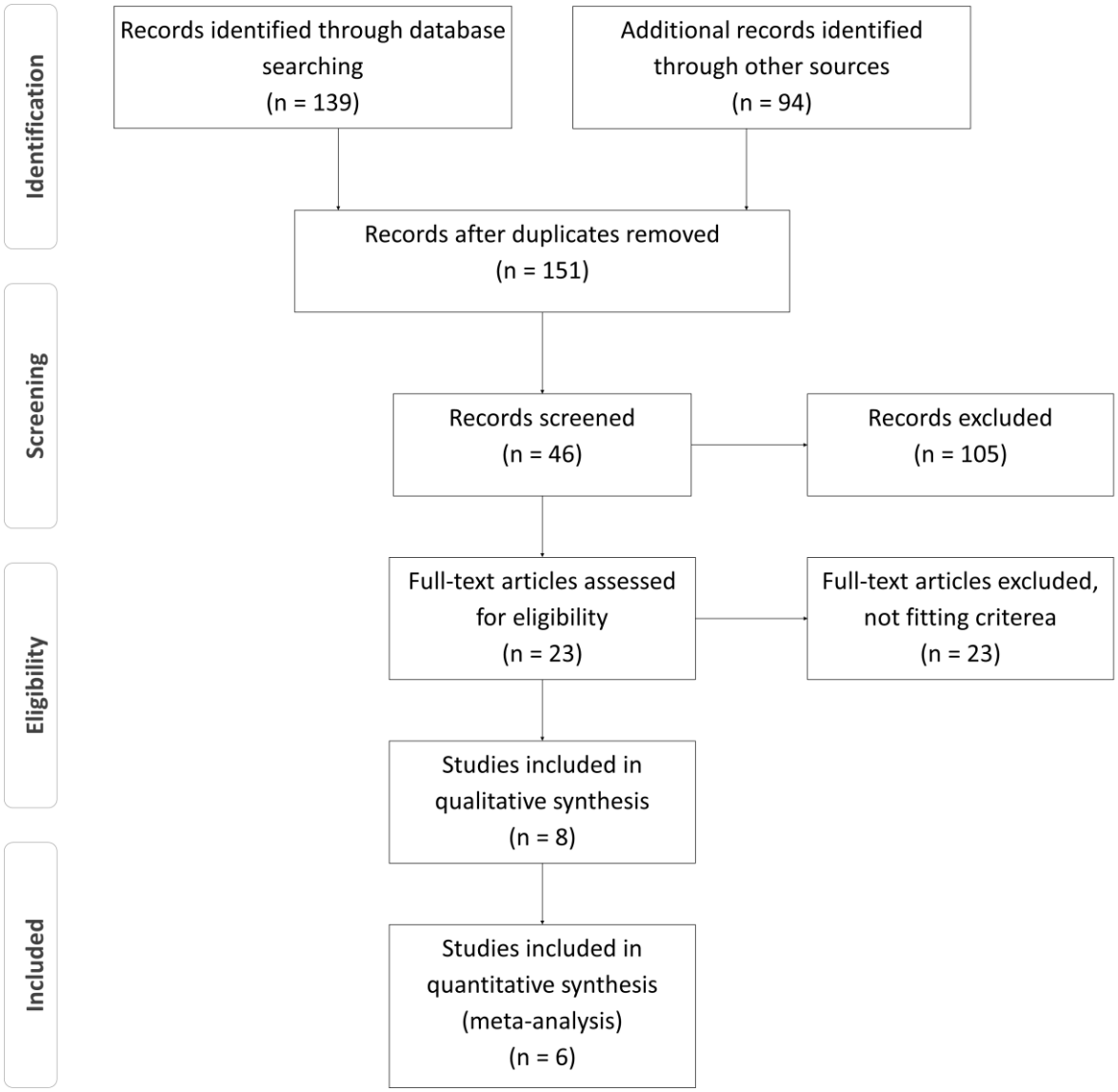


Figure 2.15 - The PRISMA flowchart diagram of the study inclusion process.

Table 2.3 - Data abstraction of studies continuous infusion of rocuronium for deep or intense NMB.

Author (Year)	Trial Reference	Sample Size	Intervention				Comparison	Inclusive Outcome
			Rocuronium administration		Monitoring			
			Induction dose (mg/kg)	Infusion start rate (mg/kg/h))	PTC target	Stimuli interval (min)		
Baete S. (2017) [128]	NCT01748643	60	0.6	0.6	1-2	5	Moderate *vs.* Deep NMB	Administered rocuronium (mg/kg); Surgical conditions (SRS)
Yoo Y. (2015) [129]	NCT02109133	66	1	0.6	1-2	15	Moderate *vs.* Deep NMB	Administered rocuronium (mg); Surgical conditions (SRS)
Madsen M. (2017) [130]	NCT02140593	128	0.6	N/A	0-1	3-5	Moderate *vs.* Deep NMB	Surgical conditions (SRS)
Kim M. (2016) [131]	NCT02266056	61	0.6	N/A	1-2	N/A	Moderate *vs.* Deep NMB	Administered rocuronium (mg); Surgical conditions (5-stage satisfaction scale)
Martini C. (2014) [93]	NCT01361149	24	1	0.6	1-2	15	Moderate *vs.* Deep NMB	Administered rocuronium (mg); Surgical conditions (SRS); Reversal time (min)
Staehr-Rye A. (2014) [132]	NCT01523886	48	0.3+0.7	3-4	0-1	3-4	Moderate *vs.* Deep NMB	Administered rocuronium (mg); Surgical conditions (4-point scale)
Kim H. (2019) [133]	NCT02762890	56	1	0.3	1-2	10	Moderate *vs.* Deep NMB	Administered rocuronium (mg);
Mekawy N. (2012) [134]	N/A	40	0.6	0.6-0.9	1-2	N/A	Recovery Neostigmine *vs.* Sugammadex	Administered rocuronium (mg); Reversal recovery time (min)

Abbreviations: N/A, not available or no answer; SRS, surgical rating scale (1–5).

Figure 2.16 presents the results of the risk of bias assessment (detailed in Appendix 8.1.5). All publications were randomized, 25 % allocation concealment was unclear, 63 % showed low bias in participants and personnel blinding, and 88 % of the studies blinded the outcome assessment. None reported an unclear or high risk of attrition or reporting bias. Because of the uncertainty in preserving the allocated NMB level, other unclear bias was identified in one study, attributed due to absent information on monitoring interval, and two other studies with a high risk of other bias as a result of lack mentioning calibration of the monitoring device and/or unreliable rocuronium infusion and adjustments methods. Because of the reduced number of studies included, the data was insufficient to conduct subgroup analysis or a reliable funnel plot asymmetry evaluation.

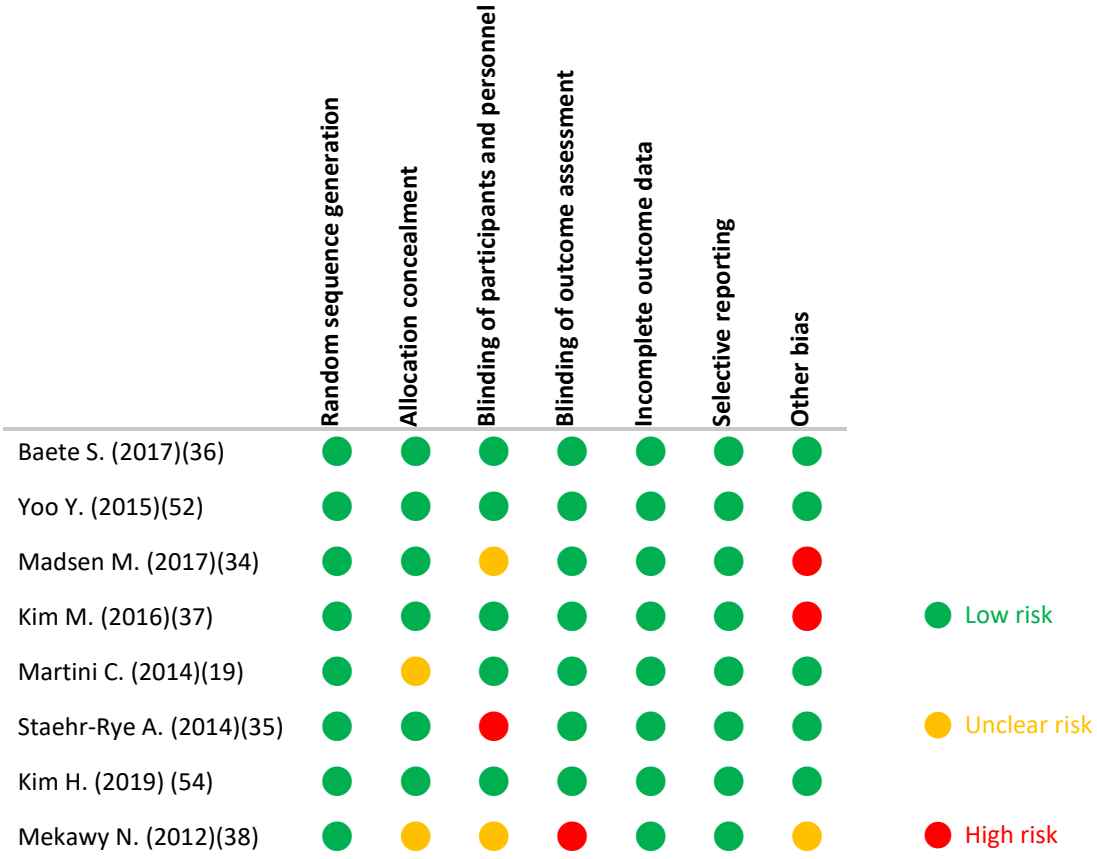


Figure 2.16 - Diagram for studies risk of bias per domain.

The two main features, with a direct impact in ensuring the accuracy of preserving the allocated NMB level, are rocuronium administration and monitoring parameters. These features were also important in the bias assessment, revealing “unclear” and “high” risk on the column of other bias. Although the impact of this source of bias remains uncertain, due to the complexity of defining and adopting an ideal methodological protocol for maintaining deep NMB, it can be admitted the quality of studies was high, and the risk of bias did not compromise the results.

Rocuronium administration

Only Baete S. [128], Kim M. [131], and Kim H. [133] quantified the amount of rocuronium used for each group, including a total of 177 participants. Data was standardized for analysis. A meta-analysis of the amount of rocuronium administered to maintain deep versus moderate NMB showed a mean difference of 0.251 mg/kg/h (0.169 to 0.334 for 95 % CI) (see Figure 2.17) with an I^2 of 54.81 %, proving a significant heterogeneity between studies. Specifically, the mean (SD) amount of rocuronium for deep NMB was 0.743 (0.167) mg/kg/h and 0.475 (0.088) mg/kg/h for moderate NMB.

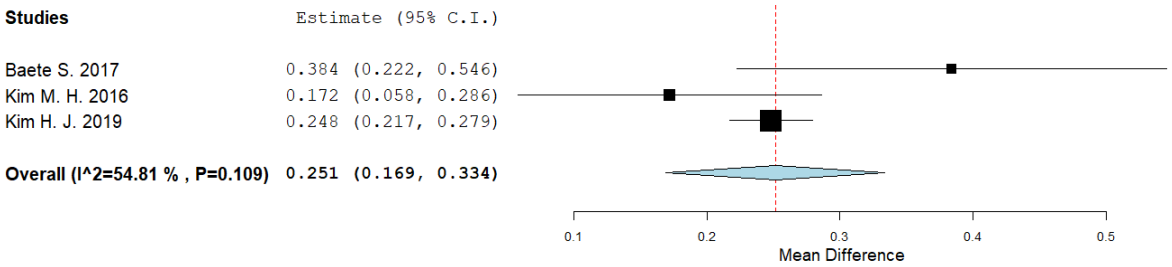


Figure 2.17 - Meta-analysis and forest plot of rocuronium administration of included studies (milligram per kilogram per hour), with a mean (SD) amount of rocuronium for deep NMB of 0.743 (0.167) mg/kg per hour and 0.475 (0.088) mg/kg per hour for moderate NMB.

Results show that the mean amount of rocuronium required to maintain deep NMB compared to moderate NMB is equivalent to 0.82xED_{95} of additional rocuronium per hour (95 % CI of 0.554-1.09xED_{95}). Nevertheless, these results cannot provide a decisive conclusion on the adequate amount of rocuronium to be used. The quantity of rocuronium required to maintain the NMB level can vary significantly for each patient, and the intended doses mentioned in the studies anesthetic procedures can be misleading. As such, the NMB maintenance must be individualized for each patient and guided by appropriate NMB monitoring. Other studies [128, 134], reported similar amounts of required rocuronium to maintain the 1-2 PTC relaxation level (0.689 (0.162) and 0.72 (0.39) mg/kg/h). Although these values are within the range of infusion requirements, it also showed a significant dosage increase over the recommendation of 0.6 mg/kg/h.

Surgical conditions

Surgical conditions assessment was performed in 6 studies (with 397 participants), recorded on a 5-point scale (83 %), or 4-point scale (17 %) and were included in the meta-analysis. Although there is no gold standard, 5-point Leiden surgical rating scale quantification has been well accepted and was considered for the analysis [93]. After normalization to a scale of 1 to 5, the surgical conditions in deep NMB improved by an estimated mean difference of 0.653 (0.451 to 0.856 for 95 % CI) (Figure 2.18). The outcome of calculation resulted in an I^2 of 48.4 %, showing a moderate level of heterogeneity between studies. Specifically, a mean (SD) score of 3.673 (0.261) for moderate and 4.239 (0.383) for deep NMB, improving surgical conditions from good to optimal.

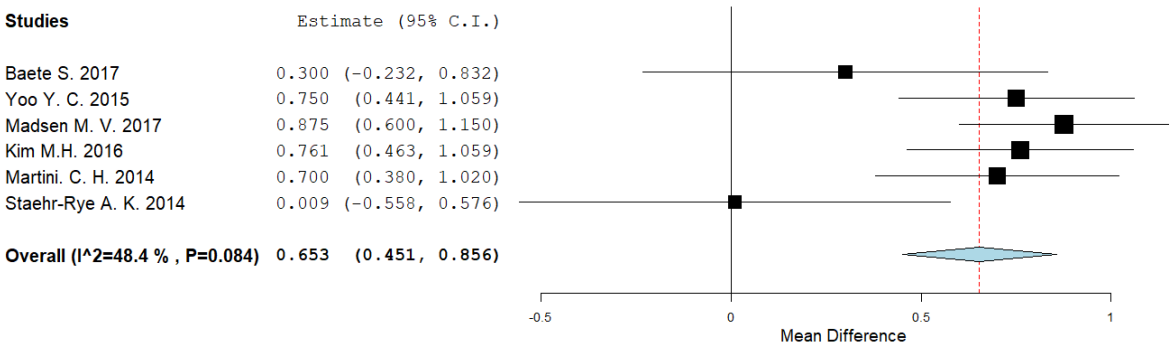


Figure 2.18 - Meta-analysis and forest plot of surgical conditions of included studies, with a mean (SD) of 4.239 (0.383) surgical conditions score for deep NMB and 3.673 (0.261) for moderate NMB.

Five of the studies included were conducted for laparoscopic surgeries and one for upper laparotomy. In both types of surgical procedures, the abdominal wall relaxation is fundamental to enhance surgical conditions. Other studies have compared deep to moderate NMB [6, 7], reporting 99 % of good or optimal conditions under deep NMB, explaining the interest in the use of this approach [136]. Meta-analysis results further proved that deep NMB improves surgical conditions over moderate NMB in 0.653 of a 5-point scale, which is considered substantial and proves the relevant applicability in improving surgical conditions. Despite that, results show significant heterogeneity.

Sensitivity analysis

In the evaluation of the meta-analysis, it was not possible to reliably perform sub-groups, funnel plots or meta-regression analysis due to the reduced number of suitable studies included. A sensitivity analysis was executed to examine the findings' strength.

The uncertainty in maintaining the allocated NMB level, generated by the non-robust monitoring and dose adjustment methods, was recognized as other bias. By removing these studies from the meta-analysis, results did not significantly alter the estimated mean difference and showed very low heterogeneity (6.7 %, Appendix 8.1.6.1). On the other hand, both Madsen M. [130] and Staehr-Rye A. [132] considered a lower-range target of PTC 0 to 1. Though not statistically significant, the removal of these studies from the meta-analysis resulted in a mean difference of 0.694 (0.525 to 0.863 for 95 % CI) with 0 % between-study heterogeneity (Appendix 8.1.6.2). Moreover, often in NMB studies, the blockade degree is measured very sporadically during surgeries, aiming to relate it with surgical conditions assessment in specific stages of the procedure. Studies with more frequent PTC measurements provide more information and have a direct impact on rocuronium adjustments. However, the sensitivity analysis, including the studies with PTC measurements done every 15 minutes or less, showed no significant difference (0.609 [0.352-0.866] mg/kg/h, I^2 = 57.8 %, Appendix 8.1.6.3).

Within the sensibility analysis context and limitations, it revealed a similar improvement (0.61-0.69) in surgical conditions, supporting the results obtained. From the overall analysis, it is possible to notice

that the heterogeneity is mostly driven by Baete S. [128] and Staehr-Rye A. [132] studies. Both show a smaller effect in the surgical conditions. A possible explanation may be the shorter surgery duration, which implies an inferior sample of the data acquisition instances. This observation is supported by Park S. [6] reports, that stated that an higher frequency of measurements and multiple assessments of surgical conditions during surgeries increases the sample and sensitivity to detect a difference between two levels of NMB.

Sugammadex reversal

Several studies have investigated the response instigated by different doses of sugammadex after applying deep NMB via rocuronium infusion [134, 136–140]. The expected time of reversal, after 4 mg/kg of sugammadex, is reported having a duration of 2-3 minutes [134, 137, 139, 140]. Only two of the studies included in this analysis have evaluated the reversal with standard dosing of sugammadex, reporting substantially different results. This can be explained by the fact that the reversal agent administration was performed at different phases of the NMB. While Martini C. [93] administers sugammadex at the end of the surgery (regardless of the NMB degree) resulting in a reversal time of 5.1 (2.4) min, Mekawy N. [134] waited until *T2* recovery to infuse the reversal agent taking 2.47 (0.51) min to recover. Meta-analysis was not possible to be conducted due to insufficient study reports.

2.2.2 STRATIFICATION OF THE DEEP NMB

Following a similar approach used in the study conducted in the previous section, the review was further extended aiming to perceive the approaches adopted for different ranges of the deep muscle relaxation (also associated with level 5 and 6 of the new depth of block classification for NMB monitoring, see Table 2.2). This study applied a one-arm approach.

2.2.2.1 Systematic search methodology

Based on PRISMA guidelines, this study addressed a systematic search following the same approach of the review study described in section 2.2.1 (search strategy is detailed in Appendix 8.1.1). Thus, it included all publications worldwide till February 28th, 2019, independently of language or publication status, from systematic database search (at PubMed, ISI Web of Science, Cochrane Library) and Google Scholar search engine. Likewise, study inclusion and exclusion criteria were the same (details in Appendix 8.1.2), except that studies should include surgical procedure with general anesthesia with rocuronium administration via continuous infusion for deep NMB considering a range of 0-10 PTC responses. Snowballing was performed for the included studies bibliographies. After examination of full texts, scanning for discrepancies and redundancies, studies were included if the criteria were applicable.

Data extraction from the publications included was independently conducted. The significant parameters collected from the studies were the following:

- Rocuronium administration: induction dosage, instant and rate of infusion start, rocuronium adjustment principles;
- Monitoring specifications: device and measurement site, PTC target and time interval between PTC evaluations;
- Duration of the procedure;
- Reversal information: amount and time point of sugammadex administration.

If not directly provided, the data was estimated and normalized following the instructions in the Cochrane handbook and reported as mean (SD) [126, 127].

2.2.2.2 Findings of the search

A total of sixteen studies fit the criteria and were collected and analyzed. There is wide variability in the methodologies of these studies in terms of monitoring and rocuronium administration parameters to maintain deep NMB using continuous infusion. Important features such as the nerve selection, stimulation patterns applied, the time interval between evaluations, as well as the induction dose, time point of starting the infusion, and adjustments may vary according to each study protocol, surgical procedure, anesthesiologist preferences or other clinical purposes/reasons. These approaches have a direct impact on the NMB degree assessment and, consequently, on the rocuronium and reversal drug amount required. Relevant data were extracted and listed in Table 2.4. Respective outcomes are detailed in Table 2.5, including the participants' characteristics (weight, BMI), rocuronium required (amount and duration of administration), PTC measurements (target and accomplished results), and time of reversal after 4 mg/kg of sugammadex.

Rocuronium administration

Regarding the rocuronium administration parameters, most studies (56 %) use 2xED_{95} as induction dose before starting continuous infusion (range of 0.6-1 mg/kg). All apply the induction dose in a single bolus, except Staehr-Rye A. [132] that divides into two phased-bolus intercalated by intubation. To avoid an overdose, the bolus that produces the desired peak effect and adequate intubation conditions should be selected.

Table 2.4 - Study design and methodological approaches included in the studies [Range Minimum – Range Maximum; Mean (SD)].

AUTHOR (year)	PARTICIPANTS		ROCURONIUM ADMINISTRATION				NMB MONITORING					SUGAMMADEX REVERSAL		AIM OF THE STUDY	PROCEDURE
	Sample size (N)	ASA	Induction dose (mg/kg)	Instant to start infusion	Initial infusion rate (mg/kg/h)	Adjustments	Device	Nerve	CAL	PTC target	Stimuli interval (min)	Time point	Amount (mg/kg)		
Baete S. (2017) [128]	60 (30)	I-III	0.6	After intubation	0.6	Target titrated	TOF-Watch® SX	Ulnar	yes	1-2	5	End of surgery	4	SC in Moderate vs. Deep NMB	Bariatric laparoscopic surgery
Georgiev S. (2011) [115]	80 (N/A)	I-II	0.6	After intubation	0.3-0.6	N/A	TOF-Watch	Ulnar	N/A	0-10	N/A	*T1* 3-10%	4	Bolus vs. Continuous infusion reversal with sugammadex	Gynecological surgery
Kim H. (2019) [133]	56 (28)	I-III	1	N/A	0.3	Adjusted rate	TOF-Watch® SX	Ulnar	yes	1-2	10	End of surgery	4	Quality of recovery after Moderate vs. Deep NMB	Robotic gastrectomy
Kim H. (2009) [117]	75 (48)	I-II	0.6	After the start of surgery	0.54	Adjusted rate	TOF-Watch	Ulnar	N/A	0-5	5	-	-	Recovery time of single bolus vs. continuous infusion	Laparoscopic or microscopic surgery
Kim M. (2016) [131]	72 (30)	I-III	0.6	After induction	N/A	Target titrated	TOF-Watch® SX	Ulnar	N/A	1-2	N/A	End of surgery	2-4	SC, IAP and pain in Moderate vs. Deep NMB	Laparoscopic colorectal surgery
Lee H. (2015) [141]	60 (30)	I-II	0.6	30 min after initial dose	0.42-0.6	Adjusted rate	TOF-Watch® SX	Ulnar	yes	1-2	6	End of surgery	4	Influence of mild hypothermia on sugammadex reversal	Abdominal surgery
Madsen M. (2017) [130]	128 (63)	I-III	0.6	After intubation	N/A	Add bolus	TOF-Watch® SX	Ulnar	yes	0-1	3-5	End of anesthesia	4-16	SC in Moderate (bolus) vs. Deep (infusion) NMB	Upper laparotomy
Martini C. (2014) [93]	24 (12)	I-III	1	0	0.6	Add bolus + adjust infusion rate	TOF-Watch® SX	Ulnar	yes	1-2	15	End of surgery	4	SC in Moderate vs. Deep NMB	Laparoscopic surgery
Mekawy N. (2012) [134]	40 (40)	I-II	0.6	N/A	0.6-0.9	Target titrated	TOF guard	Ulnar	yes	1-2	N/A	*T2* detection	4	Neostigmine vs. sugammadex reversal	Sinonasal surgery
Nonaka T. (2013) [135]	35 (N/A)	N/A	0.9	*T1* of 25% recovery	N/A	N/A	N/A	Ulnar	N/A	1-2	N/A	End of surgery	4	Effect of rocuronium and sugammadex	Hepatic and non-hepatic surgery
Rex C. (2009) [137]	52 (51)	I-III	0.6	0	0.42	Dose adjusted	TOF-Watch® SX	Ulnar	yes	0-10	N/A	*T1* 3-10%	4	Effect of sugammadex after sevoflurane vs. propofol anesthesia	General anesthesia procedure
Soto-Mesa D. (2015) [139]	32 (32)	I-II	0.6	0	0.3-0.6	Adjust rate	M-NMT (KMG)	Ulnar	yes	0-10	5-6	*T1* 3-10%	2-4	Effects of different doses of sugammadex	Gynecological laparoscopy
Staehr-Rye A. (2014) [132]	48 (25)	I-II	0.3 + [2min] + 0.7	PTC >0	0.3-0.4 [142]	Target titrated	TOF-Watch® SX	Ulnar	yes	0-1	3-4	End of surgery	2-8	SC in Moderate vs. Deep NMB	Laparoscopic cholecystectomy
Van Brangtegem E. (2014) [140]	39 (20[a])	N/A	1	N/A	N/A	Target titrated	N/A	N/A	N/A	1-2	N/A	End of surgery	2-4	Sugammadex based on LBW or TBW	Laparoscopic bariatric surgery
Yamamoto S. (2015) [138]	80 (40)	I-II	1	*T1* of 10% recovery (at fascial)	0.42	Target titrated	TOF-Watch® SX	Ulnar and facial	N/A	Facial *T1*=10% Ulnar PTC=[0-5]	N/A	Stop of rocuronium infusion	2-4	Corrugator supercilii vs. adductor pollicis reversal	Orthopedic, gynecological and urological surgery
Yoo Y. (2015) [129]	67 (34)	I-II	1	0	0.6	Target titrated	TOF-Watch® SX	Facial	yes	1-2	15	End of surgery	N/A	SC in Moderate vs. Deep NMB	Low-pressure robotic-assisted laparoscopic

[a] data provided by the author. Abbreviations: N/A – Not available or no answer; NMB – Neuromuscular Blockade; N – number of participants enrolled in the deep NMB via infusion of rocuronium with applicable inclusion criteria; ASA – American Society of Anesthesiologists classification; CAL – calibration; PTC – post-tetanic count; SC – Surgical conditions; IAP – Intra-abdominal pressure; LBW – Lean Body Weight; TBW – True Body Weight; M-NMT (KMG) - kinemyography (KMG) using the Mechanosensor Neuromuscular Module Transmission (GE Healthcare, Helsinki, Finland).

Table 2.5 – Outcome data of the studies after deep NMB. Reported as [Range Minimum – Range Maximum] or Mean (SD).

Authors (year)	Participants		Rocuronium administration		Monitoring		Reversal time after 4 mg/kg of sugammadex (min)
	Weight (kg)	BMI (kg/m²)	Amount (mg/kg/h)	Duration (min)	PTC target	PTC target measured	
Baete S. (2017)	N/A	40 (3)	0.98 (0.38)	61.3 (15.1)	1-2	N/A	N/A
Georgiev S. (2011)	N/A	N/A	N/A	120-300	0-10	N/A	1.31 (-)
Kim H. (2019)	67 (3) [a]	24 (0.5) [a]	0.63 (0.7) [a]	121 (6.5) [a]	1-2	N/A	N/A
Kim H. (2009)	60.5 (14.4) [a]	22.9 (5.7) [a]	0.94 (0.38) [a]	60-120	0-5	N/A	-
Kim M. (2016)	60.4 (9.7)	23 (1.2)	0.62 (0.24) [a]	249.2 (62.3)	1-2	N/A	N/A
Lee H. (2015)	59.9 (7)	22.5 (2.8) [a]	0.72 (0.39)	162 (66)	1-2	N/A	2.08 (0.99)
Madsen M. (2017)	N/A	26 (4.7)	N/A	276 (116)	0-1	N/A	N/A
Martini C. (2014)	83 (10)	25.9 (3.9)	1.12 (0.51) [a]	144 (35)	1-2	1.6 (1.5)	5.1 (2.4)
Mekawy N. (2012)	75.9 (14.9) [a]	N/A	0.52 (0.17) [a]	104.5 (19.5) [a]	1-2	N/A	2.47 (0.51)
Nonaka T. (2013)	N/A	N/A	0.68 (0.16)	N/A	1-2	N/A	2.73 (1.32)
Rex C. (2009)	72 (13)	25.2 (4.75) [a]	0.445 (-)[a]	141 (-)[a]	0-10	92 % [c]	1.34 (0.69) [a]
Soto-Mesa D. (2015)	63.2 (15.45) [a]	23.65 (5.1) [a]	N/A	94.95 (40.33) [a]	0-10	N/A	1.61 (0.65) [a]
Staehr-Rye A. (2014)	N/A	26.75 (1.25) [a]	N/A [b]	39 (4.5) [a]	0-1	91 % [c]	N/A
Van Brangtegem E. (2014)	N/A	N/A	N/A	N/A	1-2	N/A	1.85 (0.83)
Yamamoto S. (2015)	57.3 (15.5) [a]	22.85 (4.3) [a]	0.36 (0.12) [a]	N/A	0-5	2.6 (2.27)	2.48 (0.63)
Yoo Y. (2015)	67.3 (N/A)	23.6 (2)	1.19 (0.33)	111 (21)	1-2	1.6 (0.6)	N/A

[a] Approximated value calculated based on formulas from [126, 127]; [b] Reported total amount: median (range) = 80 (71–91) mg; [c] Reported the overall percentage of the monitoring accuracy. Abbreviations: N/A – Not available or no answer; PTC – post-tetanic count; BMI – Body-mass index;

Saldien V. [143] indicated that the injection of a bolus followed by continuous infusion has the advantage of achieving a relatively rapid and stable level of NMB. The time interval between the induction bolus and the start of the infusion has a direct impact on the maintenance of the desired degree of muscle relaxation. Studies considered different approaches for time point to start infusion following the initial bolus: 1) after a specific period; 2) when a predefined NMB monitoring result is achieved, or 3) at a determined anesthetic/surgical event (*e.g.*, intubation/incision). It should be taken into account that individual variability is significant; thus, the instant when the infusion should be initiated can vary from patient to patient. Taking this into account, in order to preserve a certain NMB degree through a balanced drug input, the instant to start infusion should be based on patient-specific monitoring assessment instead of indirect parameters such as time interval or stage of the procedure.

From the studies reporting initial infusion rate, 92 % considered 0.3-0.6 mg/kg/h of rocuronium, except Mekawy N. [134], which adopted a 0.6-0.9 mg/kg/h rate for the maintenance of the PTC target. None of the included studies reported relevant information regarding the techniques or infusion systems/tools used, and little data is provided regarding the protocol for dose adjustments. These dose adjustment practices are crucial to restore the desired NMB level and should be carefully

managed. Infusion rate changes can take some time to alter and reset the desired NMB degree. In contrast, some studies use an additional bolus as the NMB adjustment method, administering doses as high as 0.6 mg/kg [132]. Such amount can lead to excessive depression of the neuromuscular function, which often completely nullifies the NMB response (PTC = 0); therefore, delaying the restoring of positive measurements, which may compromise the maintenance and accuracy in ensuring the desired NMB level along the procedure.

Some studies report the overall amount of rocuronium administered to maintain the NMB level during the procedure (69 %). Unadjusted values were calculated and normalized (mg/kg/h) to perform a homogenous data analysis of the results. Since estimated measurements were used, the results cannot provide a robust conclusion, yet it can give some insight on approximated values of rocuronium required to maintain deep NMB. From the analysis, the maintenance of deep NMB level requires approximately 0.746 (0.36-1.19) mg/kg/h of rocuronium. Differentiating the reported results according to the adopted PTC targets in 0-10, 0-5, and 1-2 responses, mean calculations estimate 0.445, 0.650, and 0.808 mg/kg/h of rocuronium, respectively. This suggests that a wider range and higher maximum of PTC requires less amount of rocuronium. These results are within the range of infusion recommendations, yet 1-2 PTC target studies required a significant increase over the recommended dose [113, 119–121].

Monitoring of deep NMB

Regarding the NMB assessment performed in the studies included in this review, acceleromyography using the TOF-Watch® SX device is the most used system, usually monitoring at the adductor pollicis after ulnar nerve stimulation (88 %). Device calibration is a crucial step to assess the extent of NMB; however, several studies lack information regarding this task (38 %).

As mentioned, PTC stimulation is essential to assess and characterize deep NMB, delivering decisive information on the relaxation status that can be beneficial to adjust the NMB accurately [77, 143]. As verified in the previous analysis, one important feature is the pre-selected PTC target. The different ranges of PTC target adopted in the studies analyzed were: 0-1 PTC in 12.5 % of the studies; 1-2 PTC in 56.3 %; 0-5 PTC in 12.5 %; and 0-10 PTC in 18.8 %. Wider PTC range (*e.g.*, 0-10 or 0-5 PTC) allows some leeway in rocuronium adjustments to maintain the NMB level. Although these targets provide enough muscle relaxation, while guaranteeing adequate immobility and good surgical conditions, are out of the range that assures a complete abdominal wall/diaphragm relaxation. Moreover, measurements of 0 responses, which can be caused by overdosing, are inadvisable due to the limitation of the NMB monitoring below it.

Another important parameter to consider, to ensure the maintenance of the NMB degree, is the time interval between PTC measurements during the surgical procedure. Approximately 44 % of the studies did not refer to any information regarding the frequency of PTC monitoring. From the remaining publications, 66 % considered evaluations between 3-6 minutes, and 33 % adopted a time interval between stimuli of 10 to 15 minutes. Knowing that there is a need to wait for the motor end-plate to recover before a subsequent PTC evaluation and that higher frequency of measurements increases sensitivity to detect a difference between two levels of NMB, 3-6 minutes is the ideal time interval [6, 10, 145]. In contrast, monitoring done too rarely or inconsistently promotes not only subsequent disturbances and inaccurate measurements but also a more extended period in which the clinician is blind to changes of the NMB level that may occur. This can be aggravated when the desired NMB aims for a narrow PTC range (*e.g.*, PTC 1-2), further complicating the dose adjustments to restore and ensure the target maintenance.

Although one of the main focus of the study's methodology was to secure a certain NMB level, several studies (69 %) do not mention the monitoring actually achieved during the procedures, namely regarding PTC results. This limits the understanding of accuracy in preserving the proposed deep NMB level continuously.

Martini C. [93], Yoo Y. [129] and Yamamoto S. [138] reported the mean (SD) of the PTC measurements. While Yamamoto S. aimed for a PTC of 0-5, achieving a mean of 2.6 (2.27) PTC, a smaller amount of rocuronium was administered (0.36 (0.12) mg/kg/h). In turn, Martini C. and Yoo Y., which targeted 1-2 PTC, reported a mean (SD) of 1.6 (1.5) and 1.6 (0.6) PTC, requiring 1.12 (0.51) and 1.19 (0.33) mg/kg/h of rocuronium, respectively. Alternatively, Rex C. [137] and Staehr-Rye A. [132], which pursued PTC targets of 0-10 and 0-1, reported 92 % and 91 % of PTC measurements within range, during the procedure. Rex C. required approximately 0.445 mg/kg/h of rocuronium and Staehr-Rye A. lack to report rocuronium consumption, limiting the comparison and significant deduction of this outcome.

Sugammadex reversal

Several studies investigate the response generated by different doses of sugammadex after deep NMB with rocuronium infusion [134, 136–140]. As before, two methodologies of reversal with 4 mg/kg of sugammadex can be distinguished: 1) administration at the end of the surgery or after stopping rocuronium infusion (73 %); or 2) after NMB recovery detection to a moderate level (27 %).

From reported results on these two groups, a mean (SD) of 2.85 (1.17) min and 1.68 (0.47) min was required to recover to TOF-ratio > 90 %, respectively. As expected, after waiting for spontaneous recovery, patients require less time to reverse the NMB fully.

The time of reversal after sugammadex is dependent on the administered dose and the NMB degree when the reversal agent is given. Although it enables a rapid and effective reversal [146], the introduction and appropriate use of this drug is expensive and not always available.

2.3 CHAPTER OVERVIEW

Deep neuromuscular blockade is an essential element of general anesthesia and presents important benefits for safe intubation and optimal surgical conditions. After a background description, a review was conducted over the studies using continuous infusion of rocuronium when aiming to maintain a safe and stable deep level of NMB. This two-part revision describes the evidence on specific parameters and outcomes compared to conventional approaches and, also, it explores the same approach for different degrees of deeper NMB. To date, the studies conducted may show conditioned evidence strength, yet have proven the importance of the methodology to ensure good dose-effect relationship.

From this research, it can be verified that the rocuronium administration methods used may vary substantially, suggesting a slight increase in the NMBA demand over the indicated standards doses. Regarding the monitoring, it can be concluded that the use of PTC in the ulnar nerve using AMG devices is an adequate form of NMB evaluation. This is a crucial component for the efficient regulation of the rocuronium administration to guarantee the desired level of deep NMB and, ultimately, to facilitate the reversal process. It has been suggested that the coupling of appropriate NMB monitoring with individualized rocuronium drug delivery can provide an advanced means for the maintenance of the deep NMB, which, further on, can potentially be optimized by the application of PK-PD models.

3 STUDY DESIGN AND METHODS

The relationship between NMB monitoring and rocuronium infusion for the maintenance of the aimed deep NMB is the central issue for the conception and development of the closed-loop control system. Thus, besides understanding the background and assessing the current literature, additional complementary proceedings were carried out to further support this study.

First, the experimental intervention admitted in a previous clinical trial conducted at CHUP was studied to gain a better grasp of the methodological concepts applicable in the operating room setup. From the data acquired in this same trial, it was possible to conduct a study to assess the monitoring limitations in terms of the data transmitted in the TOF-Watch® SX monitor display. The defective and unreliable NMB monitoring is one of the main concerns in the development of this research. To tackle this, a tool to individualize the stimulations during surgical procedures was conducted to ensure a more accurate assessment of the NMB transmission. Ultimately, a comprehensive interpretation of a group questionnaire was conducted to perceive the main users' experience and contributions towards the proposed system.

After perceiving the limitations of the monitoring and the technical requirements necessary to support the development of a system that ensures the reliable maintenance of the deep NMB, a methodology for a clinical investigation study was established. The study protocol and data acquisition methods are included and described next.

3.1 PRELIMINARY STUDIES

Four complementary studies were conducted to support the fundamental concepts and methods to be considered in the clinical study, and, further on, contributing for the design of the control system for the maintenance of deep NMB.

3.1.1 CLINICAL TRIAL

A randomized controlled trial conducted from September 2016 to March 2017 in CHUP, proposed the use of deep neuromuscular blockade and the consequent suppression of the EMG activity to improve the overall stability of an anesthetic procedure. The goal was to assess the effect of deep NMB on the Bispectral Index (BIS, measures the depth of anesthesia) variability and the required effect-site concentrations of propofol (hypnotic) and remifentanil (analgesic). This work's main intervention was to evaluate and compare the anesthetic protocol maintaining deep NMB (intubation bolus of 0.6 mg/kg followed by continuous infusion) and sugammadex reversal versus the standard NMB procedure (intubation bolus of 0.6 mg/kg). This clinical trial was funded by a grant from Merck, Sharp & Dohme (MISP 51415), performed according to Good Clinical Practice (GCP) guidelines and pharmacovigilance directives. Approval of the protocol was obtained Merck Sharp & Dohme (MSD Portugal) and Portuguese National Ethics Committee for Clinical Research and was registered in both, clinicaltrials.gov (NCT02484651) and EudraCT (2014-005238-76), before patient enrolment.

From the primary objectives of this study, it was possible to assess the effect of the NMB level in the NMBA demand, the subsequent monitoring outcome during the procedure, as well as the main features of the reversal at the end of surgery. A secondary objective was to study the quality of the recovery using the Postoperative Quality of Recovery Scale to see if maintaining a deep NMB level during surgery has an impact on the patients' quality of recovery [146, 147].

The findings of the study suggested that deep NMB and sugammadex reversal may account for reduced propofol requirements during maintenance (20 %), reduced EMG activity, and faster recovery times (50 %). However, it does not seem to impact the analgesic requirements nor BIS variability, and the possible beneficial impact on hemodynamic stability needs to be better explored. In turn, the results regarding rocuronium administration and NMB monitoring for each group are summarized in Table 3.1.

The fundamental advantages of deep NMB have been advocated only to provide better or safer immobility conditions for the patient. The results of this study suggest that deep neuromuscular blockade followed by sugammadex reversal may challenge the way NMB drugs are currently employed and how it can impact the management of the hypnotic component of anesthesia. Therefore, it proves the clinical interest for an optimized solution that can promote stable and safe maintenance of the deep NMB degree. The experimental intervention and results obtained from this clinical trial allowed to ascertain some grounding methods for the current research on the maintenance of deep NMB to be included in the concepts of the clinical study design.

Table 3.1 - Overall NMB results of the clinical trial. Results as mean (SD).

		Standard NMB (n = 32)	Deep NMB (n = 31)
Demographics			
Age		52.5 (10.3)	53.4 (7.9)
Weight (kg)		75.2 (14.5)	70.8 (13.8)
Height (cm)		163.9 (7.7)	165.2 (9.2)
BMI (kg/m^2)		27.8 (4.1)	26.0 (4.7)
Rocuronium administration			
Induction (mg)		44.4 (10.9)	42.7 (8.3)
Infusion (mg/kg/h)		-	0.82 (0.51)
Total (mg)		51.1 (12.3)	161 (76.4)
Duration of the infusion (min)		-	107.4 (34.8)
NMB monitoring			
Time to TOF=0 (s)		100 (50)	126 (71)
Time to TOF recovery (min)		34.8 (17.4)	-
Time to PTC recovery(min)		-	12.5 (5.2)
PTC monitoring every 5 minutes			
Amount of PTC stimuli (50 Hz)	Total	5.4 (3.3)	22.2 (6.8)
	1-2 PTC	2.9 (2.3)	15.7 (6.5)
Amount of PTC stimuli (100 Hz)	Total	17.1 (7.3)	0.5 (0.8)

3.1.2 TOF ERRORS DURING MODERATE NMB

As been mentioned in the previous sections, despite the many guidelines and recommendations over the years strongly suggesting the use of NMB monitoring every time muscle relaxants are administered, there is still a lack of objective evaluation of the blockade in routine anesthesia. Some experts claim that it might not be even necessary [65, 148].

Among the many reasons for rejecting the use of NMB monitoring, stands out the lack of accuracy and reliability concerning the blockade assessment. Thus, taking into account these reports, a retrospective study was conducted to evaluate the occurrence of errors when using the TOF-Watch® SX® monitor, specifically regarding the defective displaying of data after TOF stimuli.

Fifty years have passed since the introduction of TOF monitoring, and there are still substantial accounts on complications resulting from the inappropriate assessment and reversal of the NMB [106]. In summary, for the TOF monitoring, a baseline reference response is obtained before NMB drug administration (the responses are individually detected with the same intensity, TOF-ratio = 100 %). After the NMBA dose for tracheal intubation, it quickly reduces and abolishes all four responses.

During this phase, the responses to TOF stimuli present fade, which is characterized by the progressive magnitude weakening of the subsequent twitches (*T1* > *T2* > *T3* > *T4*), so that each response is smaller than the preceding [77]. When the induction dose effect is overcome, the TOF response recovers one by one until all four responses are reestablished (see Figure 2.6). The values of TOF-count or TOF-ratio are the variables that these NMB monitors typically display, and the information that anesthesiologists take into account to manage the NMB administration and reversal (TOF-ratio > 90 % is required for safe extubation) [25, 61].

In the past, TOF-Watch® SX has been known as the gold standard for NMB monitoring and remains the only device approved for clinical research. Despite that, observations when using this monitor suggested that measurement errors could be present, an hypothesis that has been addressed in some studies [105, 149]. Also, it has been reported that an error in the TOF interpretation has led to inappropriate conduct that resulted in prolonged ventilation/sedation and delay of curarization (FDA Report Number 3002807818-2012-00001). These findings supported the execution of a study to evaluate the occurrence of errors when using the TOF-Watch® SX monitor in a well-controlled clinical scenario, maintaining a moderate NMB. In this study, two types of errors were defined, and their incidence was assessed.

3.1.2.1 Materials and methods

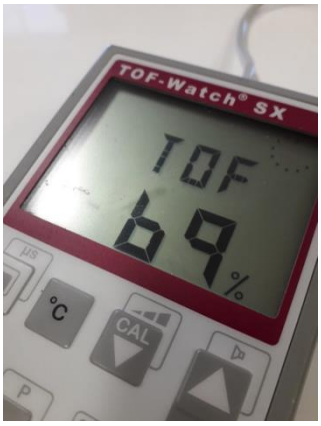
Data from 31 adult patients with ASA score of I-III, undergoing general anesthesia with propofol and remifentanil via TCI, were retrospectively analyzed. These were patients included in the standard group of the clinical trial conducted at CHUP (NCT02484651) (section 3.1.1). Institutional review board approval and written consent were obtained from the patients enrolled in the study.

Before induction, the skin was degreased, and the NMB monitoring setup was standardly performed at the adductor pollicis using TOF-Watch® SX. Calibration was carried out according to manufacture specifications [106]. The TOF response assessment was performed every 15 seconds throughout the surgery and acquired through TOF-Watch® SX Monitor software (Organon, Dublin, Ireland).

After the loss of consciousness, all patients received an induction dose of rocuronium (0.6 mg/kg), followed by the tracheal intubation. During maintenance of anesthesia, additional bolus would only be administered if required by the surgeon to improve surgical conditions. At the end of the surgery, if TOF-ratio was below 90 %, NMB was reversed with neostigmine (0.04 mg/kg) plus atropine (0.02 mg/kg).

From the data acquired, it was intended to characterize and evaluate the incidence of two types of monitoring display errors. Error type 1 was defined by a TOF response in which the fade effect on the

four twitches is absent, meaning that *T1* > *T2* > *T3* > *T4* was not present (see Figure 3.1), this was named “invalid” response.



Mode	Tw1	Tw2	Tw3	Tw4	TOF
	%	%	%	%	%
TOF	46	39	25	32	69

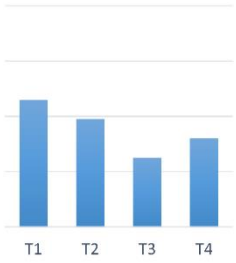
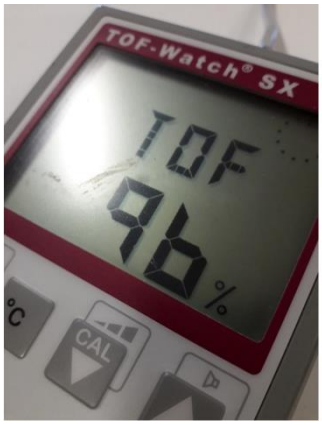


Figure 3.1 - Illustration of error type 1 example. TOF-Watch® SX® displays TOF-ratio of 69 % while values of *T1* to *T4*, recorded via TOF-Link, show that fade was not present since *T4* was higher than *T3*.

Error type 2 was analyzed only for “valid” TOF responses during the last 30 minutes before extubation for each case. Type 2 error was defined as the occurrence of a TOF-ratio > 90 % with a low amplitude of *T1* (see Figure 3.2). In other words, it consists of a valid TOF, in which the TOF-ratio result displayed in the device is over 90 %; however, its *T1* value is inferior to 70 %. This value was established arbitrarily by the authors as a suitable threshold to assume the recovery of NMB is high enough to ensure a superior recovery of the NMB and ensure increased safety to perform the tracheal extubation.



Mode	Tw1	Tw2	Tw3	Tw4	TOF
	%	%	%	%	%
TOF	54	53	52	51	96

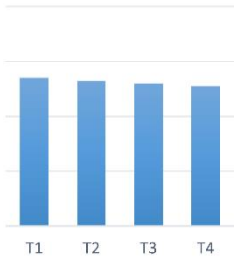
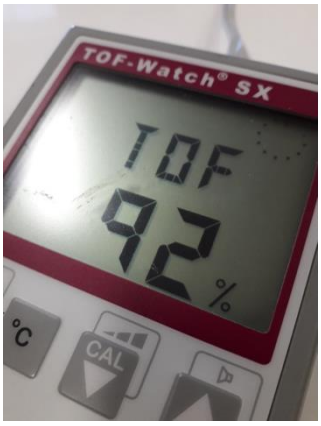


Figure 3.2 - Illustration of error type 2 example. TOF-Watch® SX® display TOF-ratio of 96 % while the real value of *T1*, recorded by the TOF-Link, was below 70 % despite the presence of a valid TOF response with fade effect.

Thus, it was hypothesized that adequate reversal would require a TOF measurement that fulfills three criteria: faded responses between *T1* and *T4*; TOF-ratio above 90 %; and a *T1* above 70 % of the initial reference (see Figure 3.3).

After the analysis of the error, the number of patients that met the criteria mentioned above was evaluated to assess the incidence of patients that achieved improved extubation conditions. Thus, it

evaluated the percentage of patients in which a valid TOF was measured in the 30 minutes before tracheal extubation, with a TOF-ratio over 90 % and *T1* > 70 %.



Mode	Tw1	Tw2	Tw3	Tw4	TOF
	%	%	%	%	%
TOF	80	79	76	73	92

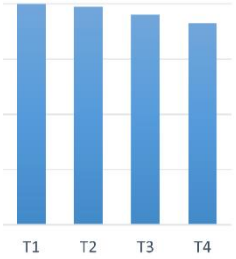


Figure 3.3 - Illustration of TOF-Watch® SX® displaying 92 % TOF-ratio in which raw values, recorded by the TOF-Link, prove the presence of fade effect and *T1* over 70 %.

3.1.2.2 Results

Results were reported as mean (SD). Data analysis showed a duration of the procedures of 129.3 (43.8) min, allowing to perform 361.2 (182.7) TOF stimulations, in which 276.2 (173.9) were positive TOF responses (TOF > 0), that were valid for error analysis. Error analysis showed that 42.0 (17.5) % of the TOF measurements show type 1 errors, and 63 (45) % showed type 2 errors. In the last 30 min, it was possible to detect TOF-ratio > 90 % in all cases, and every patient was extubated according to GCP guidelines with no reported complications. Nevertheless, the raw data of these measurements of TOF-ratio > 90 % were analyzed, in which 39 % of the patients showed a persistent type 1 error, 32 % a type 2 error, and only nine patients presented no errors and verified the achievement of all response criteria defined for adequate extubation.

3.1.2.3 Discussion and final remarks

Often clinicians rely on the monitors' measurements outcome without ensuring its validity. The information displayed on the screen of the monitoring device, which is limited to the TOF-count or TOF-ratio outputs, can often be inaccurate or incomplete and, thereby, misguide the anesthesiologist during the maintenance and recovery of the NMB. Professionals can assume TOF measurements present fade and that a TOF-ratio > 90 % is enough to rule out residual paralysis. However, this is not always the case. First, non-faded TOF responses are displayed as valid monitoring result without specifying the lack of fade. Secondly, the fourth (*T4*) and first (*T1*) responses can have similar, however low amplitudes, indicating TOF-ratio > 90 %. Thus, the clinician can assume that there are adequate recovery and enough conditions to extubate the patient, despite not achieving higher magnitudes (closer to baseline), which may lead to inappropriate curarization and residual paralysis complications.

Frequently studies are conducted to investigate sources of errors, either from humans or machines. Using TOF-Watch® SX Monitor software, it is possible to obtain the raw data and contrast it to the data being provided to the monitor display. The aim was to see if the display can instigate clinicians to draw inaccurate conclusions. Error analysis showed a type 1 error in 42.0 (17.5) % of TOF measurements, indicating that the monitor display's output can frequently misguide the clinician during the procedure and lead to unsuitable approaches in NMBA dosing. One of the main reasons many anesthesiologists reject the routine use of an objective method to monitor NMB is the absence of an adaptive and reliable monitor. This error analysis results provide some support for those claims.

From the TOF stimuli performed in the last 30 min before extubation, that did not measured error type 1, it was possible to assess error type 2. This error was detected in 63 (45) % of the valid TOF measurements, thus displaying a TOF-ratio over 90 % in the device, but with a T1 inferior to 70 %.

The number of patients that detected at least one TOF measurement with TOF-ratio over 90 % and T1 above 70 % in the 30 minutes before performing extubation was evaluated. From this analysis, it was possible to detect that only nine patients (29 %) had a valid TOF measurement with no errors before being extubated.

The usage of NMB agents during surgeries occurs every day worldwide, and the incidence of incomplete recovery of neuromuscular function remains significant, which may contribute to adverse respiratory events and an increase in morbidity and mortality [59], [151]. This study aimed to evaluate the accuracy of TOF measurements, establishing and investigating a fair approach to define recovery criteria to ensure improved extubation conditions. Although, these error analyses show significant drawbacks in terms of the outcome generated, which may increase the untrusting feeling by the professionals, the use of NMB monitoring during the procedures should not be rejected. However, careful assessment of the NMB function must be done during the procedures, being essential to evaluate the neuromuscular relaxation after the administration of NMB agents.

This study addresses the inaccuracy or defective displaying of data in the TOF-Watch® SX monitor device acquired after TOF stimulations. However, it should be emphasized that the error analysis is not regarding the monitor itself or the stimuli response values, but only regarding the data transmitted via the screen display. The monitor should provide additional information regarding the fade effect and amplitude of the twitch responses to support the clinicians' decision making regarding dosing or residual NMB. Although this study only proved TOF-Watch® SX errors, other monitors have shown similar approaches with non-robust outcomes. Further studies should be conducted to assess the incidence of faulty decisions generated due to the inaccurate/partial data displayed. Also, additional

efforts should be made to improve the data transmission by the monitoring devices to avoid errors that may misguide professionals' conduct.

In the context of this project, this study allowed to acknowledge some of the limitations of the TOF-Watch® SX device and that there is an urgent need for an advanced monitoring device to ensure an accurate assessment adapted to daily practice and individual patients' needs.

3.1.3 INDIVIDUALIZED MONITORING

Ideally, when NMBAs are administered, precise monitoring should be undertaken to guarantee a correct assessment of neuromuscular blockade extent. Among different types of monitoring, the most accurate relies on a quantitative and objective evaluation of the mechanically evoked responses triggered by an electrical stimulation delivered from a peripheral nerve stimulator. To do so, a set of stimulation patterns are available to evaluate the neuromuscular transmission in the different stages of the surgery and the patients' NMB degree. Often, these are inadequately applied and/or require a manual action (as detailed in sections 2.1.2.1 and 2.1.3.1).

Recently, Carla Mota conducted a study (as a Master thesis of Mestrado Integrado em Bioengenharia at FEUP), on the development of an innovative approach of a stimulator that performs a customized and reliable evaluation of the neuromuscular blockade during surgical procedures. The goal was to define the stimulation patterns according to the individuals' responses, allowing for a personalized and more adequate NMB assessment. For this purpose, it was created an electronic circuit and an interface developed in LabVIEW (National Instruments, 2016, USA). This system allows the user to set the system to apply the stimulus according to the intended attributes (Figure 3.4).

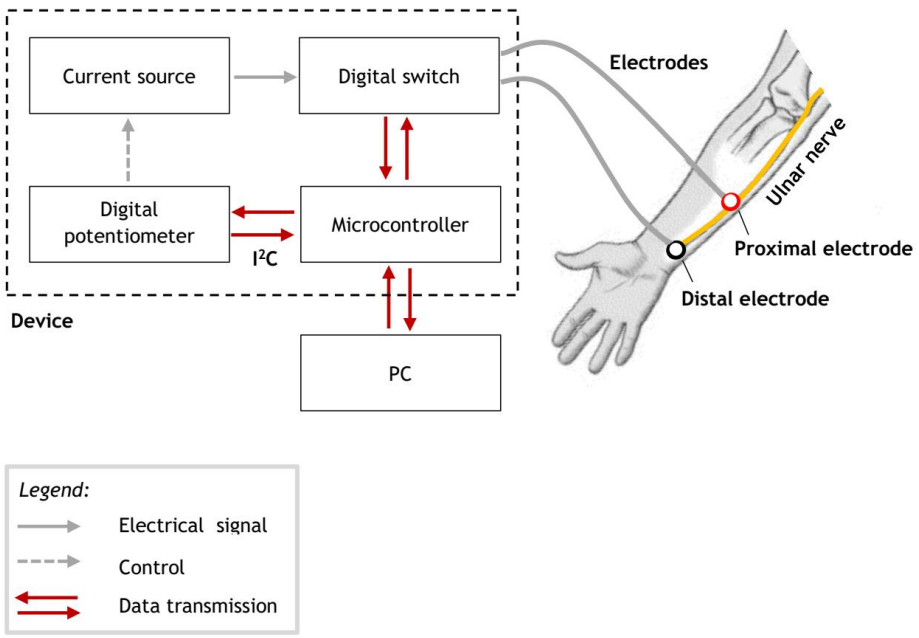


Figure 3.4 - Diagram of the individual NMB stimulator system [152].

The resulting device did not accomplish all the requirements of the ideal system, yet, it can overcome some drawbacks of existent stimulators, by providing a personalized stimulation to the patient. Current and voltage are correctly controlled, and stimulus characteristics are according to the conceptual principles of each pattern. From this work, an intuitive and easy-to-use system was developed. It proposed an improved neuromuscular stimulator that provides a personalized stimulation attending to the ongoing responses of each patient.

Joining individualized NMB monitoring and adequate rocuronium administration according to the stage of the procedure, without the necessity of any manual action can be a valuable addition to the final control system. Despite the potential of this merged solution, the personalized stimulation tool was not tested and validated for NMB monitoring in humans. Thus, for the AMG-based monitors available to be used in this project, the performance restrictions regarding stimulation response must be considered to provide appropriate feedback for the administration of rocuronium and to ensure the maintenance of the degree of NMB throughout a surgical procedure.

3.1.4 QUESTIONNAIRE TO USERS

Many surveys have been previously conducted regarding the management of neuromuscular blockade in terms of monitoring and clinical practice around the world. Most of them are related to the incidence of PORC and the development of appropriate guidelines for improved patient care. Overall, the main concerns are the dismissal of NMB monitoring and the lack of agreement regarding the best way to perform the appropriate assessment of the NMB function. Thus, there is still a high variability regarding the use of NMB monitoring, which is reflected in the substantial incidence of residual paralysis [3, 148]. Based on the unclear clinical practice regarding the neuromuscular blockade management and taking into account the primary goal of this project in developing a control system for the maintenance of deep NMB, a focus-group questionnaire was conducted with anesthesiologists, as the main users of such a product.

The purpose of these focus-group questionnaire was to better understand their view regarding a closed-loop approach to maintain deep NMB, and the requirements and specifications that many users consider essential to include in such a system. Two main components of the work were taken into account: the NMB monitoring and the rocuronium administration.

The group included a convenient sample of participants from the anesthesiology department of CHUP, who were arbitrarily chosen to answer as users and experts on the field. The scope of the questionnaire comprised the information about their usual practice on deep NMB, what are their

knowledge on the current market, and assess the receptivity to a feedback control system for the maintenance of deep NMB during surgeries.

3.1.4.1 Methodology and results

The questionnaire was specifically designed to gather data on how anesthesiologists use monitor devices and how they enroll in the dosing of NMBA, namely rocuronium. They were conducted between September 2018 and March 2019, gathering input from interns and specialists in the anesthesia field.

The questionnaire was divided into three parts. First, the benefits and limitations encountered in the habitual clinical practice for the use of deep NMB were considered. Secondly, the aim was to perform an overview analysis to understand the user's knowledge of the current market as well as their interest and receptivity on a controlled system to improve deep NMB. Lastly, to grasp their opinion on how such a solution would impact the everyday practice (detailed in Appendix 8.2.1). The questionnaire was conducted to 11 interns and 9 specialists in anesthesia (N = 20). The mean experience in the anesthesiology field of this sample was of 3.8 (2.7) years (mean (SD)). The report of the results is described next, and more detailed information can be consulted in Appendix 8.2.2.

Current practice

Results showed that the most used monitoring device is TOFscan® (50 %), followed by TOF-Watch (32 %) and last the GE Datex NMT (18 %). While TOFscan® is a new device with rising potential and broad distribution on many hospitals, TOF-Watch® manufacturing and sale has stopped for several years now.

The main reasons to use NMB monitoring during surgical procedures is to avoid residual paralysis and perform appropriate reversal (44 %), to set and personalize the NMB level to each patient (22 %), to improve surgical conditions (14 %), intubation (11 %), NMBA dosage (6 %) and reduce other drug consumption (3 %). On the other hand, the main limitations detected by users when using NMB monitoring are: calibration/measurement errors (47 %), monitoring distrust (13 %), difficult applicability (13 %), and unavailability (13 %).

Regarding the monitoring stimulation used to assess the NMB level, all users apply the TOF pattern; 55 % also apply the PTC stimulation, and only 15 % use TET or DBS stimuli. Moreover, as standard practice suggests, all users consider the adductor pollicis as the NMB monitoring site, yet, 15 % of the population measured the relaxation at orbicularis oculi and 15 % at the great toe.

Concerning the induction of deep NMB, several users do not apply this degree of muscle relaxation in every anesthesia (95 %), which can be explained by the different procedures that may not require the use of NMBA or the short duration of the surgeries.

Regarding the drug to generate the NMB, rocuronium is always used by 65 % of the users, 30 % use it in over half of anesthetic procedures, and only 5 % use it sometimes. However, when questioning about using rocuronium as a muscle relaxant via infusion, users rarely (69 %) or never (31 %) use it.

The primary reference for selecting the rocuronium dose is the ED_{95} (90 %), just a small number of users consider personal experience (5 %) or surgical conditions (5 %) as the basis for NMBA dosing. Furthermore, 89 % of the anesthesiologists consider monitoring for guidance in rocuronium administration. When asked about the dosage approach and regulation for deep NMB, 20 % of the users rely on NMB monitoring to guide deep NMB, 30 % opt to regulate via requested bolus, and 50 % of the respondents were unable to answer or did not know. These results show a significant unfamiliarity regarding the administration of NMBA for this depth of muscle relaxation.

The benefits of using sugammadex have already been disclosed. Most users rely on this drug for NMB reversal, due to specific reversal action towards the NMBA, such as rocuronium. These results suggest the use of this NMBA generates a rising interest in the reversal agent and vice-versa. It may also explain the results regarding postoperative complications, which rarely (63 %) or never (37 %) are detected.

Market

From the available NMB monitors used, the main issues reported by the users were: the reliability of measurements, the accuracy of calibration, and the device fragility. Regarding the reliability of the devices, results show that a significant amount of users was able to detect measurement error (94 %). Nonetheless, 78 % recognize the advantages of an advisory system coupling infusion and monitoring, for personalized rocuronium administration during deep NMB. These benefits include the ability to control/individualize administration (34 %), the stable NMB maintenance (22 %), avoiding overdosing and residual curarization (33 %), and improve the overall anesthesia (11 %). None of the respondents identified such a method is commercially available.

The closed-loop approach is a technique frequently used. In order to understand its applicability in this field, it is important to understand its main limitations. 80 % of the users were unable to answer, showing there is a lack of acquaintance in terms of this technique. Regarding the main features of interest for a system of this kind, the users listed three main specifications: easy applicability, reliability of the system, and user-friendliness.

Control deep NMB proposal

A brief presentation to the users was conducted regarding what this project aims and comprises, by describing the features and outcomes of the intended system, designed for the stable maintenance degree of deep NMB (1-2 PTC). From the acquired data, 89 % of the respondents acknowledged the usefulness of such a product, 94 % would be appealing to use during surgical procedures, and 71 % believe that it may increase the deep NMB application. Based on a sensitive approximation, anesthesiologists estimated the value of such a system could range from 100-2500 € or, in turn, approximately 10-20 € per patient.

3.1.4.2 Users contribution

Despite the promising results, there are important weaknesses in this study. First, regarding the limited sample amount, which is significantly low, and the mean years of experience of the focus group, which underrepresents the understanding of the subject by the routine users. Nevertheless, this group provided insight on the current practice and specifics of the anesthetic needs/flaws. From the overall results, there is significant inexperience regarding deep NMB mostly due to lack of trust in the NMB monitoring, but also regarding the techniques and approaches to improve the maintenance of this depth of muscle relaxation.

Concluding, results proved the introduction of an advisory system for controlling the deep NMB maintenance is of major benefit to most anesthesiologists and can provide a vital solution for the routine practice. In addition, the feedback obtained from these questionnaires was able to deliver information on important variables/features to be included in the design of the control system for the maintenance of deep NMB.

3.2 CLINICAL STUDY FRAMEWORK

At this point, both NMB monitoring and the rocuronium infusion specifications and variables were carefully determined. First in the conception and development of the clinical study design, and ultimately to provide a reliable structure for the development of the closed-loop control system for deep NMB.

3.2.1 STUDY PROTOCOL

The use of deep NMB brings a new challenge for the administration of rocuronium together with monitoring, namely regarding the inter-individual variability of the responses. Considering the previously assessed concepts for the maintenance of deep NMB, it was possible to define a protocol

strategy for an observational study conducted at CHUP from April to August 2019 (the portuguese version of the protocol is included in Appendix 8.3.1).

The study was divided into three phases:

1. **Data acquisition –** Perform rocuronium administration for the deep neuromuscular blockade using an initial bolus dose of 1 mg/kg of Fat-free mass followed by continuous infusion, guided with TOF-Watch® SX monitoring. At the end of the surgery, the NMB reversal is conducted with sugammadex. Considering the clinical trial approach and results, that indicate the variability of rocuronium demand for adults is approximately 30 % [153], and analyzing the studies conducted for the assessment of the NMB response [154] (that included data from 23 patients), it was estimated that data from 30 patients would be adequate. However, considering that the study is observational, 40 patients were included in order to increase the statistical significance of the sample and its representativeness. For acquisition purposes, develop a computational platform to acquire data in real-time of rocuronium infusion (via ALARIS infusion pump) and monitoring results (TOF-Watch® SX).
2. **Data analysis and development of control approach –** Perform the analysis of the results obtained from the data acquisition, focusing on rocuronium infusion and PTC effect produced. Study the intubation dose effect on each subject and the rocuronium demand for the maintenance of deep NMB, here characterized by 1-2 PTC responses. Based on the information gathered, propose an algorithm for individualized rocuronium administration and test it in simulation.
3. **Advisory system test and validation –** Implement the developed and simulated control approach in the interface. This system aims to support the anesthesiologists' clinical practice in real-time by ensuring the maintenance of deep NMB continuously. This phase is intended to evaluate the control systems' performance and compare it to the phase 1 results.

To support this study, additional monitors could be included in the other hand to assess the NMB, namely the TOFscan® (Dräger, Lübeck, Germany) and/or the GE Datex Ohmeda Aisys NMT (GE Healthcare, USA) available in the hospital. Another feature to be explored regards the use of 100 Hz adaptive PTC stimulations (that consists of 100 Hz tetanus followed by a 3-second pause and 1 Hz Single-Twitch until the absence of response), when standard 50 Hz measured zero responses, aiming to quantify intense/complete NMB (i.e., when 50 Hz PTC = 0). This was based on experimental assessments conducted in the previous clinical trial, which showed that it is possible to evaluate the neuromuscular function during total suppression of the standard PTC measurements. Therefore, when the assessment of the NMB below the standard PTC is canceled and the duration to recover

positive values is unknown, the 100 Hz PTC can provide support in estimating the recovery of positive 50 Hz PTC values.

The study was designed to be conducted on patients scheduled for routine general anesthesia with a minimum of 90 minutes. For study inclusion, characteristics should include human adults (18-80 years old), classified as ASA I-IV (American Society of Anesthesiologists class), undergoing a surgical procedure that permitted the administration of rocuronium via continuous infusion for deep NMB. Exclusion criteria comprised patients with neuromuscular diseases, severe cardiovascular, hepatic or renal pathologies, that have contraindications for any of the drugs used, that are pregnant or nursing or that present a BMI > 35 kg/m^2.

As an observational study, no randomization was done, and patient confidentiality was preserved. Except for the mentioned methods, the described protocol did not significantly change the usual clinical practice, nor presents additional cost for CHUP.

Patients and surgical teams were all blinded to NMB evaluation; however, the anesthesiology team was not, in order to control rocuronium dose requirements and ensure the maintenance of the NMB target. Moreover, a researcher was always present to ensure the adequate equipment setup and data recording, and constantly assist the anesthesiologist in charge if critical deviations of essential clinical signals from the protocol intended ranges occurred.

For each phase of the study protocol, the designed procedure and requirements are as follows:

Phase 1 - Data acquisition

1. NMB monitoring with the TOF-Watch® SX monitor as the reference, and, if available additional NMT ASYS modular monitor or TOFscan® on the opposite hand;
2. Calibration of NMB monitors after patients' loss of consciousness (usual procedure);
3. Administration of rocuronium intubation dose of 1 mg/kg of fat-free mass (FFM);
4. Stimulation every 3 minutes for evaluation of Post-Tetanic Counts;
5. If 9 minutes after the intubation dose, the monitoring did not detect deep NMB (PTC less than or equal to 2), an additional 0.3 mg/kg (FFM) rocuronium is administered;
6. After at least two positive PTC are detected, in at least two successive evaluations, continuous infusion of rocuronium is initiated at 10 µg/kg/min (recommended dose);
7. Guided by the continuous PTC monitoring every 3 minutes, attempt to maintain 1-2 PTC responses by manually adjusting the rate of rocuronium infusion;
8. Suspend rocuronium infusion after surgical dressing;
9. Administer sugammadex for reversal according to dose recommendations (4 mg/kg of TBW);
10. Initiate extubation and patient awakening only when TOF-ratio > 90 % and *T1* > 70 %.

Phase 2 - Data analysis and development of control approach

1. From the data obtained in phase 1, conduct an offline analytical study and develop an algorithm to personalize the administration of the rocuronium to be incorporated into a user interface, as an anesthesiologist advisory system, for the control and maintenance of deep NMB.

Phase 3 - Advisory system test and validation

1 to 5. Same as phase 1;

6. After at least two positive PTC are detected, in at least two successive evaluations, rocuronium infusion is started according to the control system developed in phase 2;
7. During the procedure, every 3 minutes, the system receives the NMB monitoring result (PTC responses), which is expected to guide the rocuronium infusion according to the algorithm directives in order to ensure the maintenance of 1-2 PTC measurements. At each adjustment suggested by the system, is up to the anesthesiologist responsible for validating or rejecting its implementation;

8 to 10. Same as phase 1;

The collaborative anesthesiologists in charge of the case were familiarized with the study protocol and, if deemed necessary, could interrupt the execution of the protocol at any given time. Other drug administrations were also based on the anesthesiologists' discretion.

Approval of the protocol was obtained from the Research Coordinating Office and the Ethics Committee at CHUP (reference 2018-209 (184-DEFI/183-CES)) under the title "Development of an anesthesiologist advisory system to improve the deep neuromuscular blockade via rocuronium infusion". Agreement and informed consent were obtained from the patients enrolled in the study (referring documentation included in Appendices 8.3.2 and 8.3.3).

3.2.2 INTERFACE AND SETUP FOR DATA COLLECTION

After defining and selecting the main requirements and specifications for the clinical study, a computational platform/interface was developed for the accurate data acquisition. Thus, the main information to include is patient demographic data, rates and volumes of rocuronium infusion, NMB monitoring responses, as well as register other observations and events. This information should support the visualization of patient status throughout the procedure and assist in the dose adjustments via a compliant and straightforward display.

For that purpose, LabVIEW software (National Instruments, 2016, USA) was used for the development of the interface, ensuring complete data acquisition and display during clinical tests. A full report is created and updated in real-time during the procedure. This acquisition interface was accomplished, and the display of the functionalities and process is presented in Appendix 8.4. The accomplished platform was developed with the prospect of providing a basis for a further upgrade, particularly to integrate the closed-loop control system.

3.2.2.1 Device communication and setup

For data acquisition, it is vital to ensure the device communication between the syringe pump and NMB monitors with a laptop. In line with the study protocol, to support the NMB assessment of TOF-Watch® SX, TOFscan® was also included in the setup. Furthermore, additional configurations were required and are described next.

ALARIS infusion pump

As has been previously performed [155], an application was created to control the syringe pump infusion. Thus, rocuronium administration was always performed via an ALARIS syringe pump (BD, Becton, Dickinson and Company, USA), including the induction bolus. Thus, to ensure high performance, the set up for simple operation on drug infusion and alarm detection was designed and implemented based on the information provided in the Technical Service Manual for Asena ® Syringe Pumps (ALARIS medical UK Ltd, 2002-2005). This configuration enables to bridge the communication for most ALARIS infusion pumps available in CHUP, using a serial RS-232 to USB converter.

Before starting the experimental testing, a standard syringe with rocuronium was inserted, locked with the clamp, and the plunger was held fixed with the finger grips in the posterior part of the pump, ensuring appropriate conditions to start using (see Figure 3.5).

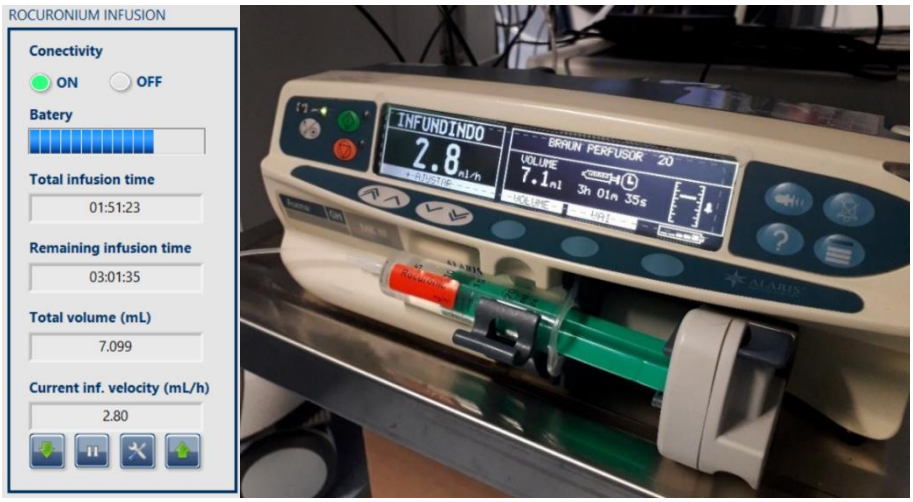


Figure 3.5 - The user-interface for data information of the ALARIS syringe pump status and infusion parameters.

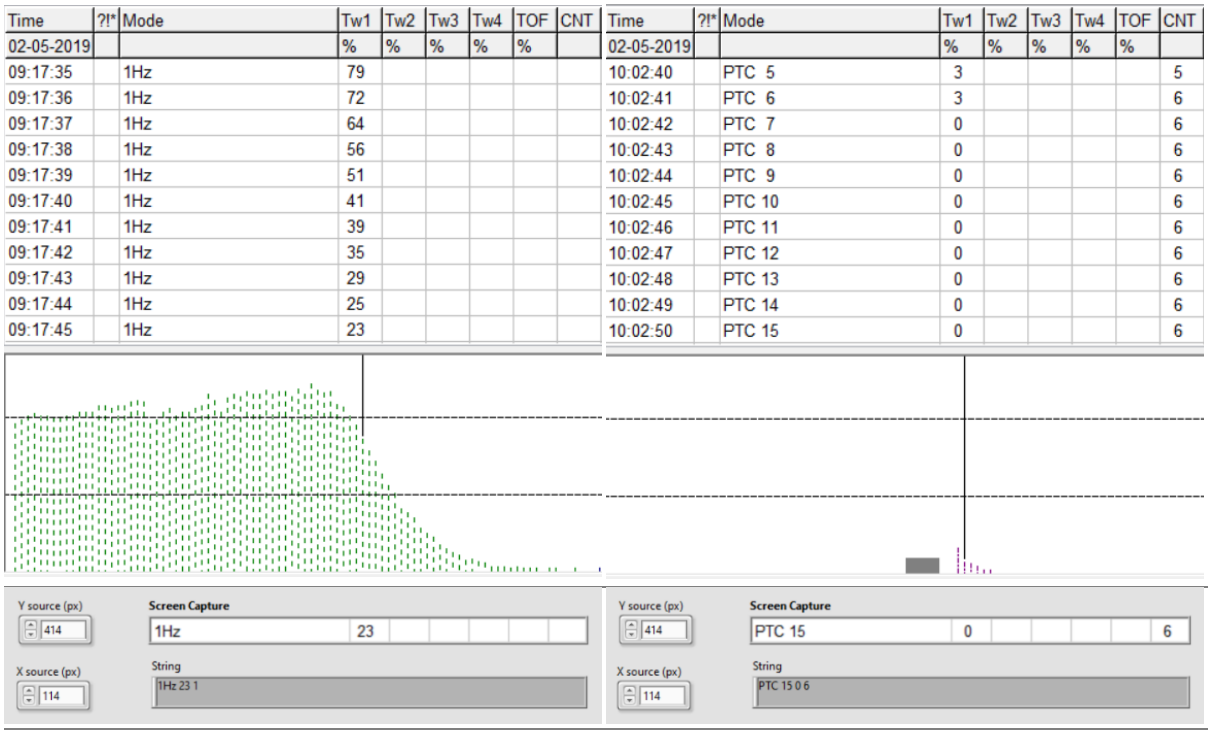
The syringe pump is the first device to be configured in the user interface. During the procedure, rocuronium administration was carried out, and the syringe pump provided and recorded information in real-time to a laptop. Connectivity, battery status, total infusion time (starting at the initial bolus), remaining infusion time (relative to the available amount of drug in the syringe and the current infusion rate), total administered volume (mL) and current infusion velocity (mL/h) were recorded and updated every second, and displayed in the interface for visualization.

TOF-Watch® SX

TOF-Watch® SX data acquisition was performed via TOF-Watch® SX Monitor software (version 2.5INT, Organon, 2007). This program records and displays all relevant data (twitches, body temperature, transducer sensitivity, stimulation mode) from the TOF-Watch® SX in real-time, via an optical fiber cable pared with TOF-Link USB interface plugged to the laptop.

TOF-Watch® SX Monitor software is a program that makes real-time data accessible to further processing. It allows for two basic options: 1) one logging and displaying real-time recorded data, and 2) displaying, exporting, and printing of previously recorded data. Therefore, the measured data could not be directly exported and included in the RelaxAn interface. To tackle this issue, an optical character recognition (OCR) approach was developed in LabVIEW and included in the interface.

OCR consists of the processing by which a machine vision application reads text and/or characters through image analysis. To do so, the region of the screen that displays the information of the last measurement recorded in TOF-Watch® SX Monitor was repeatedly printed via a screen capture technique and converted into an image. The set of prints allowed to create an extensive image library of the different measurements recorded in the TOF-Watch® SX Monitor software. The digital image bank was then applied together with a tool from LabVIEW for prototyping and testing image processing applications, known as NI Vision Assistant, which includes the OCR Training Interface. This tool was used to teach and train a character recognition algorithm (saved as a character set file), specified to be able to read the last TOF-Watch® SX Monitor measurement and convert it into a string. This way, it was possible to continuously acquire TOF-Watch® SX monitoring data in real-time and display the recorded measurements during the procedure in the user interface. It must be taken into account the training and algorithm development was focused on ST and PTC measurements only. This restriction is related to the focus of the NMB evaluation, which was selected to specify the assessment of the induction kinetics, via evaluation of the depression after initial bolus (ST), and the deep NMB assessments during the procedure (PTC), respectively illustrated in Figure 3.6.



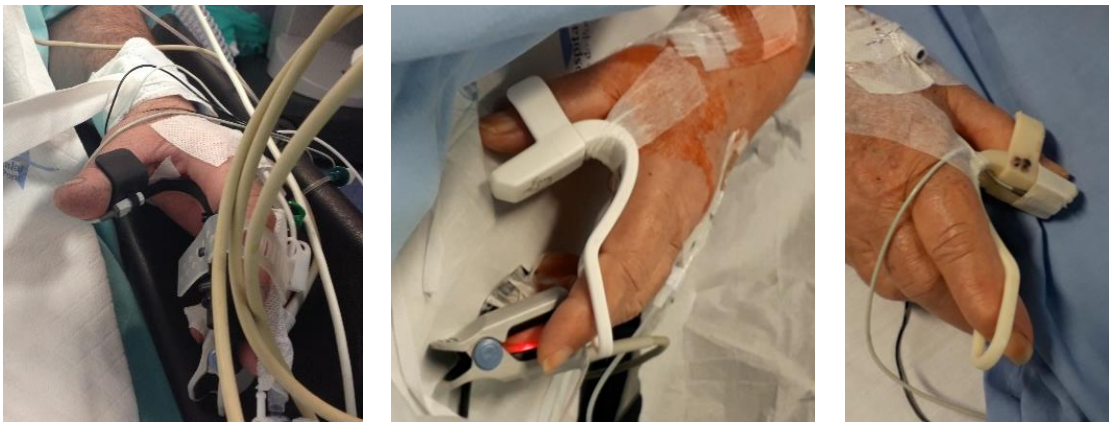
Time	?!*	Mode	Tw1	Tw2	Tw3	Tw4	TOF	CNT
02-05-2019			%	%	%	%	%	
09:17:35		1Hz	79					
09:17:36		1Hz	72					
09:17:37		1Hz	64					
09:17:38		1Hz	56					
09:17:39		1Hz	51					
09:17:40		1Hz	41					
09:17:41		1Hz	39					
09:17:42		1Hz	35					
09:17:43		1Hz	29					
09:17:44		1Hz	25					
09:17:45		1Hz	23					

Time	?!*	Mode	Tw1	Tw2	Tw3	Tw4	TOF	CNT
02-05-2019			%	%	%	%	%	
10:02:40		PTC 5	3					5
10:02:41		PTC 6	3					6
10:02:42		PTC 7	0					6
10:02:43		PTC 8	0					6
10:02:44		PTC 9	0					6
10:02:45		PTC 10	0					6
10:02:46		PTC 11	0					6
10:02:47		PTC 12	0					6
10:02:48		PTC 13	0					6
10:02:49		PTC 14	0					6
10:02:50		PTC 15	0					6

a b

Figure 3.6 - Illustrative examples of the TOF-Watch® SX last a) ST and b) PTC measurements recorded, followed by the print capture and conversion to string text.

Another issue encountered during the setup for data acquisition was the pre-load piece used on the hand, which was unavailable in CHUP due to unknown reasons. As has been mentioned, TOF-Watch® SX manufacture and selling has been ceased for some years and so its accessories. In order to solve this problem, the pre-load piece of TOFscan® was replicated in INEGI (Instituto de Ciência e Inovação em Engenharia Mecânica e Engenharia Industrial, Portugal), by applying a reverse engineering technique. Thus, a new silicon piece (80 shore A hardness) was then materialized to be used in the TOF-Watch® SX monitoring site (see Figure 3.7). A special thanks to Professor Rui Neto for the production of this part.

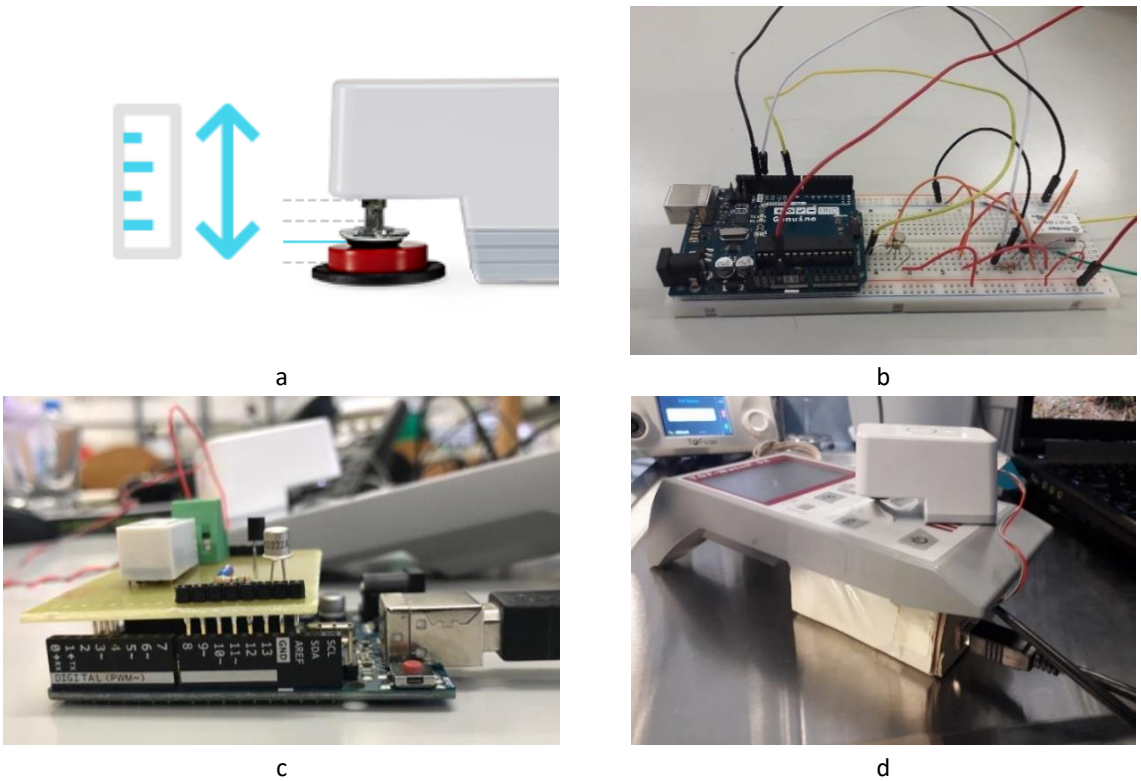


a b c

Figure 3.7 - a) TOF-Watch® SX original, b) TOFscan® original, and c) TOFscan® replicated pre-load pieces to monitor the response of the adductor pollicis muscle.

Besides ensuring the returning of the thumb to the baseline position, this solution also provided a closer approximation of the movement limitation in the opposite hand (performed by TOFscan®), minimizing the difference between devices.

Lastly, another issue that had to be solved was the need for the manual activation of PTC stimulation every 3 minutes in TOF-Watch® SX. The first approach considered to tackle this limitation was using a timer to alarm the researcher responsible for performing the manual button push; however, this was too cumbersome and with a high probability of failure. Alternatively, adding a MicroBot Push (Naran Inc. ©, Gyeonggi-do, South Korea), which consists of a wireless robotic button pusher, was proposed to tackle this issue and promptly press the PTC command button on the device. This solution was easily placed and attached to the surface of the TOF-Watch® SX monitor and was able to press the button at the desired time interval automatically. The wireless option was limited by the need for an app that requires a Bluetooth connection to set the time for push activation. Together with Diana Duarte (a student of Master in Biomedical Engineering at FEUP), a system that remotely controls the motor of the MicroBot Push component and, subsequently, activates the PTC action, was developed based on the Arduino Integrated Development Environment (Arduino software, USA). The system was further translated and implemented in a Printed Circuit Board (PCB) to automatically trigger PTC stimuli every 3 minutes (Figure 3.8).



a b c d

Figure 3.8 - a) MicroBot Push device, b) preliminary approach of the circuit with Arduino, c) optimized solution in PCB for a more ergonomic solution d) coupled and placed under the TOF-Watch® SX monitor.

TOFscan®

Data transmission of TOFscan® measurements to a laptop was performed via an optical cable TOF-RS1 coupled with a USB-SERIAL convertor USB-RS232, that together with the software TOFscan® Reader Multi permitted the recording of the each NMB evaluations of the monitor during the procedure.

TOFscan® Reader Multi creates individualized files of the NMB monitoring, which are updated at each input (each measurement). This data could be accessed and converted to the user interface for continuous visualization of the PTC responses from TOFscan® monitoring throughout the surgery.

3.2.2.2 Data processing and recording

Data acquisition was continuously performed for the main variables of rocuronium infusion and NMB monitoring in both monitors, which were then transferred for plot visualization in the interface.

For rocuronium administration, besides the plot of the infusion rate during the procedure, it also continuously calculated the total administered volume in time, expressed in mg/kg/h (in a secondary axis). This parameter represents the calculation of the current rocuronium amount administered to the patient over time (see example in Figure 3.9).

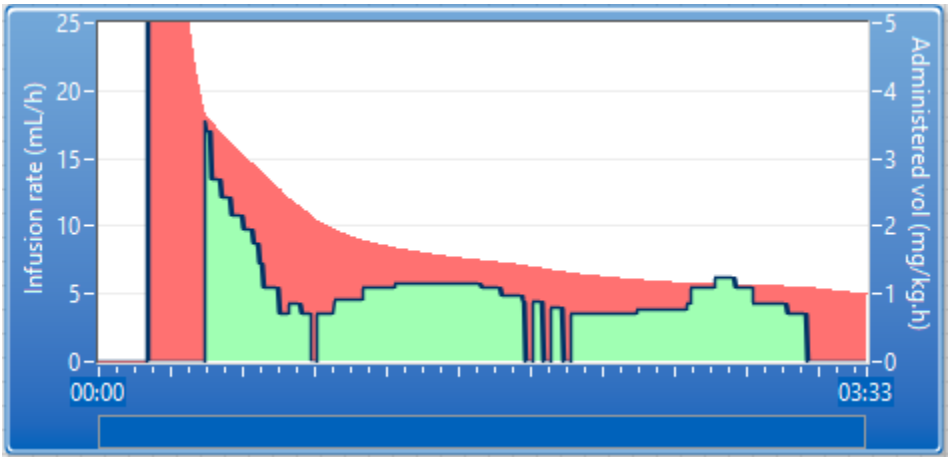


Figure 3.9 - Graphic visualization of a patients' case of the rocuronium administration during the procedure: infusion rate recorded in mL/h (green) and overall administered volume calculated in mg/kg/h (red).

From the OCR output of the TOF-Watch® SX responses, it was possible to automatically characterize individual's induction kinematics, by detecting the main instances of the ST response depression after the initial bolus (time for ST = 90 %, time for ST = 75 %, time for ST = 50 %, time for ST = 25 %, time for ST = 10 %, time for ST = 0 %), that allowed to calculate relevant indicators of the NMB setup (slopes of ST between 90-10 % and 75-25 %). Besides that, from the PTC measurements data, it was also possible to detect the time to recover first PTC and, likewise, assess the recovery profile by evaluating the slope expressed in the PTC measurements, reflecting the dynamics of the recovery from the initial dose.

Besides the ability to acquire the number of responses obtained after the tetanic stimuli, the OCR provided the information on the amplitude of each count, that allowed to calculate the area under the curve of that PTC measurement (AUC_{PTC}). The evaluation of this variable was essential to distinguish between the same result of PTC by providing additional information on the magnitude of response. In other words, the AUC_{PTC} measured along the time gave a more refined indication of how the NMB response trend unrolled, which provided some insight and support for the rocuronium adjustments (see appendix 8.5). Likewise, AUC_{PTC} of TOFscan® PTC measurements was also calculated. The NMB data measured in both devices were included and plotted in the interface throughout the procedures to support the rocuronium administration (see Figure 3.10).

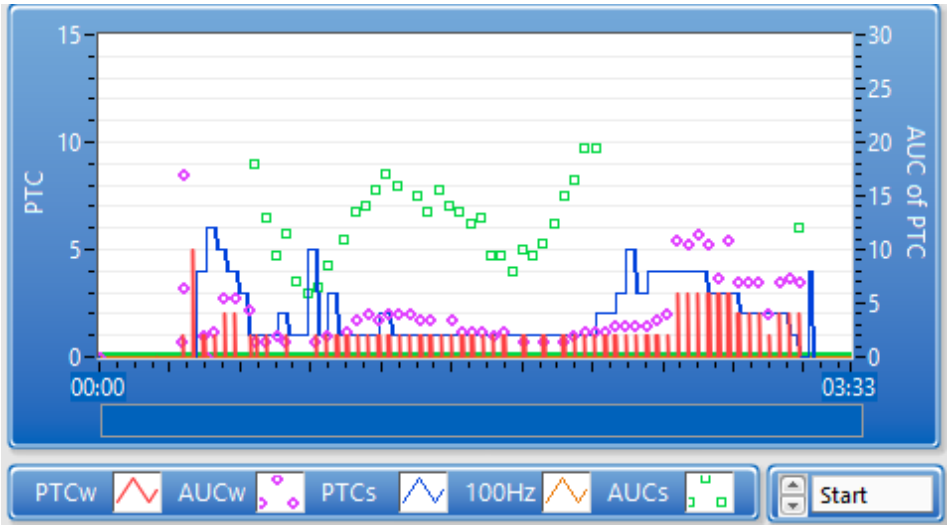


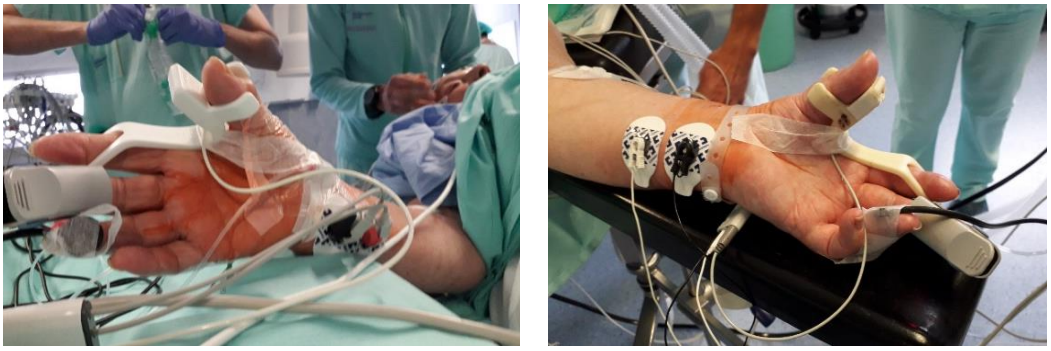
Figure 3.10 - Graphic visualization of a patient's NMB monitoring during the procedure. PTCw – PTC response of TOF-Watch® SX (red line); AUCw – AUC of PTC response of TOF-Watch® SX (pink markers); PTCs - PTC response of TOFscan® (blue line); 100Hz – 100 Hz PTC response (orange line); AUCs – AUC of PTC response of TOFscan® (green markers).

The output values were recorded in a delimited spreadsheet file for future offline analysis. The heading of the file included the patients' static data (weight, height, age, sex, BMI, FFM) and the infusion setup information (rocuronium concentration, induction dosage). Next, for the continuous registry of the NMB data, the recording included, for the rocuronium administration, the current total volume administered and infusion rate. For the NMB monitoring, besides the exported files from each monitor software, the output file from the data acquisition interface included the PTC and AUC_{PTC} records of both devices along the time. Both, the file recording and the graphic plotting, were continuously performed throughout the surgery, being updated every second. In parallel, important events were also recorded in a time series file, particularly registering: other drug administration (*e.g.*, propofol, remifentanil, lidocaine, sugammadex); the loss-of-consciousness; the TOF-Watch® SX calibration; the intubation step; the 100 Hz PTC stimuli measurements; the disturbances during NMB evaluation; among other uncategorized information.

3.3 DATA ACQUISITION

The data acquisition was carried out, corresponding to phase 1 of the clinical protocol proposed for this research project (described in section 3.2.1). The monitoring protocol was based on standard ASA guidelines. Upon arrival in the operating room, patients were monitored continuously with an electrocardiogram, pulse oximeter, non-invasive blood pressure, BIS, central temperature, and NMB monitoring. Anesthesia was performed using an intravenous technique for the hypnotic propofol, the analgesic remifentanil, and the NMBA rocuronium. TCI was used for remifentanil and propofol administration via syringe pumps (Fresenius Orchestra Base Primea, Homburg, Germany), with effect-site target concentrations titrated to achieve and maintain a BIS value between 40-60 (BIS, Medtronic, Minneapolis, USA) and the mean arterial pressure was maintained between [-30 % +30 %] of the patient's baseline value. The blood pressure and ventilation were carried out with the Aisys Anaesthesia system (GE Datex Ohmeda, General Electrics, USA).

The interface was started, confirming equipment connection and communication for data acquisition. The two different AMG monitors devices, TOF-Watch® SX and TOFscan®, were placed at the adductor pollicis muscle in both arms, selecting the most accessible monitoring site for TOF-Watch® SX (see Figure 3.11). Considering TOF-Watch® SX remains the only NMB monitor approved for clinical trials, it was the reference device to guide the rocuronium infusion. Thus, if disturbances or issues with the monitoring site were detected, it could be easily accessed and corrected.



a b

Figure 3.11 - Neuromuscular blockade monitoring setup of one individual's adductor pollicis muscles with a) TOFscan® and b) TOF-Watch® SX during the clinical study.

For the monitor setup, the skin was degreased, two electrodes were placed over the ulnar nerves near the wrists, and contractions were measured at the tip of the thumb, by the accelerometer sensors inserted in the pre-load pieces. After the loss of consciousness, calibration was carried out in TOF-Watch® SX according to manufacture specifications (CAL 2) [106]. For a more approximate setup between both devices, TOFscan® intensity of stimuli was set for the closest higher step value of the response obtained by TOF-Watch® SX supramaximal (*e.g.*, TOF-Watch® SX calibration intensity of 33 mA, TOFscan® intensity set to 40 mA).

All patients received 1 mg/kg of FFM of rocuronium for intubation, followed by continuous ventilation. At this point, in TOF-Watch® SX, the assessment of the NMB function was acquired with constant Single-Twitch stimuli (1 Hz) until the response was nullified, to observe the depression curve generated by the induction dose. ST monitoring was followed by continuous TOF stimulus every 15 seconds, primarily to confirm onset (TOF-ratio = 0) and appropriate conditions for intubation and, secondly, to ensure the absence of moderate NMB function during the procedure. On the other hand, TOFscan® measured TOF response continuously until onset detection. Subsequently, after tracheal intubation was complete, PTC measurements were applied every 3 minutes in both devices.

The initial dose was determined in order to be sufficient to ensure quick and good intubation conditions and to override PTC measurements for some minutes (achieve complete block, PTC = 0). After the recovery of at least two consecutive PTC measurements above zero, constant infusion of rocuronium was started and titrated to maintain the target range of 1-2 PTC (reference from TOF-Watch® SX monitoring). In the case of deviations from the target values, primarily, the infusion rate was adjusted ± 10 % from the current infusion rate. Secondly, if the response substantially remained over 1-2 PTC, or if the surgical team requested for better surgical conditions, a small bolus was given according to the anesthesiologist's discretion. If, on the other hand, measurements were continuously null (PTC = 0) due to overdose, the infusion would be stopped until positive PTC recovery. As designed, to accomplish this, an Alaris infusion pump (BD, Becton, Dickinson and Company, USA) was used to perform the continuous infusion and rate adjustments required to regulate the rocuronium administration. A picture of the data acquisition setup is presented in Figure 3.12.

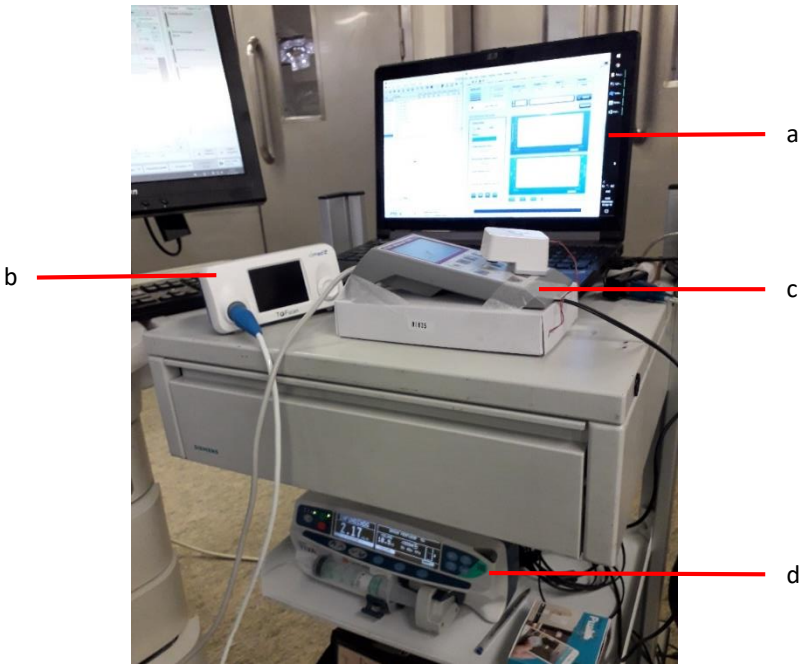


Figure 3.12 - Data acquisition setup station during the clinical study including a) laptop; b) TOFscan®; c) TOF-Watch® SX and; d) Alaris syringe pump.

After the surgical dressing at the end of the surgery, propofol and rocuronium infusions were stopped, followed by the NMB reversal with 4 mg/kg sugammadex. For all participants, extubation was carried out when TOF-ratio reached 90 %.

Normothermia was ensured during the NMB monitoring and, although both hands were secured to avoid interferences, any artifacts or external disturbances during measurements (*e.g.*, due to positioning or handling of the patient) were recorded throughout the procedure.

3.4 CHAPTER OVERVIEW

Based on underlying studies conducted on the available techniques and their limitations regarding both, the NMB monitoring and the continuous rocuronium administration, it was possible to understand and define the methodology's requirements and concepts for the improved maintenance of deep NMB during surgical procedures. In addition, to support the design of a clinical study, a questionnaire was conducted to anesthesiologists, as experts on the field, to gather their input on important features for the approach and, ultimately, for the closed-loop control system development.

Accordingly, a clinical investigation study was proposed, and an interface for the data acquisition was developed for an advanced and reliable assessment of the patients' NMB performance.

4 CLINICAL STUDY RESULTS

The scope of this clinical study was to gather data from patients undergoing surgical procedures with deep NMB. The aim was to record and analyze their performance regarding dosing and NMB response, to support the development of an approach to control and improve the maintenance of the deep neuromuscular blockade.

From the data collected, it was possible to perform two supporting analyses: 1) a study on the NMB monitoring by the comparing TOFscan® and TOF-Watch® SX monitoring responses during the procedure; and 2) a study of the rocuronium pharmacokinetic-pharmacodynamic relationship in estimating the post-tetanic count effect, during the maintenance of deep NMB. The outcomes of these investigations were submitted for journal publication.

4.1 TOF-Watch® SX versus TOFscan®

From comparing two analog devices it is expected that similar outcomes should be obtained under the same NMB conditions. Previously, the influence of calibration to compare the TOF-Watch® SX and the TOFscan® has been investigated, reporting poor agreement during the onset and recovery phases of the NMB and good agreement in the reversal phase [13]. A similar study concluded that there was a good agreement between both devices throughout the neuromuscular recovery [154]. Both of these studies' approaches were related to non-deep NMB monitoring. In contrast, this study aims to compare the two most widely used acceleromyography-based monitors, TOF-Watch® SX and TOFscan®, by additionally assessing the difference between PTC measurements obtained during the deep neuromuscular blockade maintained via continuous infusion of rocuronium.

TOF-Watch® SX, which has been extensively used over the last few decades, is the only device approved for research trials with NMB monitoring [106]. However, it is no longer being manufactured, and its limited availability has created an interest in studying other monitors capable of accurately

evaluating the NMB. The TOFscan®, which relies on the same acceleromyography principles, is a commercially available device with growing use in anesthesiology.

4.1.1 ANALYSIS METHODS

Demographic data (age, sex, ASA class, true-body weight, height, body-mass index, fat-free mass), rocuronium induction dosing (induction dose, mean infusion rate), and the infusion and procedure durations were recorded. Results are expressed as mean (SD).

First of all, for equivalent comparison between monitors, a paramount issue that needed to be solved is related to the different outputs of the PTC results recorded in each device. While TOF-Watch® SX registers the number of evoked responses until the fade is over (detection of first 0 counts), TOFscan® records the total number of positive twitches after the tetanic stimuli (see Figure 4.1). For the analog comparison of measurements, the TOFscan® PTC recordings were revised and normalized manually. Another critical feature that differs between monitors is the number of twitches applied after the tetanic stimuli in the PTC measurement. While the TOF-Watch® SX applies 15 impulses, TOFscan® applies 10 (illustrated in Figure 4.1). Thus, to perform a fair comparison, a threshold of 10 responses was established for TOF-Watch® SX PTC measurements (i.e., results of 10-15 PTCs were defined to the maximum scale value of 10).

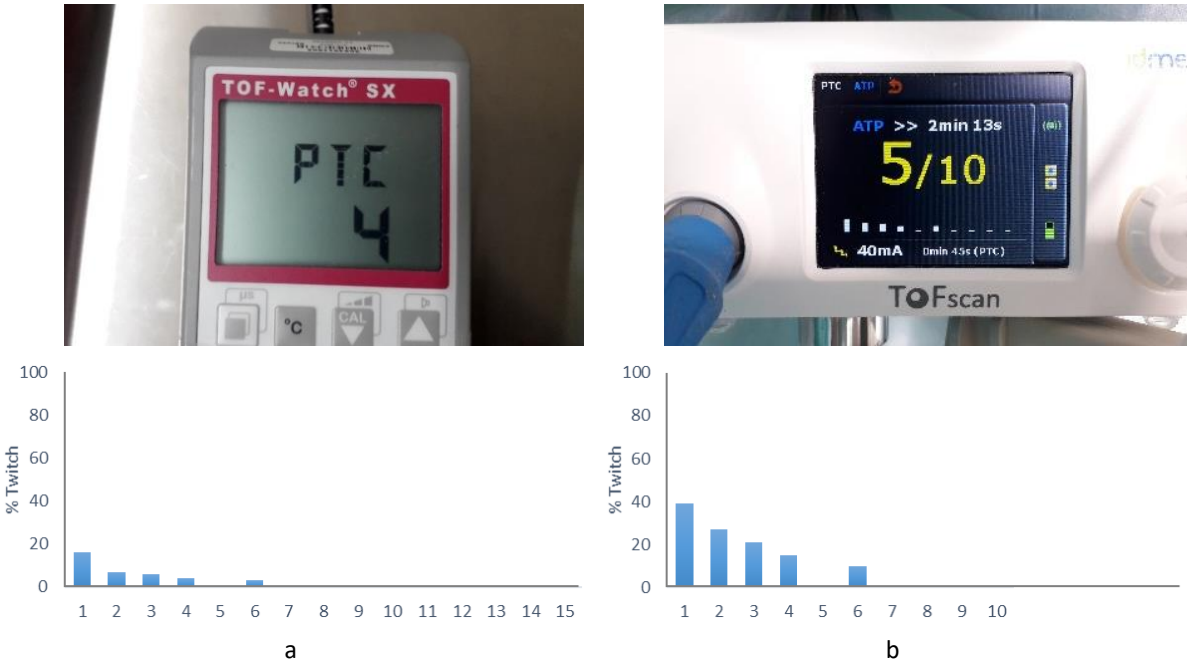


Figure 4.1 - Example of the distinct methods of data display and output of a PTC stimulus in a) TOF-Watch® SX and b) TOFscan®.

For cross-monitor comparisons, the stimulation current and time to onset detection following the initial bolus were recorded. Following the onset detection, the data was divided into two phases for the PTC monitoring analysis: 1) the induction phase, which represents the period after the onset until

continuous infusion was started, and 2) the maintenance phase, which we defined as the remaining time of the procedure until rocuronium infusion was stopped.

At the induction phase, to assess the difference of monitoring results, two parameters were recorded in each device: in the installation of the complete block, evaluate the percentage of patients that had a positive result in the first PTC stimulus; and, then, at the recovery from it, the mean time required to detect the first positive PTC. At the maintenance phase, relevant data recorded relates to the number of PTC stimuli applied during the infusion and the percentage of responses within, under, and above the 1-2 PTC target.

After linear interpolation of the merged data to match sample size, it was possible to assess the differences between the pairs of measurements between both devices. First, the absolute difference between pairs of measurements was categorized into four classes: Good (if the difference was 0-1 PTCs), Admissible (if the difference was > 1-2 PTCs), Intermediate (if the difference was > 2-5 PTCs) and Poor (if more than 5 PTCs). Also, to appraise the variance between monitors in both phases, the differences between pairs of measurements were assessed. For validation of normal distribution, Q-Q plots were evaluated. The differences between the results obtained from each monitor were assessed with a paired t-test (parametric) or Wilcoxon signed-rank test (non-parametric). The null hypothesis was considered significant when a two-tailed p-value < 0.05. All analyses were performed using the GraphPad Prism software (GraphPad PRISM Software, Inc., version 8.4.0, USA).

For the estimation of the agreement between device measurements, a Bland–Altman analysis was performed with the calculation of bias (SD) and limits of agreement with 95 % CI for the paired measurements of all subjects [155, 156]. The device comparison was independent of individuals' conditions during the procedure; thus, the variance between and within-subjects was not included in the analysis.

4.1.2 RESULTS

Data from 30 patients were included in this study. The procedures performed included elective abdominal and neurosurgery with a mean duration of 192.57 (91.79) min. The demographic and baseline characteristics of the studied population and rocuronium dosing are presented in Table 4.1.

The mean (SD) stimulation current of TOF-Watch® SX was 44.63 (11.98) mA and 47.00 (10.88) mA for the TOFscan®, with a mean difference of -2.37 (-3.40 to -1.34, for 95 % CI, $p < 0.0001$) mA. For all patients, the rocuronium induction bolus was sufficient to provide appropriate conditions for successful intubation. The onset time measured in TOF-Watch® SX and TOFscan® were 85.6 (39.4) s and 141.2 (53.1) s with a mean difference of -47.7 (-65.0 to -30.4 for 95 % CI, $p < 0.0001$) s, respectively.

Table 4.1 - Demographic data and rocuronium used during the induction and infusion phases for the population sample.

Patient sample size		n = 30
Age		63.1 (10.4)†
Sex	**Male**	11
	Female	19
ASA class	**I**	0
	II	25
	III	5
	IV	0
True Body Weight (kg)		73.1 (13.4)†
Height (cm)		162.3 (8.6)†
Body-mass index (kg/m^2)		27.7 (4.3)†
Fat-free mass (kg)		47.3 (10.0)†
Rocuronium induction dose (mg/kg)*		0.65 (0.09)†
Rocuronium via continuous infusion (mg/kg/h)*		0.59 (0.24)†

†data reported as mean (SD) of the sample (n = 30); *reference of true-body weight.

At the induction phase, after the absence of positive TOF measurements, intubation took place, and PTC monitoring was started. The first PTC stimulus performed (in the first 3 min after intubation) using TOF-Watch® SX detected a positive response in 26.7 % of the patients, while TOFscan® detected in 56.7 %, before reaching the complete block. Later, the detection of the first PTC above 0, showing the recovery from the complete block, was recorded after 27.52 (14.41) min in TOF-Watch® SX and 24.27 (12.82) min in TOFscan®, showing a mean difference of 3.26 (0.57 to 5.94, for 95 % CI, p = 0.019) min.

The maintenance phase represents the period when rocuronium continuous infusion occurs, which had a duration of 163.36 (95.76) min. The results of PTC monitoring during the infusion in each device are reported in Table 4.2.

Table 4.2 - NMB monitoring measurements during the infusion phase for both TOF-Watch® SX and TOFscan® devices. Data reported as mean (SD) and the difference [TOF-Watch® SX - TOFscan®] was assessed using paired t-test (n = 30).

	TOF-Watch® SX	**TOFscan®**	**Difference (95 % CI)**	**p-value**
PTC measurements	51.2 (30.8)	54.8 (34.2)	-3.6 (-5.8 to -1.3)	0.003
% PTC = 0	14.0 (13.2)	22.9 (21.9)	-8.8 (-14.2 to -2.2)	0.1442
% PTC = 1-2	64.8 (15.3)	39.6 (23.4)	25.2 (14.9 to 35.6)	< 0.0001
% PTC > 2	21.2 (10.4)	37.6 (28.6)	-16.4 (-27.7 to -5.0)	0.006

For the included study population, a total sum of 3630 post-tetanic stimuli was applied in the two devices. For purposes of comparing the extent of variance between post-tetanic measurements, due to the non-coincident instances of measurement, linear interpolation was performed to estimate the

monitoring values for the data points within the same range. A total of 1865 pairs of post-tetanic measurements were valid for analyses (237 in the induction phase and 1628 in the maintenance phase). The absolute difference was calculated and classified for both phases of the analysis. The results are illustrated in Figure 4.2.

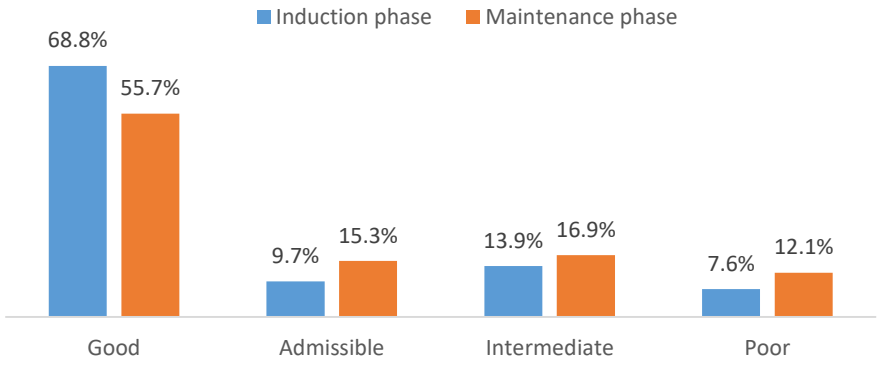


Figure 4.2 - Incidence and classification of the absolute difference between TOF-Watch SX® and TOFscan® pairs of PTC measurements, during induction (n = 237) and maintenance phases (n = 1628).

The induction phase measurements did not present a normal distribution; therefore, non-parametric tests were used for the statistical analysis. Median [25th to 75th percentile] of the differences between TOF-Watch® SX and TOFscan® measurements was 0.00 [-1.18 – 0.00] (p-value < 0.0001, with Wilcoxon rank sums test) PTCs. In turn, during the maintenance phase, normal distribution was admitted, and the mean difference in PTCs devices was -1.05 (-1.19 to -0.91 for 95 % CI, p < 0.0001, with paired t-test) PTCs. Additionally, through the Bland-Altman analysis, the bias between TOF-Watch® SX and TOFscan® measurements was calculated over the range of responses obtained for this phase, results showed a bias (SD) of -1.05 (2.81) PTCs, with 95 % limits of agreement of -6.55 to 4.45 (Figure 4.3).

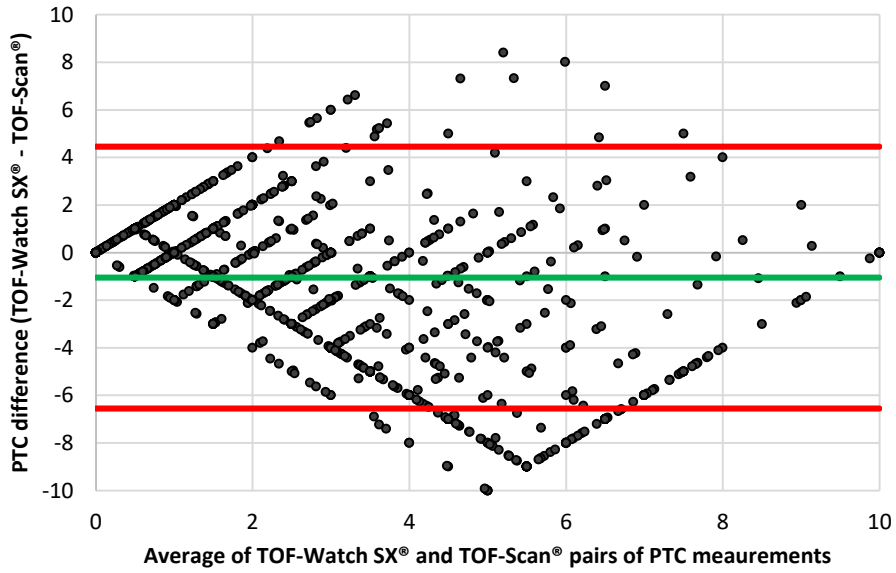


Figure 4.3 - Bland-Altman plots showing the bias (green) between pairs of post-tetanic measurements of both monitoring devices for the maintenance phase (n = 1628). Respective upper and lower limits of agreement (red) are also illustrated. Each point represents a pair of measurements performed in 30 patients.

After the sugammadex reversal, all patients were successfully extubated within 3-6 min with no complications.

4.1.3 FINDINGS AND DISCUSSION

Regarding the rocuronium administration, this was based on the use of a bolus injection, using the FFM formula, followed by a continuous infusion, which has the advantage of achieving a relatively rapid and stable level of NMB [143]. The fat-free mass formula [39], has shown better predictive accuracy in estimating reasonable dosages for normal weight and moderately obese patients. Thus, providing a good fit for the representative population sample included in this study. For clarification purposes, the induction bolus dose was recalculated for the true-body weight, allowing to relate to the standard dosing reference used. The mean (SD) amount shows a slight increase over the 2xED_{95} dose (0.61 mg/kg), providing appropriate intubation conditions for all patients. In turn, during the continuous infusion steady-state is admitted, with a rocuronium infusion rate of 0.59 (0.24) mg/kg/h, consistent with recommended ranges [113, 120, 121].

The study's findings on the NMB monitoring indicate that there are some differences between both devices after the initial bolus. The onset times in both devices were within the expected values [20], with TOF-Watch® SX taking a significantly shorter time of approximately 47.7 s. This result is supported by Murphy G. [154], which reported the time of onset for the TOFscan® was nearly a minute longer than the TOF-Watch® SX. As suggested, this may indicate that clinicians may be performing intubation before appropriate tracheal intubation conditions.

After onset, PTC stimulations are essential for assessing and characterizing the deep NMB. TOFscan® measured a positive response at the first PTC stimuli in 30 % more patients than TOF-Watch® SX. As previous studies have reported [13, 153], at the setup of the complete block after the induction dose of rocuronium, the TOFscan® can detect the remaining NMB function while the TOF-Watch® SX cannot. Moreover, the TOFscan® showed higher sensitivity and amplitude of twitch responses, to both TOF and PTC monitoring, than the TOF-Watch® SX. The reason for this difference may lie in the processing of the neuromuscular response or the baseline technique of each device. Since the twitch height of TOF-Watch® SX is defined based on the calibration performed and measures the thumb movement in a single-axis, in turn, the TOFscan® uses a non-calibrated technique and measures the motion of the same finger via a three-dimensionally sensitive sensor.

For the maintenance of a low PTC target of 1-2 responses, rocuronium adjustments are difficult to ascertain. Thus, the proposed approach considered a 3-minute interval between PTC stimuli, allowing for adequate motor end-plate recovery and the acquisition of a significant sample of measurements

crucial for guiding individual rocuronium demand [6]. Furthermore, the time interval between the induction bolus and the start of infusion has a direct impact on the maintenance of the desired degree of muscle relaxation; therefore, it was defined based on patient-specific monitoring, more specifically when PTC recovery is detected. The recovery of the first positive PTC in the TOFscan® was detected approximately 3.26 min sooner than the TOF-Watch® SX.

As can be observed from the findings mentioned above, there is a significate difference between the measurements in each device at the onset and recovery from the induction bolus. These results can potentially be explained by the contrasting sensitivity of each device in evaluating and processing the neuromuscular response when rocuronium plasmatic concentration changes significantly, indicating a dynamic inconsistency of the NMB monitoring. Taking this into account, the induction and the maintenance phases were distinguished in the analysis.

In both induction and maintenance phases, the evaluation of the absolute differences between paired measurements was classified accordingly. Results showed overall good agreement between the monitors. Nevertheless, intermediate and poor agreement differences were also substantial.

For comparison between pairs of measurements at the induction phase, the non-parametric test indicates there is a significate difference between pairs of measurements, nonetheless has distribution around zero.

During the maintenance phase, although the desired target was 1-2 PTC, the percentage of measurements within that range was not as effective as it could be; nonetheless, it provided a good fit for the study. The paired t-test indicated a mean difference between the pairs of measurements of about 1 PTC over TOF-Watch® SX, showing a good approximation between measurements.

Likewise, Bland-Altman analysis showed a bias of -1.05 PTC, allowing to conclude that, although there is an agreement between devices, the TOFscan® presents a higher response sensitivity. From the analysis of the limits of agreement and distribution, it is possible to observe that differences between measurements may not be consistent over the range of values and that the agreement between devices may not be as accurate as expected. Moreover, the variability of measurement differences is conditioned by the scale output of the post-tetanic measurements, evidenced in the Bland-Altman plot pattern.

The response instigated by sugammadex after deep NMB depends on the administered dose and degree of muscle relaxation when given. In this study, the time point of reversal administration was performed differently for each patient, and therefore, no significant conclusions were made regarding the monitoring of NMB recovery.

4.1.3.1 Limitations

As an observational investigation, the study setup was developed considering the usual clinical practice of the general anesthesia. The findings of this work should be interpreted within the limitations of the studied population and the data evaluation methods. Specifically, the reported results may be affected by the integer and discrete assessment of the PTC response, in which the data interpolation may conditionally appraise the NMB response. Further studies should be conducted to better describe the difference between monitoring during deep NMB.

In this study, the neuromuscular monitoring relied on the assessment of blockade using a two-arm technique, overlooking the influence of the dominant hand. A previous study [158] did not find significant differences between two arms, and thus there was no need to randomize the placement of each monitor.

Additionally, acceleromyography-based monitoring provides one of the most used and reliable methods in detecting the stimulation response objectively. Although the free movement of the thumb was ensured at all times, these recordings can often be affected by artifacts, patient positioning, or unstable twitch responses that may reflect some inaccuracy in detecting the NMB degree.

4.2 PK-PD MODELING FOR DEEP NMB

PK-PD models can describe the relationship between drug administration and its effect over time. Therefore, they are often used in TCI systems to accurately regulate the dosing of the drug for a predefined target plasma or effect-site concentration [45]. Most PK models for rocuronium were studied to predict and assess the PD relationship of TOF response (non-deep NMB) after the induction bolus [14–19].

The PK-PD relationship of rocuronium in adults, considering a three-compartment model, has been investigated based on Wierda J. [14] PK model by Saldien V. [143] and De Haes A. [159] (from now on referred to as SW and HW models respectively). De Haes A. performed the study in myasthenic patients and matched controls to describe the time course of action of rocuronium, comparing the results with the Sheiner L. model [49]. Based on the same principles, Saldien V. conducted an analysis of rocuronium PK-PD relationship in infants, children, and adults.

Based on the control/adult data of these two PK models from the literature, this work aims to estimate PD parameters to predict the effect of PTC responses during deep NMB, using continuous infusion of rocuronium. Following, by evaluating and comparing the estimated and measured responses, the PK-PD modeling accuracy for deep NMB is assessed.

4.2.1 ANALYSIS METHODS

Demographic data (age, sex, ASA class, TBW, height, BMI, FFM), rocuronium dosing (induction dose, mean infusion rate), and duration of the procedure were recorded. Similarly, NMB monitoring is detailed for the study population, including the number of PTC stimuli applied, the percentage of responses within the 1-2 PTC range, as well as measurements under (PTC = 0) and above (PTC > 2) the target.

The detailed data of the three-compartment models studied by De Haes A. and Saldien V., included in this study, are presented in Table 4.3.

Table 4.3 - Saldien-Wierda (SW) and Haes-Wierda (HW) pharmacokinetic models' parameters for rocuronium [142, 158].

	SW model	**HW model**
V_1 **(mL/kg)**	35.6	42
V_2 **(mL/kg)**	72	40
V_3 **(mL/kg)**	122	69
k_{10} **(min^{-1})**	0.126	0.076
k_{12} **(min^{-1})**	0.209	0.124
k_{13} **(min^{-1})**	0.050	0.021
k_{21} **(min^{-1})**	0.163	0.130
k_{31} **(min^{-1})**	0.015	0.013
k_{e0} **(min^{-1})**	0.168	0.150

Abbreviations: k_{e0} - rate constant between central and effect compartment; *kij* - rate constant for equilibration between compartments i and j; *V1, V2, V3* - distribution volumes of central and peripheral compartments.

The accuracy of the PK-PD modeling is often assessed by comparing the estimated and measured *Cp* of the drug, usually obtained by venous blood samples taken during the procedure. In contrast, similarly to Vermeyen K. approach [160], this study describes a method for selecting a PK-PD model that provides a better estimation of the PTC effect, based on the measurements obtained during the maintenance of deep NMB and without taking blood samples. To the authors' knowledge, no PK-PD study has been conducted to predict the PTC effect.

Based on the PK-PD modeling concepts for anesthesia (described in section 2.1.1.2), a parametric approach was used to assess the predicted effect based on the inter-compartment connection between the central compartment and effect-site. Thus, the relationship between plasma (*Cp*) and effect-site concentration (*Ce*) can be estimated, based on the model described by Sheiner L. [49]

(described by Eq. 6: $dCe/dt\ (\mu g/mL) = k_{e0}(Cp - Ce)$), where k_{e0} is the rate constant between central and effect compartments.

From the rocuronium administered throughout the procedure, both *Cp* and *Ce* were calculated for each PK model during the procedure for all subjects. Based on the Hill equation (Eq.7: $Effect = E_0 + (E_{max} - E_0)\, Ce^{\gamma}/(Ce_{50}^{\gamma} + Ce^{\gamma})$), the pharmacodynamic relationship between *Ce* and the effect can then be calculated [51, 160].

The *Effect* represents the estimated PTC outcome. E_0 is the baseline response when no drug is present. Thus it was defined by the maximum PTC output of 15 (considering the TOF-Watch® SX scale). E_{max} is the maximal effect, assuming the value of 0 PTC responses. Ce_{50} represents the effect-site concentration of rocuronium associated with 50 % of maximal drug effect, and γ is the steepness of the concentration-response curve.

As no previous studies regarding the pharmacodynamics during deep NMB were found, this study proposes an approach to compute these values for each patient data set. From the derived effect concentration (*Ce*) relationship of each model, and the PTC measurements obtained for each patient, the pharmacodynamic parameters of Ce_{50} and γ were individually calculated. To do so, a non-linear least squares regression method was used for the evaluation of the dose-response relationship.

The pharmacodynamic parameters obtained allowed for the individual estimation of the PTC effect for each model (PTC_{SW}^{ind} and PTC_{HW}^{ind}) for all subjects. These were compared to real measurements obtained during the procedure, PTC^{m}. Additionally, aiming to investigate the variability and accuracy of the models' ability to predict the PTC effect, the average Ce_{50} and γ values resulting from the previous data analysis were used as new PD parameters to estimate the effect. These were denominated PTC_{SW}^{avg} and PTC_{HW}^{avg}, respectively. Likewise, the difference between measured and newly predicted PTC measurements was assessed.

TOF-Watch® SX records PTC response as integers and measurements were performed every 3 minutes. In turn, PTC_{SW} and PTC_{HW} were estimated continuously with decimal precision. The predicted effect values at the instances of the PTC monitoring were compared with the respective observed results, evaluating the difference between estimated and observed measurements.

The predictive performance accuracy of both PK-PD models was analyzed by assessing the performance error (PE), median PE (MDPE), median absolute PE (MDAPE), and wobble [161, 162], to evaluate which model provided a better approximation in estimating the deep NMB effect. For PTC measurements, PE calculations were performed with:

$$PE_{PTC} = PTC_{measured} - PTC_{\text{predicted}} \qquad \text{Eq. 8}$$

These variables were calculated for each patient and then summarized as mean (95 % CI). All analyses were performed using the GraphPad Prism software (GraphPad PRISM Software, Inc., version 8.4.0, San Diego, CA, USA). Patient inter-individual variability was not included in the analysis, limiting the patient-specificity to the PD characteristics of each subject.

4.2.2 RESULTS

Thirty patients undergoing elective abdominal and neurosurgical procedures were enrolled in this study. Cases had a mean duration of 219.3 (76.4) min. The demographic and baseline characteristics of the study population, as well as the rocuronium used, are presented in Table 4.4

The induction bolus provided appropriate intubation conditions and abolished the initial PTC measurements in all subjects, taking approximately 26.3 (10.4) min to recover a positive PTC response. Next, the infusion was started and manually adjusted along the procedure to maintain 1-2 PTC. The length of the infusion was approximately 190.2 (78.3) min, during which, a mean (SD) of 58.2 (25.7) PTC stimuli were applied. For this population, 65.9 (13.9) % of the observed measurements were within the NMB target, 12.6 (11.0) % were below (PTC = 0), and 21.5 (9.5) % were above the target (PTC > 2). The rocuronium used via continuous infusion for the maintenance of the NMB degree showed a demand of 0.56 (0.18) mg/kg/h (reference of TBW).

Table 4.4 - Patient characteristics and rocuronium dosage (mean (SD) or n).

Patient sample		n = 30
Age		62.1 (11.6)
Sex	**Male**	15
	Female	15
ASA class	**I**	0
	II	25
	III	4
	IV	1
True body weight (TBW) (kg)		72.4 (13.4)
Height (m)		1.64 (0.09)
BMI (kg/m^2)		27.1 (4.6)
FFM (kg)		48.7 (9.9)
Rocuronium induction dose (mg/kg)*		0.68 (0.10)
Time to first PTC recovery (min)		26.3 (10.4)
Rocuronium via continuous infusion (mg/kg/h)*		0.56 (0.18)
Duration of rocuronium infusion (min)		190.2 (78.3)

*reference to TBW. Abbreviations: BMI - body mass index; FFM – Fat-free mass; NMB – Neuromuscular blockade.

For each subject, according to the rocuronium infusion, the PK calculations for *Cp* and *Ce* were estimated for the length of the procedure. Aiming to assess the patient-specific values of Ce_{50} and γ, nonlinear regression was used to achieve the best fit between modeled and real data. A total of 1955 post-tetanic count stimuli were included in the analysis. The resulting pharmacodynamic parameters estimated for the SW model were a Ce_{50} of 0.879 (0.509) µg/mL and a γ of 2.912 (1.726), and 1.498 (0.753) µg/mL and 4.130 (2.489) for HW model. A patient case example of the measured and estimated parameters is shown in Figure 4.4. Table 4.5 shows the MDPE, MDAPE, and wobble assessment, which evaluate the PK-PD bias, accuracy, and total intra-individual variability.

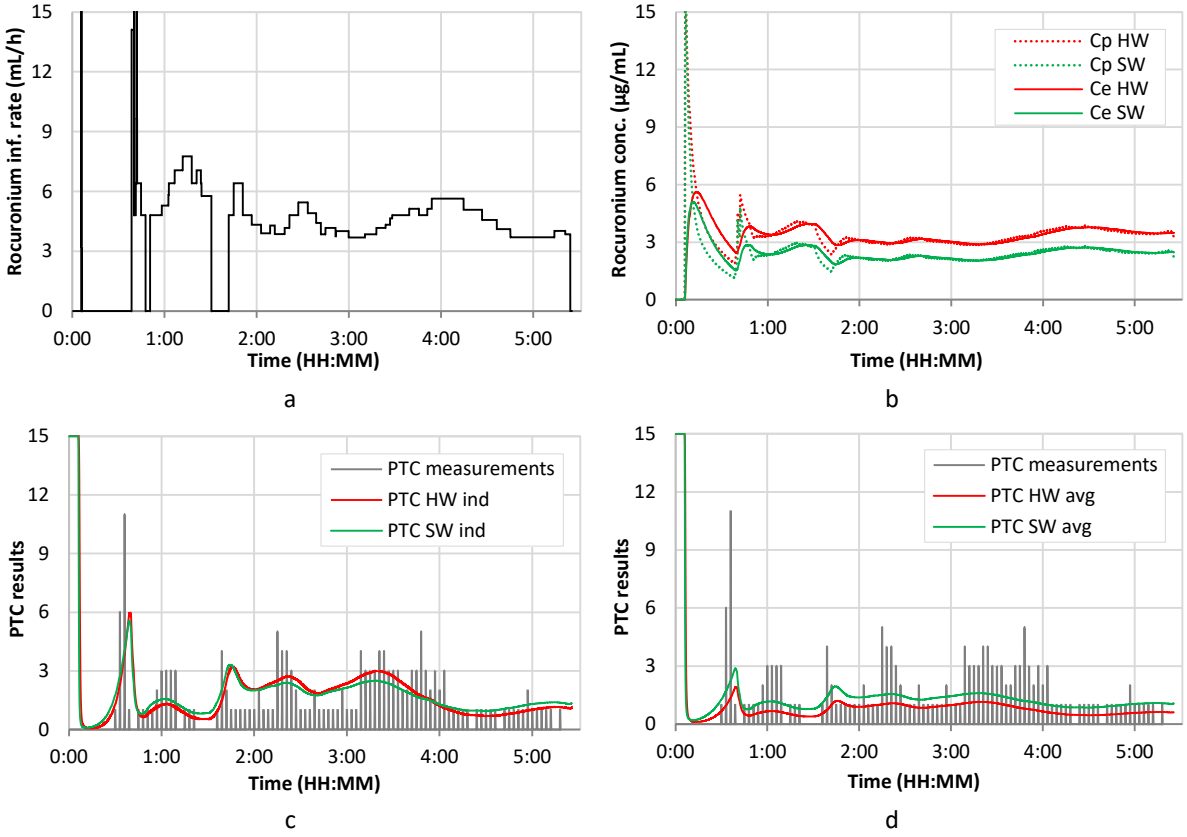


Figure 4.4 – Example of a patient NMB performance including a) rocuronium infusion rate (mL/h); b) calculated rocuronium *Cp* and *Ce* (µg/mL) according to each PK model; c) PTC observed measurements *vs.* predicted PTC effect based on the individually estimated PD parameters (Ce_{50} and γ) for each model; and d) PTC observed measurements *vs.* predicted PTC effect based on the average PD parameters (Ce_{50} and γ) of each model, during a surgical procedure. *Cp* – rocuronium plasma concentration; *Ce* – rocuronium effect-site concentration; HW – Haes-Wierda PK model; SW – Saldien-Wierda PK model; PTC – post-tetanic count.

Table 4.5 - Prediction error of the estimated PTC effect, obtained from Saldien-Wierda (SW) and Haes-Wierda (HW) pharmacokinetic models combined with individual and average pharmacodynamic parameters, for the study population (n = 30). Results as mean (95 % CI).

	PTC_{SW}^{ind}	PTC_{HW}^{ind}	PTC_{SW}^{avg}	PTC_{HW}^{avg}
MDPE	-0.24 (-0.36 to -0.12)	-0.14 (-0.26 to -0.03)	-0.33 (-0.76 to 0.09)	-0.29 (-0.86 to 0.27)
MDAPE	0.67 (0.54 to 0.81)	0.63 (0.49 to 0.76)	1.00 (0.70 to 1.30)	1.18 (0.78 to 1.58)
Wobble	0.53 (0.43 to 0.63)	0.53 (0.44 to 0.63)	0.69 (0.54 to 0.84)	0.70 (0.54 to 0.86)

Abbreviations: PTC- Post-tetanic counts; MDPE - median performance error; MDAPE - median absolute performance error.

4.2.3 FINDINGS AND DISCUSSION

As performed in the previous study, the rocuronium used by the population included in this study was recalculated for the TBW reference. Likewise, the corresponding amount of rocuronium administered at the induction shows a small increase over the standard dose. Appropriate intubation conditions were achieved for all patients, which promptly attained the complete NMB (PTC = 0).

The time interval between the induction bolus and the start of infusion was established to be at the recovery of PTC measurements. The time to detect recovery of the first PTC was within the expected duration, in agreement with previous studies [20].

The mean rocuronium demand during infusion was 0.56 (0.18) mg/kg/h, consistent with the recommended ranges of infusion for the NMB degree maintenance [113, 121]. Although the mean percentage of PTC responses measuring within the NMB target was not as accurate as expected, it provided a satisfactory fit for this analysis.

Regarding the PK-PD modeling methods, a parametric approach was used to calculate the estimated effect-site concentrations, which was established based on the principles of a three-compartment model for PK, combined with an effect compartment relating to the PD (Figure 2.2) [45, 49].

From the combination of each model's parameters, *Cp* of rocuronium was estimated throughout each surgical procedure. Then, the *Cp* relationship with *Ce* was also calculated, based on the corresponding inter-compartment rate constant k_{e0}. Previous studies have demonstrated that the k_{e0} parameter can only be used with the PK model from which it was derived, and that small changes to it do not lead to significant changes [159, 163].

To create the pharmacodynamic model, the standard approach to describe the concentration-effect relationship in anesthesia was used, which is based on the "Hill equation" concept. This is a model framework well accepted to describe the NMB [49, 160]. The PK study was linked to the PD based on established assumptions for the E_0 and E_{max} parameters, which were restricted to the range limits of the PTC evaluation scale.

The regression analysis performed to individually determine Ce_{50} and γ parameters resulted in an approximate prediction of the PTC effect for both models. However, when comparing to the observed PTC measurements, although both approximate to 0, the MDPE of the HW model showed a smaller bias. Also, both models exhibited negative bias, indicating the estimation was mostly above the measured values. From the MDAPE assessment, a similar approximation in both PK-PD models was perceived, with a slightly smaller deviation from the target in the HW model over the SW model.

Wobble values prove the equal within-subject variability in PE for both models. Overall, the individual PK-PD study showed similar performance for both models.

The population mean (SD) values of Ce_{50} and γ obtained for each model show a significant statistical dispersion, indicating these parameters are distributed over a wide range. Furthermore, these results show some approximation to the Ce_{50} and γ reported by the source studies of Saldien V. and De Haes A. (0.954 µg/mL 2.9; 1.65 µg/mL 4.28 respectively). Although it has been suggested that modifying the γ does not affect the effect outcome (in non-deep NMB) [160], this agreement is rather not expected for Ce_{50} for the deep NMB. In other words, considering a deeper level on NMB, the Ce_{50} for the PTC is likely to be higher than the Ce_{50} determined for ST or TOF responses used in the source studies.

Despite this interpretation, the resulting mean values of Ce_{50} and γ were used to recalculate the PTC effect for all subjects. From the analysis of the difference between the PTC_{SW}^{avg} and PTC_{HW}^{avg} with the measured PTC responses, MDPE indicates a similar bias for both models with a small negative difference from the observed measurements (although not significantly different from zero as the 95 % CI shows). In turn, the MDAPE reported a deviation of approximately 1 PTC inaccuracy in the prediction of the PTC effect, with the PTC_{SW}^{avg} model showing a slightly better result. Likewise, for this data, the intra-individual variability assessment showed a similar outcome for both models. Overall, there was an acceptable agreement between both average models and the measured results. Although the MDPE is not centered in zero, it is within the 95 % CI interval, indicating that there is a possibility of improving these results with more clinical data.

This study's primary purpose is related to the potential application of these PK-PD models with drug administration, such as TCI for rocuronium. Additionally, the linking of this TCI approach with a closed-loop system may allow the evaluation of the difference between the predicted and observed measurement, which can enable the adjustment of the model's parameters to accurately adapt infusion and ensure the maintenance of the desired deep NMB target.

4.2.3.1 Limitations

Some PK models developed for rocuronium have not been included in this study for several reasons. McCoy E. [165] and Kleijn H. [18] PK models use a two-compartment approach. Magorain T. model [17] neglects body weight as a covariate for the PK model. Szenohradszky J. [15], Alvarez-Gomez J. [16], and Cooper R. [19] studies did not report the equilibrium rate constant between central and effect compartments (k_{e0}), which is essential for estimating the *Ce* and, consequently, the pharmacodynamic outcome. Trials were conducted to include the k_{e0} variable in the coefficient

estimation, using the proposed non-linear least square method; however, the regression analysis performed poorly, therefore being rejected for this study.

The findings of this study should be interpreted within the limitations of the approach and the population included. The PK models included were previously studied and developed based on smaller amounts of rocuronium administered and non-deep levels of NMB. For the current approach, it must be taken into account, that the assessment of the degree of NMB is subject to the limits of PTC monitoring, which can affect the PK-PD modeling outcome.

4.3 CHAPTER OVERVIEW

An investigation study was conducted at CHUP for patients undergoing deep NMB during surgical procedures. From the data gathered, it was possible to conduct a study comparing two equivalent acceleromyography-based NMB monitors often used in routine practice, the TOF-Watch® SX and the TOFscan®. Findings suggest that for deep NMB, the TOF-Watch® SX and the TOFscan® have contrasting sensitivity when rocuronium plasmatic concentration changes significantly - onset and recovery stages - and an approximate difference between measurements of 1 Post-tetanic count in the maintenance phase.

Additionally, a study of the rocuronium pharmacokinetic-pharmacodynamic relationship in estimating the post-tetanic count effect for the maintenance of deep NMB was addressed. To accomplish this goal, a non-invasive approach was considered to evaluate the accuracy of effect prediction during de NMB, based on two PK models from the literature. Findings indicate that it is possible to obtain an acceptable estimation of the PTC effect; however, further studies should be conducted for optimization purposes, including population inter-individual variability analysis. Nonetheless, the PK-PD models' ability to predict the effect may provide some insight on rocuronium administration during routine clinical practice, specifically to improve the maintenance of the desired deep NMB.

5 CLOSED-LOOP CONTROLLER FOR DEEP NMB

In recent years, critical advances in automated drug infusion have been introduced, with feedback strategies to control the patient's anesthesia. A paramount advantage in investigating the control of the neuromuscular blockade, specifically using rocuronium, is related to the fact that there is no explicit interaction between the NMBAs with the habitual hypnotic drugs and opioids. Thus the study of the NMB regulation can be carried out separately from the hypnosis and nociception control.

The use of closed-loop systems in drug delivery has significant benefits to the anesthesia practice by being consistent, performing analysis of the response, and act based on structured data models. Thus, by employing a variety of control methods, these systems are reactive, predictive, individually adaptive, and safe. Additionally, it allows the anesthesiologist to focus on higher-clinical tasks and decisions. A closed-loop control system for the maintenance of deep NMB was designed and developed, named the RelaxAn (*'Relaxed Anesthesia'*).

5.1 CLOSED-LOOP CONTROL METHODS

During general anesthesia, the NMB drug administration must consider different parameters for each patient, yet each case is different, and the response to the same drug may vary. Several closed-loop systems have been proposed to tackle this issue and improve the amount of drug delivered, allowing for variation in the individual's response to the drug, with minimum recovery time [58, 165].

In the last decades, the techniques that have been proposed for the computer-controlled infusion of NMBA, couple the data information from a syringe pump and a neuromuscular function monitor, to automatically compute the measured parameter and use an algorithm designed to convert the difference between the measured and the target effects into a new dose or infusion rate adjustment.

Two main classes of algorithms have been described: the direct closed-loop systems and the PK-PD modeling approach. Direct closed-loop systems are model-free, adjust the dose to minimize the difference between the target and the measured NMB degree, without any assumption about a mathematical relationship between dose and effect [167]. The PK-PD approach calculates the dose or infusion rate according to a model that describes the relationship between dose, concentration, and effect. Through this method, the dosage is adjusted to minimize the difference between the target and predicted NMB. These are usually used via TCI techniques. When the NMB measurement is included in the algorithms' input, the model can be improved by adjusting some of its parameters, which can minimize the difference between the predicted and the measured values [45].

5.1.1 TECHNIQUES AND CONTROLLERS FOR THE NMB

Many studies have been performed, aiming to understand the suitability of different closed-loop control techniques [168]. Some approaches, based on PID control (proportional, integral, and derivative), have been investigated and analyzed, applying different methods to determine the desired parameters (*e.g.*, fixed-parameter, on-line auto-calibrated, multiple-model switching) [168–170]. All show high stability and system adaptation to different individual requirements and patient dynamics [171–173].

The use of a classical PID scheme with feedback control has been one of the most used methods in the field. However, the human body is a highly nonlinear system, and during the anesthesia, it might experience adverse situations, limiting the performance of a traditional PID controller. Other techniques have been proposed to tackle this issue and reliably control these nonlinear systems, such as fuzzy logic and neural network controllers [174–179]. The effectiveness of these approaches showed favorable results for control application and could easily be adapted to different NMBAs.

Since the first closed-loop control system for NMB was proposed in 1980 by Brown [181] (using pancuronium), many others have been studied over the years, proving the interest on such a solution for the anesthesiology field [181–184]. Early in 2004, Mendonça T. introduced *Hipocrates*, an automatic system for controlling the NMB via the continuous infusion of a non-depolarizing NMBA, which has been extensively validated. This system was based on incorporated PID control strategies and online adaptation to the individual requirements/ characteristics, showing advanced robustness [186]. In turn, *McSleepy* is a closed-loop system developed to provide anesthesia for induction, maintenance, and recovery by controlling the depth of hypnosis based on the BIS, the analgesia based on the Analgoscore, and the muscular relaxation using phonomyography. This system detects deviations of TOF-ratio over 25 % and gives the anesthesiologist the option to administer a bolus or not [186, 187]. Additionally, Janda M. *et al.* combined the control of BIS-based depth of hypnosis and

muscular relaxation from EMG assessment, using decentralized MIMO control (Multiple-Input Multiple-Output). Through this approach, for the NMB, a model-based predictive controller was used, aiming to ensure a *T1* target of 10 %, via infusion of mivacurium [189].

From these investigations, it is possible to conclude that several experimental control and assistance systems have been successfully validated and implemented for the NMB; however, they are not widely accepted for routine practice. The reasons for this include technical problems regarding the signal quality, the need for plausibility checks to rule out artifacts, and user-friendliness [189]. Besides that, all approaches and developed systems found in the literature focus on the control of non-deep NMB.

5.1.2 CONCEPTION AND DEVELOPMENT OF RelaxAn

For the design and development of a control system to improve the maintenance of deep NMB during surgical procedures, two fundamental requirements were preserved for safety reasons:

1. the induction dose was set to 1 mg/kg of FFM to rapidly guarantee optimal intubation conditions and promptly attain the complete block (PTC = 0), and;
2. the rocuronium continuous infusion starts only at the recovery of at least two positive PTC measurements.

Taking these conditions into consideration, three main parameters were studied: the expected time from the induction bolus until recovery of the first PTC; the starting rate of the continuous infusion, and; the adequate rate adjustments to perform throughout the procedure to maintain the deep NMB. For the estimation of the time of the PTC response recovery and the starting rate of the continuous infusion, a regression analysis was performed for the data obtained in the clinical study previously conducted (chapter 3). In turn, a closed-loop control system is proposed for the adjustments of the infusion for the maintenance of deep NMB.

5.1.2.1 Regression analysis for early indicators

The kinetic parameters after induction bolus can provide information on the patients' speed of distribution and absorption of rocuronium [190]. They also provide information that can help to predict the dynamic behavior during deep NMB. Thus, with SPSS (version 35 IBM ® SPSS® Statistics, Endicott, USA), automatic linear modeling regression was used to predict one or more variables based on linear relationships, considering one or more input variables from the induction of the deep NMB.

One of the first parameters of interest was the estimation of time to recover the first positive PTC after the induction bolus. SPSS regression analysis was conducted, where no strong relationship was found between the patient variables and the duration to recover from the complete blockade.

Concluding, from the results for the population studied, anesthesiologists may expect the recovery to occur after approximately 26.7 (13.3) minutes after the initial bolus (data evaluated for n = 36).

Secondly, the starting rate of the rocuronium continuous infusion was also analyzed. Results showed an accuracy of 84.1 % (including the data of 33 patients, seven were excluded for incomplete or error of data) to predict the initial infusion rate:

$$u(t)_{START}\ (\mu g/kg/min) = -0.021 \times t_{START\ inf} + 673.669 \times \frac{(PTC_i - PTC_{i-1})}{(t_i - t_{i-1})} - 0.079 * t_{ST10\%} + 77.691 \quad \text{Eq. 9}$$

In which $u(t)_{START}$ is the start rate infusion (µg/kg/min), $t_{START\ inf}$ is the time duration in seconds since the initial bolus until the infusion is being started. Calculating the gradient slope of the PTC recovery before initiating infusion, PTC_i is the last PTC measure before the infusion is started, and PTC_{i-1} refers to the PTC measured before that, and $(t_i - t_{i-1})$ is the respective time interval between these PTC responses (in seconds). The duration in seconds after the initial rocuronium bolus until measuring a Single-Twitch of 10 % is represented by $t_{ST\ 10\ \%}$.

5.1.2.2 Control of rocuronium infusion

From the data obtained in the clinical study, it was possible to measure the populations' rocuronium demand during the procedure. From the volumetric discharge to attain the target 1-2 PTC response, an approximation of the infusion demand can be plotted for each patient (see Figure 5.1).

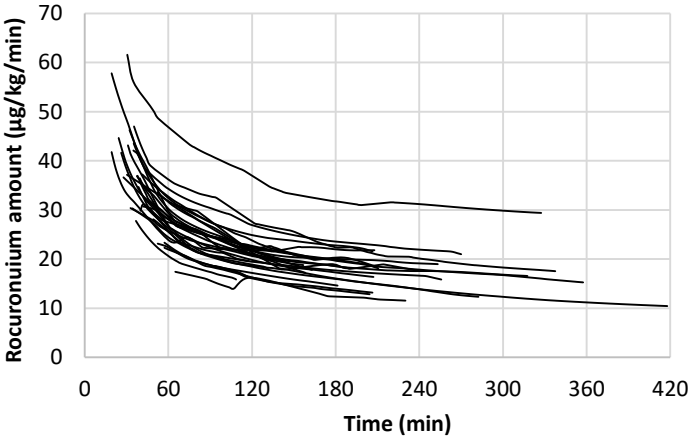


Figure 5.1 - Rocuronium infusion demand for each patient for maintaining 1-2 PTC, obtained from the clinical study.

From the profile of the curves, a pattern can be visibly recognized. The high initial rocuronium demand is related to the fact that when the infusion was initiated, the recovery from the initial bolus was still ongoing; therefore, there is a need for an additional amount of NMBA to suppress that recovery. This overturns usually requires some time to resume and ensure the desired PTC response.

Aiming to regulate and personalize the rocuronium infusion during deep NMB and ensure the blockades' stability, a closed-loop approach was proposed and is illustrated in Figure 5.2.

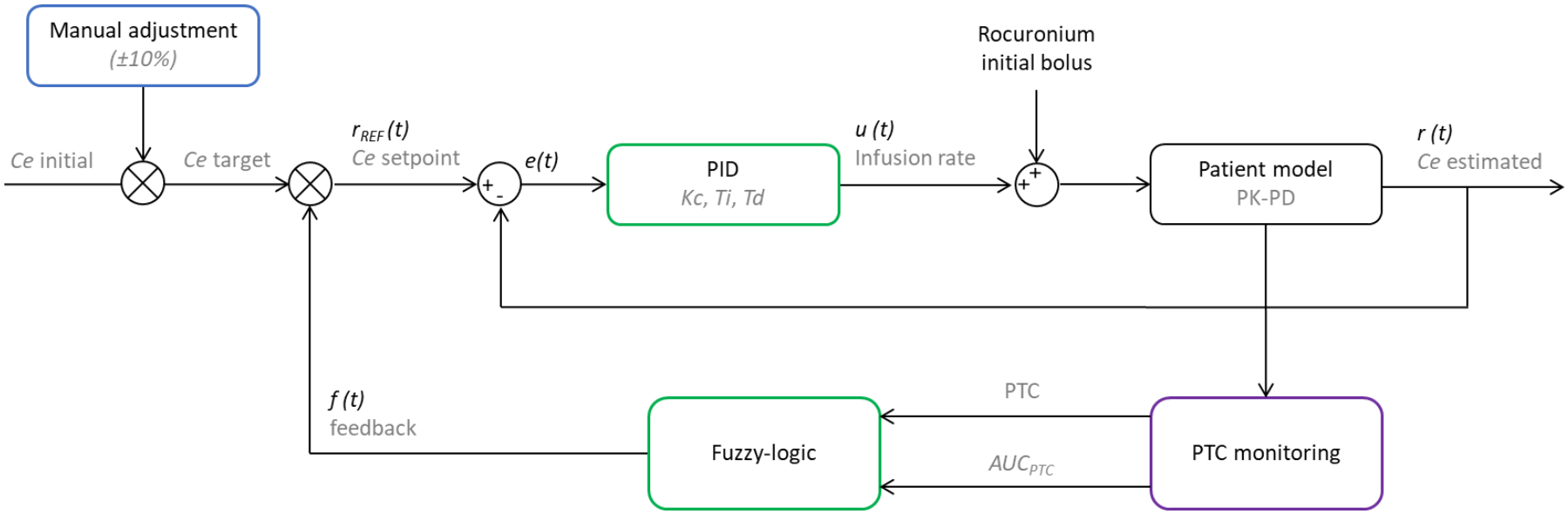


Figure 5.2 - Proposed closed-control structure for the personalized administration of rocuronium during deep NMB. *Ce* – effect-site concentration; $r_{REF}(t)$ – set-point value of *Ce* for PID control; *e(t)* – calculated error for PID control; *Kc* - proportional gain of the controller; *Ti* - specifies the integral time of the controller; *Td* - specifies the derivative time of the controller; *u(t)* – infusion rate output; *r(t)* – feedback process variable for *Ce;* AUC_{PTC} – Area under the curve calculated from post-tetanic count response; *f(t)* – fuzzy-logic feedback output value.

Based on the technique of TCI systems, the administration of the drug was design to be guided to achieve a desired effect-site concentration, taking into consideration the results from the PK-PD modeling conducted in section 4.2. In that study, the average SW model showed a slightly better performance in the estimation of the PTC effect; therefore, it was chosen to be integrated into the control system design. By including the PK-PD model in the control algorithm, according to the administered rocuronium and the patient weight, the individual's estimated *Cp* and *Ce* can be continuously estimated, as well as the predicted PTC effect.

One of the most indicated techniques for the closed-loop control of rocuronium infusion for deep NMB is to apply a PID controller. To adjust the infusion rate, PID relies on the deviation error (which corresponds to the difference between the target and estimated values) over time and its trend. For the control system, the objective of the PID included is to determine the rocuronium infusion based on the difference between the target and estimated effect-site concentrations. Aiming to attain a degree of NMB ranging from 1-2 PTC, the default value for the initial effect-site concentration is determined by the inverse calculation of Eq. 7 for a PTC_{target} = 1.5 (considering Ce_{50} of 0.879 and γ of 2.912, initial *Ce* is 1.87 µg/mL). The PID control was designed and tuned to ensure adequate adjustments of the rocuronium infusion to achieve and maintain the desired target. Thus, the PID parameters are crucial for defining the performance of the system. *Kc* (µg/min) determines the output response rate for the error input by returning the proportional gain of the controller, *Ti* (min) returns the sum the of error as integral time, and *Td* (min) is proportional to the variation rate of the process variable specifying the derivative time. Appling a simplified approach to achieve a satisfactory PID control, the parameters were estimated based on the results reported in Merigo *et al.* [173], which proposed a PID control algorithm for the automatic regulation of the NMB level. After achieving a steady-state oscillation process, an accurate advanced automatic tuning was performed in LabVIEW.

The auto-tuning process for PID control considered a step closed-loop technique. From the tuning conducted, the proportional, integral, and derivative parameters results are presented in Table 5.1.

Table 5.1 - PID parameters obtained from advanced automatic tuning in LabVIEW for the average SW PK-PD model.

Control parameter	**TCI for SW model**
***Kc* (µg/min)**	59.758
***Ti* (min)**	2.827
***Td* (min)**	0.707

Standard rules for PID controller tuning have been indicated has not suitable for the NMB control due to the complexity of this process [173]. Nonetheless, these values showed very good performance in the simulations conducted, considering the control specifications of the clinical approach (*i.e.*, initial bolus followed by continuous infusion at recovery from complete NMB), achieving as fast as possible

the desirable target, without excessive overshoots or undershoots, and avoiding major oscillations of the output variable (rocuronium infusion rate).

At this point, a TCI system for the personalized administration of rocuronium during deep NMB is completed. Nonetheless, it must be taken into account the possible inaccuracy of the PK-PD model performance. To tackle this issue, in parallel, the NMB monitoring of PTC responses was consistent with the previous approach and performed every 3 minutes in TOF-Watch® SX, during the duration of the surgical procedure, providing feedback to the system (Figure 5.2).

It must be kept in mind that the control system's task is to maintain the NMB degree between 1-2 PTC responses. Knowing the patients' response to muscle relaxants is highly variable, a fuzzy-logic control was indicated to adapt the system according to the difference between desired and measured monitoring results [191]. Also, the AUC_{PTC} provides additional information regarding the trend of the effect during the procedure. Thus, this valuable parameter has proven to have great potential in guiding the administration of rocuronium during maintenance of the deep NMB. In that sense, for the current proposal, the values of the response of PTC and respective AUC_{PTC} are assessed, providing the feedback from the error, and stability is restored by acting on the Ce_{target}, subsequently promoting adjustments to the infusion.

To define the relationship between the fuzzy-logic control input and output, a set of rules was determined based on the data acquired in the clinical study regarding the PTC and AUC_{PTC} evaluations. A total of 2338 PTC measurements were assessed and classified according to the range of the PTC response and corresponding AUC_{PTC}, in order to be implemented in a fuzzy-logic controller in the LabVIEW programming environment (fuzzy system designer report in appendix 8.6). For the input variables, six membership functions were defined based on the deviation from the target of 1-2 PTC and the corresponding range of AUC_{PTC} value (Table 5.2).

Table 5.2 - Membership function classification for the fuzzy-control system. Mean (range) values of AUC_{PTC} for the range of PTC measurements performed in 35 patients using TOF-Watch® SX.

Membership function	**PTC responses**	***AUC*$_{PTC}$**
Null	0	0
Good	1-2	4.12 (1.54-11.37)
Low	3-4	14.67 (10.79-23.29)
Mid	5-7	33.72 (24.33-48.75)
High	8-10	62.05 (54.53-71.50)
Huge	11-15	91.12 (81.32-99.73)

The output of the membership functions was defined based on the previous clinical trial (described in section 3.1.1) results, taking into account the data from the deep NMB group. For this group, the NMB

was maintained by continuous infusion, and an additional bolus of rocuronium would be administered if the monitoring response greatly deflected from 1-2 PTC. Although the data sample was not significant to allow strong conclusions to be drawn, the PTC depression effect caused by the additional doses was analyzed. Results showed a mean (SD) approximation of 0.022 (0.014) mg/kg are required to decrease 1 PTC, which corresponds to an estimated variation of 0.157 µg/mL of the *Ce* for the SW PK-PD model. Taking this into consideration, according to the difference between the measurement and desired values (error), a rough proportional approximation for each membership function was determined and included in the fuzzy-logic controller considering a simple multiple-input single-output (MISO) fuzzy system. The result of this combination produces a numeric representation that supports the determination of adequate infusion adjustments.

The fuzzy-logic evaluates the output value according to both input variables, PTC and AUC_{PTC}, and the rules of the fuzzy controller. Additionally, to avoid hazardous changes to the rocuronium infusion that could result from a monitoring or OCR error, two conditions were added to the control system. First, the input from NMB monitoring included the mean of the last two measurements (for both PTC and AUC_{PTC}). Secondly, if the difference between two subsequent PTC measurements was equal or over five responses, confirmation was required to validate/erase that unbalanced result.

Ultimately, after each PTC stimuli, the input variables of the monitoring are assessed by the fuzzy-logic control, whose output value is used as a coefficient of Ce_{target} (proportional to the error between the measured response and the desired monitoring target), thus providing feedback to adjust $Ce_{setpoint}$ accordingly. At this point, if deviations from the desired 1-2 PTC responses are monitored, the PID controller evaluates the error between the newly adjusted $Ce_{setpoint}$ and the current estimated *Ce*, performing the proper changes to the rocuronium infusion rate and restore the intended NMB degree.

5.1.2.3 Protocol and implementation in the interface

A very straightforward protocol was defined and implemented in the acquisition interface, based on the previously described concepts and development conditions. Summarizing, an initial bolus of 1 mg/kg of FFM is administered, and in parallel, the NMB monitoring is recorded. Starting with ST and after ensuring TOF = 0, tracheal intubation was performed, followed by continuous PTC stimuli every 3 minutes. After the recovery of at least two positive PTC measurements, the rocuronium infusion is initiated at a rate individually calculated (following Eq. 9). At the same time, the closed-loop control system for rocuronium infusion starts, automatically performing adjustments to the infusion in order to maintain the desired effect measurements of 1-2 PTC.

One of the most critical concerns in automatic systems in health care is safety. Besides the continuous supervision by a researcher of the overall system performance and patient status, additional functionalities were included to ensure the adequate processing of the computational system. First, the initial infusion rate was also defined as the maximum velocity of infusion as a safeguard measure against irregular output. Secondly, as a preliminary and experimental study, activation of the control system, as well as all the changes and adjustments to the infusion approach, require validation by the anesthesiologist in charge to proceed, taking his/her experience and judgment regarding the best approach for the patient care. The system can be ceased at any instant (see Figure 5.3). At this point, the RelaxAn system is complete.

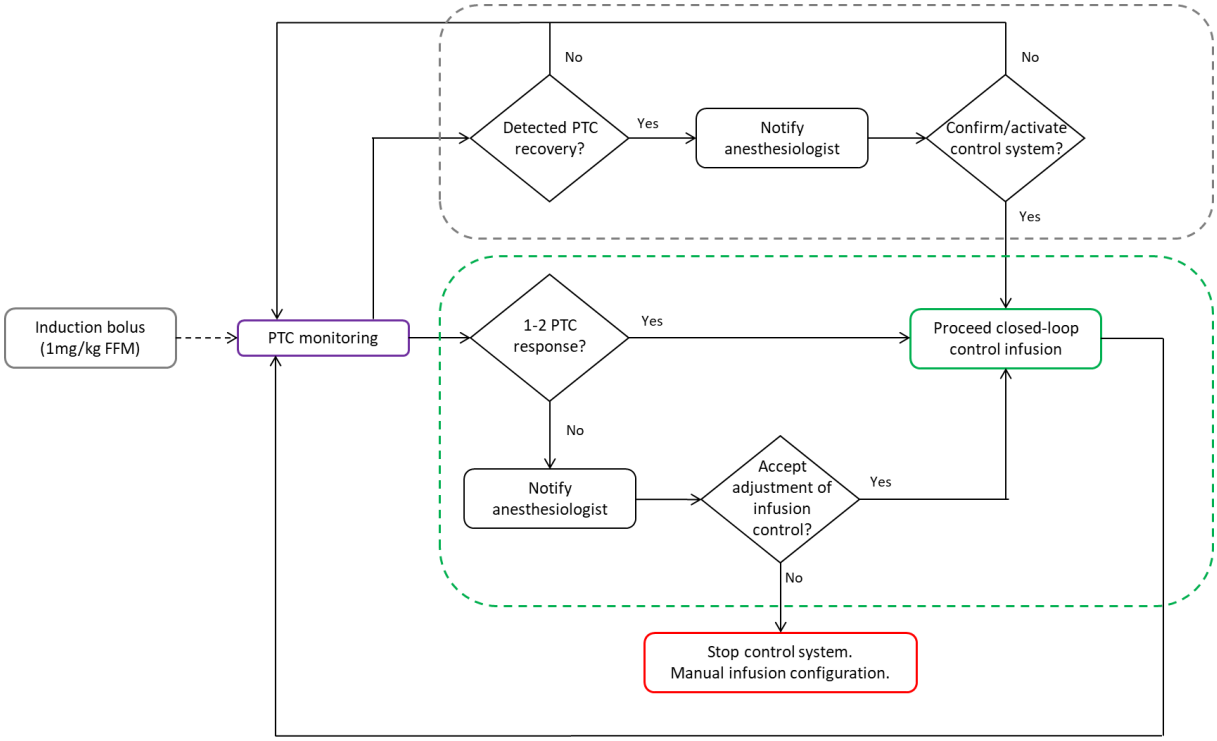


Figure 5.3 - Data acquisition protocol for closed-loop control for deep NMB. After confirmation to initiate continuous infusion (grey dashed box), the closed-loop control is initiated and semi-automatically regulated by the anesthesiologist (green dashed box).

It must be mentioned that the system was initially tested over several patients, during which it was continuously checked for additional improvements to achieve an optimized version.

The accomplishment of a control approach to individualize the rocuronium administration during deep NMB corresponds to the completion of phase 2 of the clinical protocol proposed for this research (refer to section 3.2.1).

5.2 PRELIMINARY STUDY OF RelaxAn SYSTEM

After the development of the closed-loop control system for deep NMB, experimental testing was performed for patients scheduled for routine general anesthesia with a minimum duration of 90 minutes. The current protocol enforced the routine clinical practice with all monitoring based on standard ASA guidelines and considering the same conditions of the clinical study previously conducted. This study corresponds to the preliminary testing of phase 3 of the research protocol proposed (detailed in section 3.2.1).

5.2.1 ANESTHESIA AND MONITORING METHODS

The NMB anesthesia and monitoring methods were the same for this study phase, except at the detection of recovery of at least two PTC measurements, RelaxAn was initiated to control the infusion, being guided by the feedback from TOF-Watch® SX monitor's responses. Likewise, the aim was to maintain the target range of 1-2 post-tetanic counts. By taking the error associated with the PK-PD model performance into account, in case of persistent deviations from the target values, the reference effect-site concentration could be manually adjusted ± 10 % ($Ce_{initial}$) during the procedure, to better fit each individuals' variability. Data acquisition of the TOF-Watch® SX monitor as well as from the rocuronium infusion pump were recorded in real-time to the same laptop. At the end of the surgery, propofol and rocuronium infusions were ceased, and reversal was carried out with sugammadex. Extubation was performed when the TOF-ratio > 90 %.

5.2.1.1 Data analysis

The reporting of the results includes patient data (age, sex, ASA class, TBW, height, BMI, FFM), induction dose and mean infusion rate of the rocuronium used, durations of the procedure's induction and maintenance phases, as well as the main NMB monitoring indicators (time to onset, time to detect PTC recovery). The primary outcome to be assessed is the stability of the NMB response in achieving and maintaining the 1-2 PTC range. First, the time required to achieve the PTC target after the start of the continuous infusion, and the percentage of responses within and out of the 1-2 PTC range during the procedure, were assessed. Secondly, the number of manual adjustments performed to rectify the Ce_{target} was also recorded. All analyses were performed using the GraphPad Prism software (GraphPad PRISM Software, Inc., version 8.4.0, San Diego, CA, USA). Ultimately, a patients' case report is presented as an illustration of the RelaxAn systems' performance.

5.2.2 RESULTS OF THE EXPERIMENTAL TESTS

Data from eight patients were included in this preliminary testing. Demographic data, rocuronium used, and the duration of the experimental test main stages are presented in Table 5.3 and Table 5.4.

After the detection of the recovery of at least two PTC responses, the continuous infusion was started and guided by RelaxAn feedback system continuously. As the closed-loop control was initiated when the *Cp* and *Ce* of rocuronium are decompensated by the NMB degree gradual recover, the system is expected to suppress this deflection, achieve the 1-2 PTC target as soon as possible and ensure its maintenance. The mean (SD) time required by the RelaxAn system to reach the NMB target after the start of the continuous infusion was approximately 13.0 (9.6) min. Regarding the maintenance stability of the system, the mean (SD) PTC stimuli measuring 1-2 responses was 80.6 (8.1) % for the remaining duration of the infusion. Deviation under (PTC = 0) and above (PTC > 2) were measured in 5.5 (6.2) % and 13.9 (10.9) % of the measurements, respectively. The mean (range) amount of adjustments (± 10 % of the $Ce_{initial}$) performed during the continuous infusion to ensure the stability of the desired NMB degree was 0.88 (0-7) per surgery, for this dataset.

Table 5.3 - Patient demographic characteristics data.

Patient sample size		n = 8
Age		58.8 (11.2)*
Sex	**Male**	4
	Female	4
ASA class	**I**	2
	II	4
	III	2
True Body Weight (kg)		69.8 (10.6)*
Height (cm)		164.9 (10.9)*
Body-mass index (kg/m^2)		25.6 (2.7)*
Fat-free mass (kg)		48.4 (10.6)*

*Results expressed as mean (SD).

Table 5.4 - Rocuronium dosing and duration of the induction and maintenance phases. Results expressed as mean (SD).

Induction phase	**Rocuronium induction dose (mg/kg)***	0.69 (0.08)
	Time to detect TOF = 0 (min)	1.6 (0.6)
	Time to detect PTC recovery (min)	23.0 (9.7)
	Duration of induction phase (min)	25.7 (7.3)
Infusion phase	**Rocuronium via continuous infusion (mg/kg/h)***	0.64 (0.18)
	Duration of infusion phase (min)	201.5 (94.2)

*Reference to TBW

5.2.2.1 A case report of RelaxAn application

Aiming to illustrate the performance of the RelaxAn systems' application, the process and results of a patient-case are described and presented below (see Figure 5.4). The example case refers to a female patient with FFM of 39.1 kg, that received a rocuronium induction bolus dose of 0.63 mg/kg (a reference to TBW). This dose provided good intubation conditions, monitoring TOF = 0 after 2.2 min, and providing a complete block, with PTC responses equal to zero, during 22.1 minutes. After the recovery of positive PTC responses, the continuous rocuronium infusion was started and regulated by the closed-loop controller for approximately 96.2 min. No manual adjustments were required for the duration of this procedure.

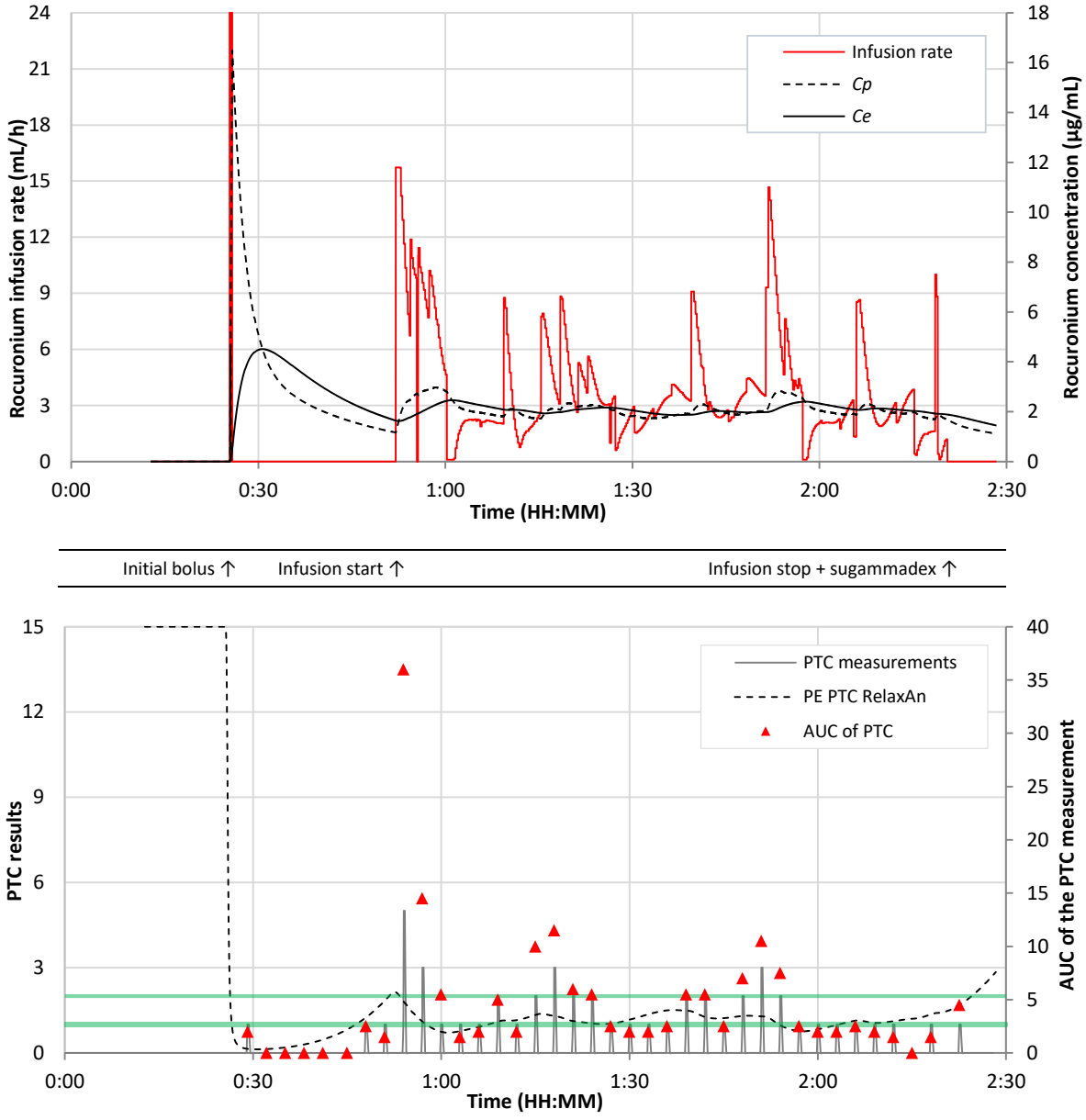


Figure 5.4 - Illustration of patient's NMB procedure with RelaxAn system throughout the surgical procedure. Graphic representation of rocuronium infusion, estimated plasma and effect-site concentrations (upper chart), as well as PTC measurements, corresponding AUC_{PTC}, and estimated PTC effect based on the average SW PK-PD model (bottom chart).

After initiating the continuous infusion, the time required to reach the PTC target was approximately 7.9 min (after 2-3 PTC measurements). From this point on, deviations from the desired target were rapidly tackled by the system, restoring the aimed NMB degree. Monitoring results show the accuracy of 1-2 PTC responses in 89.7 % of the measurements performed. At the end of the surgery, rocuronium infusion was stopped, and recovery of the NMB was performed with 3.22 mg/kg of sugammadex. TOF-ratio > 90 % was detected after 3.9 min. The patient was extubated with no complications.

5.2.3 FINDINGS AND DISCUSSION

For the conception and development of the RelaxAn system, two main conditions were fundamental for the study protocol. First, the initial bolus should always guarantee the quick depression of the NMB transmission to provide the appropriate condition for the tracheal intubation; therefore, the defined 1 mg/kg of FFM dose was preserved in this study phase. Secondly, continuous infusion control should be based on the NMB monitoring at all times, which implies that the infusion would only start at the detection of PTC recovery, consequently requiring to rapidly counterbalance the prompt NMB recovery occurring and then ensure the maintenance of 1-2 PTC.

In this preliminary study, data from eight patients were collected. Summing up, for these patients, after the initial bolus dose, the time to detect the onset and the time to detect the recovery of PTC monitoring was within the expected durations, in agreement with previous studies [20]. After starting the continuous infusion, the time needed for the NMB to achieve the desired 1-2 PTC responses was relatively quick. NMB monitoring results during the maintenance phase, show that RelaxAn system was able to provide improved accuracy in guiding the rocuronium infusion and ensuring the stability of the desired NMB degree throughout the surgical procedures. Results indicate the responses within the desired 1-2 PTC range target increased by approximately 15 % and required much less manual adjustments.

The amount of NMBA used was slightly higher than the mean recommended dose for the induction and maintenance of this NMB degree and comparatively to the demand reported in the clinical study, where the adjustments were manually performed. In turn, this result shows some agreement with the review study findings (section 2.2), yet not as high as other studies reports for the same PTC target range.

Despite these results, in some patients, there was still a need to perform manual adjustments to compensate for the PK-PD modeling inaccuracy. Further optimization and testing of this tool are crucial to obtain a more complete, user-friendly, advisory system and deliver an advanced solution that can be used in routine general anesthesia.

Although it was not the focus of the study, it should be pointed out that, for all the procedures in which RelaxAn was tested, both surgical and anesthesia professionals reported very satisfactory results. The main remarks included the excellent surgical field, the little demand in propofol and remifentanil use, and the continued stability of patients' conditions throughout the surgeries. Follow up interviews are recommended as further studies to support these reports. The case report presented is an illustrative example of these observations and shows the promising potential of the RelaxAn system for routine clinical practice.

5.3 TECHNOLOGY DESCRIPTION

The current project proposes the development of a technology designed to support anesthesiologists in personalizing and optimizing the maintenance of deep NMB. RelaxAn is the prototype application accomplished. It consists of an advisory system that aims to be used in general anesthesia by integrating the individual's data on rocuronium dosing and monitoring response to perform adequate adjustments to the infusion and ensure the maintenance of the desired deep NMB in a stable and precise manner.

This innovative technology intends to provide a pioneer and improved mean for the maintenance of deep NMB. Currently, there are not known any direct solutions that can be compared to RelaxAn. Therefore, it is a very unique and attractive solution with excellent market potential (Figure 5.5).

Figure 5.5 - RelaxAn introduction and logo.

At this point, the system is composed of hardware components of NMB monitoring and infusion pump integrated with a software component and a user interface that allows the input of information inherent to each patient and the anesthesia.

The user-friendly interface runs the presentation page, syringe configuration process, patient information, and induction setup steps described in appendixes 8.4.1 to 8.4.3. At the start of surgery, the characteristics associated with the patient (weight, height, age, and sex) are entered, as well as

the rocuronium administration setup (drug dilution, induction dose, maintenance after initial bolus). From this information, BMI, FFM, and rocuronium infusion are calculated, the setup is defined, and it is ready to initiate. Currently, the suggested process and parameters to adopt when using RelaxAn follows the previous considerations adopted in the study protocol. Nevertheless, users can choose to change and customize the induction dose and infusion strategy after the initial bolus.

During the induction phase, the anesthesiologist follows the procedure common to general anesthesia administering the hypnotic and analgesic drugs. After the loss of consciousness and subsequent calibration of monitors, the system is ready to perform the rocuronium administration at the maximum infusion rate, ensuring optimal intubation conditions and quick installation of the deep NMB. The main stages of the NMB anesthesia are guided by a message tab (at the bottom of the interface), supported by specific buttons on the system interface, as well as custom registry recordings of other information throughout the surgery (see appendix 8.4).

Alongside this, the assessment of the NMB response must be performed, namely using TOF-Watch® SX. It is suggested to apply the same stimuli methods of the study protocol (i.e., ST, followed by TOF and PTC every 3 minutes). The communication of TOF-Watch® SX Monitor software with the interface is possible via the previously developed OCR approach, which can be validated through manual buttons in the user-interface. Besides the continuous assessment of the NMB degree, this provides crucial information to the personalized control of rocuronium infusion for the maintenance of deep NMB.

Once the recovery of positive PTC responses after the initial bolus is detected and validated by the anesthesiologist, the continuous infusion can be initiated. At this point, the system switches to a semi-automatic mode adjusting the rate accordingly to achieve the Ce_{target} calculated to ensure 1-2 PTC. Additional controls are available in the user-interface for applying changes to the procedure configuration. These options include pause/resume the infusion, increase/decrease Ce_{target} (default is ± 10 %), custom adjustments including additional bolus (in mg/kg of FFM), select duration to pause the infusion, and also directly change the PTC_{target}/ Ce_{target}. At any time, the system can be stopped and be manually regulated by the anesthesiologist responsible (see appendix 8.4).

In conclusion, this system can equate to a TCI for deep NMB coupled with monitoring feedback in a closed-loop technique. By integrating a perfusion syringe control, a neuromuscular monitoring device, and a processing unit, it can individualize the rocuronium administration during the surgery.

5.3.1 FUTURE DEVICE INNOVATION

RelaxAn system preliminary testing was able to provide a successful solution for the maintenance of deep NMB. The next step to the approach is to include feedback information from NMB monitoring along the procedure to provide solid grounds for adjusting PK-PD and/or PID parameters in real-time and refine the patient-specific infusion profile. Additionally, the RelaxAn system may be integrated into a device system that would connect to commercially available NMB monitors, such as the TOFscan®, and syringe pumps connected via a serial cable that allowed to control and maintain the deep NMB during the surgeries. In a complete and upgraded approach, the invention may be embodied in the form of a single device composed of three main distinct parts: 1) a syringe pump; 2) integrated and personalized NMB monitoring (as described in section 3.1.3); and 3) a control display with buttons for user-device interface(see Figure 5.6). Moreover, the device may be connected to a tablet or mobile device to increase the accessibility and quality of the process provided during surgery.

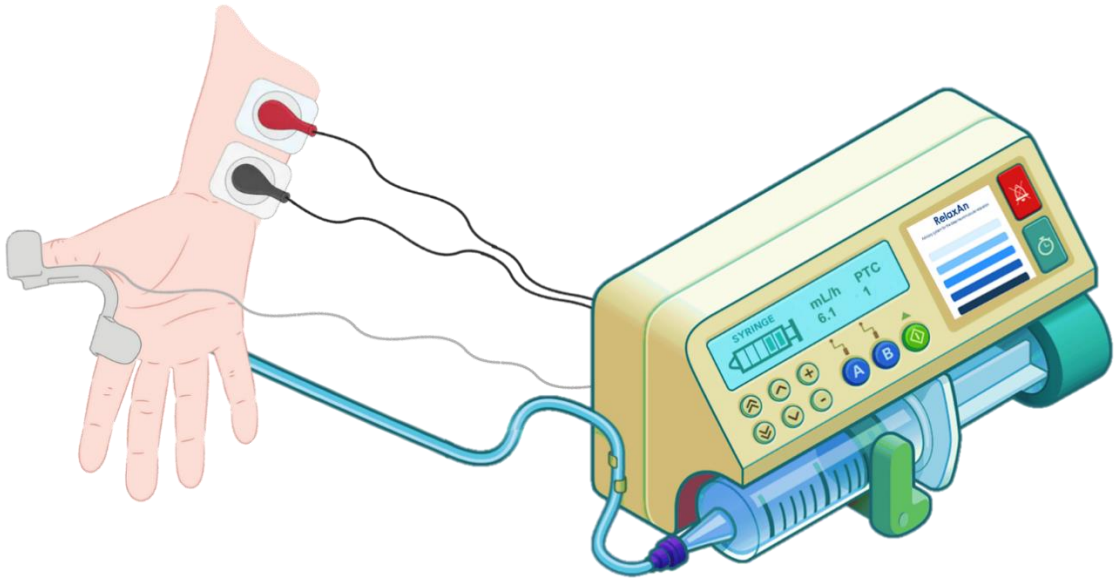


Figure 5.6 - Illustration of the innovative device proposal for the RelaxAn system, embodying all components for the control and maintenance of deep NMB: intravenous infusion of the NMBA via an infusion pump pared with continuous adductor pollicis NMB monitoring,

Such a product would be a reliable and user-friendly device that can be easily applicable to individualize the amount of rocuronium supplied to the patient during anesthesia and take into account the three phases of anesthesia: induction, maintenance, and recovery. The device would be safe to apply in every surgical procedure that uses standard deep NMB. Moreover, this would provide a valuable support tool for regulating muscle relaxation during the surgery. Thus, by performing the rate adjustments autonomously with a secure physical protocol for data communication, some of the anesthesiologists' workload may be removed.

5.4 MARKET ANALYSIS

Given the features and benefits of RelaxAn technology and evaluating the aspects of the product's potential, market dimension, and competition, the most attractive fields to introduce this system are the anesthesiology and pharmacology. Furthermore, from the relation of customer purchasing power and product value, healthcare is the most attractive market.

5.4.1 RelaxAn SOLUTION FOR THE USER NEEDS

The major issue of inadequate administration of NMBA during general anesthesia is the residual paralysis, which can impair the upper airway function and contribute to adverse respiratory events. In 2018, such adverse medical events cost the USA alone 19.5 billion dollars annually in excess [192], and in EU estimates range from €17-38 billion [193].

The main issue reported by the users, already extensively discussed throughout this work, comprises the professionals' untrusting feeling regarding the use of NMB monitoring perioperatively. To address this problem, the RelaxAn system can perform without the feedback input from the NMB response to regulate rocuronium infusion. This way, it provides a solution equivalent to TCI for deep NMB, that can be manually attuned.

Another drawback of the maintenance of the desired NMB degree is the complexity in ascertaining the NMBA demand, even when relying on NMB monitoring [113]. Continuous infusion of NMBA provides an improved solution to ensure a balanced and stable neuromuscular relaxation; however, there is wide variability in the clinical practice, and professionals do not use it very often. Most anesthesiologists administer the NMBA, often via intermittent boluses, and trust the reversal agent to ensure the proper recovery. This procedure may raise two issues, one is the fluctuating NMB, and the other regards the over administration of expensive drugs, which can also delay the recovery and carry disadvantages in terms of costs, schedules, and patient care [112]. In addition to the inherent benefits of coupling the NMBA use with adequate monitoring (which include easier intubation/extubation, better surgical conditions, and reduce postoperative complications); RelaxAn provides important time and cost advantages by reducing improper drug administration, propofol requirements, benefit hemodynamics, and also can improve the use of reversal agents.

Ultimately, anesthesia has often been compared to an aviation cockpit due to the overload of information both jobs have in the different proceeding stages and/or in emergency case situations. To tackle this issue, the RelaxAn provides an intelligent solution to an essential component of anesthesia, ensuring the successful stability in the maintenance of the NMB degree during a surgical procedure.

Therefore, this system is able to remove a concern and additional labor to the anesthesiologist, allowing him/her to focus on other vital tasks (see Figure 5.7).

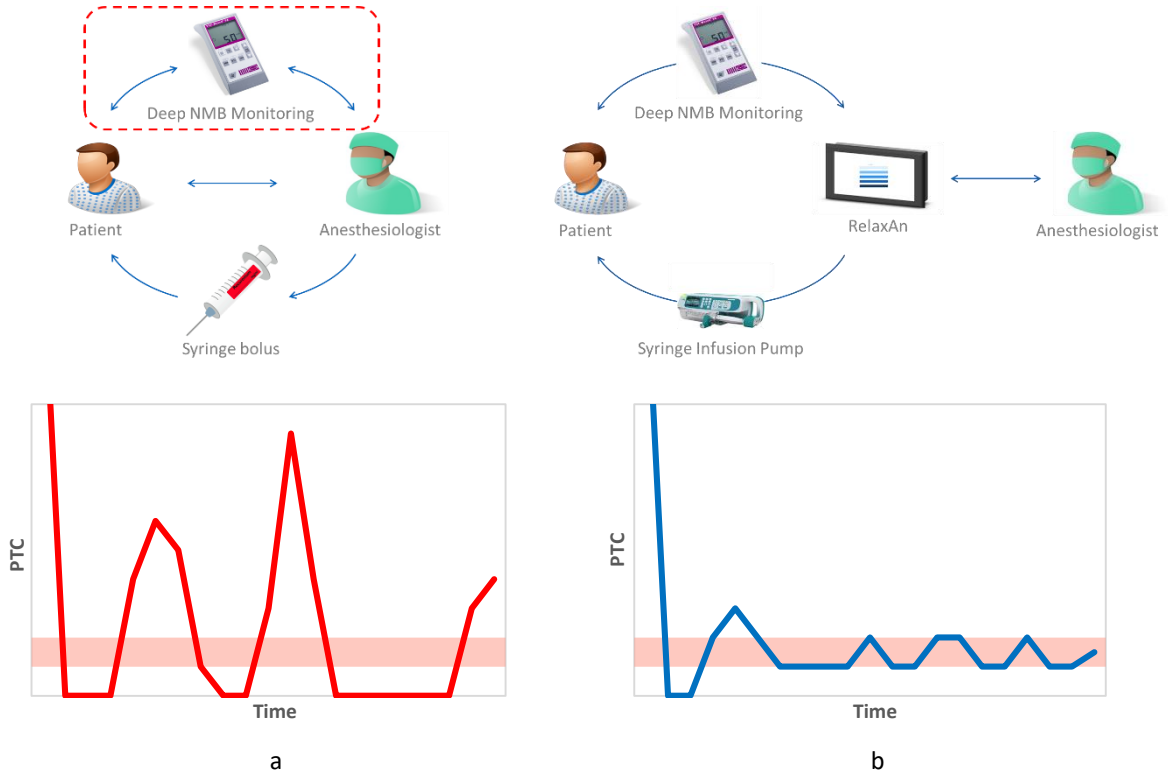


Figure 5.7 - Illustration of a) conventional approach and b) RelaxAn system for deep NMB.

5.4.2 POTENTIAL MARKET VALUE

The usage of NMB agents during surgeries occurs daily worldwide. Reports from 2008 say approximately 234 million individuals underwent a surgical procedure per year, from which approximately 60 % of these received general anesthesia and some form of a neuromuscular blockade agent [194]. More recently, in 2012, approximately 312.9 million operations took place [195], allowing to estimate more than 380 million surgeries occur currently, and approximately 50 million patients receive NMBA.

Deep level of NMB is particularly more used in procedures that require total immobility to ensure good surgical conditions, such as laparoscopic surgeries. Market research from 2017 reported that around 15 million laparoscopic procedures are performed globally every year, reaching an overall device market worth of about $8 billion and a forecast growth of 4.80 % (compound annual growth rate) in the period 2018-2025 [196]. Another market reference is the reversal agent sugammadex, which must always be used to recover after deep NMB. In 2018, Merck reported revenues of $917 million and rising [197].

Taking into account these numbers and the inaccurate or uncontrolled considerations for the administration of NMB drugs, RelaxAn is an advanced system that promotes a stable and safe deep NMB during surgical procedures, also advantageous in terms of time and cost that inadequate administration of NMB drugs entails. Furthermore, the invention of RelaxAn aims to be further optimized to achieve and deliver a product that can be used independently to promote an advanced control of the individual rocuronium administration in real-time, therefore providing a more complete and innovative system to the anesthesia market.

5.4.3 COMPETITION

Currently, the best available solution for ongoing intravenous anesthesia is via syringe pumps. However, no PK-PD models of rocuronium are included in the libraries of these devices. Therefore, they cannot estimate the drug concentrations, relying only on anesthesiologists' interpretation, which can be performed differently by each professional for each patient.

In terms of control systems for the NMB, several approaches have been studied for the automated drug infusion of muscle relaxants, considering feedback strategies, with model-free or model-based controllers. From the various closed-loop systems investigated over the years, most did not enter the market. The closest competition for this invention is a new technology device known as CONCERT-I (VERYARK Technology Co Ltd, Hong Kong). This syringe pump combines real-time closed-loop muscle relaxation monitoring technologies with a target-controlled infusion. It is a promising technology in the field; however, it is limited to the non-deep NMB degree (based on TOF measurements). No studies have been found that prove the reliability and accuracy of this technology.

5.4.4 DEVICE CLASSIFICATION AND REGULATION

In addition to the general application requirements, specifications, and end-customer needs, medical devices have to deal with relevant regulations, product safety, and risk controls. This type of device is classified as Class IIA devices by EU MDD (Medical Device Directive) and Class II by FDA (Food and Drug Administration).

The legal and regulatory requirements to be fulfilled for the exploitation of this innovation are covered by the international standard ISO 13485:2016(E), Medical devices - Quality management systems - Requirements for regulatory purposes [198]. This International Standard specifies requirements for a quality management system that can be used in one or more stages of the life-cycle of a medical device. It includes design and development, production, storage and distribution, installation, servicing and final decommissioning and disposal of medical devices, and associated activities (*e.g.*, technical support). Moreover, the system should meet the similar requirements of the EU Production

Quality assurance of Council Directive 93/42/EEC concerning Medical Devices. These directives ensure universally high safety standards for patients, by establishing standards for the approval and monitoring of medical devices, covering all aspects from design and clinical investigation to manufacturing and post-market surveillance, resulting in the certification of a product as a medical device.

5.4.5 BUSINESS PROPOSAL

The medical devices have a vast commercial field, often dominated by big brands, making the entry into the medical market more difficult. MESO (Medical Solutions, Porto, Portugal) is a start-up company that is involved in different projects in the medical field, mainly in the anesthesiology department. PersAn is an inspirational project from MESO and is one of the company's main accomplishments in the development of a complete and successful solution for the control of propofol administration during surgeries. MESO aims to provide solutions not only for the hypnotic effect but also for analgesic and immobility components, therefore supporting the development of RelaxAn. Throughout the years of investigation and growth of MESO, FEUP has been closely working in several projects promoting and contributing to the achievement of enhanced solutions for the anesthesiology field, and RelaxAn is no exception. Following the PersAn recent and successful developments in a similar system for propofol for the control of consciousness degree during surgeries, the team believes and is compelled to pursue the equivalent crescent route to provide a solution for NMB. One of the strategies may comprise the protection of the technology through a patent and, further on, having a specialized team to develop the final product, being R&D and production the two key activities of the process.

At this point, the stage of testing and validation is ongoing. After the proof-of-concept and final design definition, the next steps include the development of the product, followed by regulatory and market approval, and, eventually, pursue the commercialization of the technology (Figure 5.8).

Figure 5.8 - Stage of the RelaxAn technology development.

The lack of robust answers in the NMB field is well known and discussed in the anesthesiology community. Thus there is a clear opportunity to explore this market. RelaxAn provides a unique and complete solution for anesthesiologists, as the main users and stakeholders, and therefore are the leading market target. Specifically, it includes the rocuronium customers in major countries of Europe,

thus covering the scope of developed hospitals that conduct surgeries with general anesthesia that requires deep NMB, such as laparoscopic procedures. The increased use and availability of sugammadex permits to renew the interest of safely exploring the potential of the technology, therefore being an important asset in the foundation of this system.

It is important to maintain closer relationships with the medical devices corporates and anesthesiology experts and associations, that can promote RelaxAn in many hospitals and clinics. Also, the close relationship with foreign partners would be crucial, since one of the goals is the internationalization of the technology.

5.5 CHAPTER OVERVIEW

A closed-loop control system was designed and developed for the control and maintenance of deep NMB during surgical procedures by combining continuous NMB monitoring with a personalized infusion of rocuronium. The system is named RelaxAn. Preliminary testing showed promising results with improved accuracy by ensuring the successful maintenance of the desired NMB degree during the surgical procedures.

RelaxAn presents unique features and advantages that can benefit immensely not only for patient care, by improving surgical conditions and anesthetic stability, but also reduces the workload of the professionals and possible additional costs. This innovative solution has an encouraging business potential in the anesthesia market. Nonetheless, further improvements are expected to be explored and implemented to achieve a final product that can provide a more advanced and innovative solution to anesthesiologists worldwide.

6 CONCLUSIONS AND FUTURE WORK

Neuromuscular blockade is an essential component of anesthesia. When total immobility is required to improve surgical conditions and avoid undesirable movements, deep neuromuscular blockade is generally used. Many studies have been conducted to investigate and characterize the muscle relaxation, aiming to improve patient care during surgical procedures. Few have been conducted for deep NMB and have proven the importance of the approach. Despite that, there is still some uncertainty in routine clinical practice regarding the regulation of the NMBA administration to ensure the safe and stable maintenance of deep NMB throughout the anesthesia. Thus, the motivation of this work was to develop a solution that allows for the control and maintenance of the deep neuromuscular blockade.

In the course of this research project, an extensive background study on anesthesia practice was accomplished. Also, a complete literature review on the monitoring and continuous infusion requirements to ground the development of a system for the maintenance of deep neuromuscular blockade was completed. Beyond that, a questionnaire was conducted with a group of main users, the anesthesiologists, to prove the interest of the proposed system and perceive the requirements of a system aspiring to be accepted in the anesthesiology field.

The main technical requirements and specifications regarding the NMB monitoring and the rocuronium administration were defined. These were the basis for the design of a clinical investigation study that was proposed to support the development of an advanced solution for maintenance of the deep NMB during surgical procedures.

An interface was developed for a reliable recording and visualization of the patients' NMB performance in real-time. From the data gathered, it was possible to conduct a study comparing the

two acceleromyography-based NMB monitors used, the TOF-Watch® SX and the TOFscan®, assessing the differences between device measurements in the different stages of the procedures. Furthermore, an investigation of the rocuronium pharmacokinetic-pharmacodynamic relationship in estimating the post-tetanic count effect during the maintenance of deep NMB was addressed. This study resulted in the achievement of acceptable PK-PD modeling properties to estimate the PTC effect, which significantly benefits the guidance of the rocuronium administration in the maintenance of the desired neuromuscular blockade level.

RelaxAn is the proposed solution, designed and developed to support anesthesiologist in customizing and optimizing the maintenance of deep NMB. It combines the feedback from the continuous NMB monitoring with a compliant method of personalized infusion of rocuronium in a closed-loop technique. This innovative technology integrates commercially available hardware components of NMB monitoring and syringe pumps, in a software system and a user-friendly interface, that allows for reliable, accurate, and semi-autonomous regulation of the NMB in surgical procedures. Preliminary testing showed promising results with improved accuracy in ensuring the desired NMB level during the surgical procedures.

The foundation of this research project was defined, taking into account the routine clinical practice of deep NMB in general anesthesia. The main limitation in the course of this work was the NMB monitoring devices' uncertain precision. Despite this, the acceleromyography-based monitors provided an objective and reliable method in detecting the stimulation response and accurate feedback in guiding the drug infusion for deep NMB. Nevertheless, users have the option to discard the NMB monitoring feedback and manually use RelaxAn as a target-controlled infusion technique.

6.1 FUTURE WORK

To better understand the implications of the system's results, further studies should be performed to show the potential and applicability of RelaxAn in routine anesthesia. Additionally, crucial future work recommendations include a prospective study of the PK-PD relationship for a larger population sample and a controlled trial for the testing and validation of the approach. This research may address the analysis of blood samples to validate the plasma concentration estimated and include the intra and inter-individual variability assessment to optimize the PTC effect estimation and improve the accuracy and autonomy of the system.

Finally, it was also acknowledged that this innovative technology solution has enormous business potential in the anesthesia market. The best frame for this unique innovation is to be integrated into a prototype capable of working for other anesthesia or monitoring methods used in hospitals around

the world, making it a more attractive solution for the medical field. Another interesting approach to improve the quality of the technology would be to achieve a single device fully developed to embody all the components required for an independent, accurate, and reliable applicability of RelaxAn in routine clinical practice.

In conclusion, the main contribution of the research conducted in the course of this Ph.D. was the development of a unique method for customizing the maintenance of deep NMB. Besides providing significant advances in ensuring the individuals' total immobility and allowing for optimal surgical conditions and patient care throughout the procedures, it brings important benefits to anesthesia, by reducing the professionals' workload, as well as has the potential to decrease the time and cost associated with improper drug use.

Ultimately, the most striking point of this research was the successful performance of RelaxAn: a novel solution to an essential component of anesthesia. Through the combination of NMB monitoring feedback and a closed-loop control technique, it was possible to individualize the rocuronium drug delivery and optimize the maintenance of the deep NMB during surgical procedures.

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8 APPENDICES

8.1 SYSTEMATIC REVIEW SPECIFICS

8.1.1 SEARCH STRATEGY

8.1.1.1 Keyword concepts

Concept	MeSH	Keyword
Rocuronium	1-(17-(acetoyl)-3-hydroxy-2-(4-morpholinyl)androstan-16-yl)-1-(2-propenyl)pyrrolidinium	Rocuronium
	rocuronium bromide	Zemuron
	pyrrolidinium, 1-((2beta,3alpha,5alpha,16beta,17beta)-17-(acetyloxy)-3-hydroxy-2-(4-morpholinyl)androstan-16-yl)-1-(2-propenyl)-, bromide	Esmeron
	Esmeron	Esmerone
	Esmerone	ORG-9426
	ORG-9426	ORG 9426
	ORG 9426	
	Zemuron	
Infusions pump	Perfusion Pumps	Infus*
	Perfusion Pump	Perfus*
	Pump, Perfusion	Drug Delivery Systems
	Pumps, Perfusion	Pump
	Infusors	
	Infusor	
	Pumps, Infusion	
	Infusion Pump	
	Pump, Infusion	
	Intravenous Drug Delivery Systems	

	Drug Infusion Systems	
	Drug Infusion System	
	Infusion System, Drug	
	Infusion Systems, Drug	
	System, Drug Infusion	
	Systems, Drug Infusion	
	Infusion Pumps, External	
	External Infusion Pump	
	External Infusion Pumps	
	Infusion Pump, External	
	Pump, External Infusion	
	Pumps, External Infusion	

Deep or intense NMB	Deep and intense NMB is characterized by the monitoring of post-tetanic count stimuli (1-2 and 0 respectively).	deep
		intense
		profound
		post-tetanic
		PTC
		tetanic count
		posttetanic
		post tetanic

8.1.1.2 Search syntax

Search engine (28-06-2018)	**Syntax**
	Rocuronium infusion for deep or intense NMB
	(Rocuronium OR Zemuron OR Esmeron OR Esmerone OR ORG-9426 OR ORG 9426) AND (Infus* OR Perfus* OR Drug Delivery Systems OR Pump) AND (deep OR intense OR profound OR post-tetanic OR PTC OR tetanic count OR posttetanic OR post tetanic)
PubMed (all fields)	**43**
Web of science (All databases)	**33**
Cochrane Library (title, abstract, keywords)	**63**
Other searches	**94**
TOTAL	233

8.1.2 INCLUSION AND EXCLUSION CRITERIA

8.1.2.1 Inclusion criteria

1) Human adults (over 18 years old) classified as ASA I-IV;
2) Randomized clinical trials, controlled trials, and cohort studies;
3) Included studies that conduct surgical procedure with general anesthesia with rocuronium through continuous infusion as muscle relaxation anesthesia for profound neuromuscular blockade; *
4) Reported data on the amount of rocuronium administered during the procedure, rating of surgical conditions or reversal time after 4 mg/kg of Sugammadex;
5) Included comparative outcomes of moderate NMB or intermittent rocuronium administration.

*for deep neuromuscular blockade with 0-2 PTC range for the study of moderate vs. deep NMB (section 2.2.1) and 0-10 PTC range for the study of the layers of deep NMB (section 2.2.2).

8.1.2.2 Exclusion criteria

1) Studies including pediatric or animal as participants;
2) Case reports studies;
3) Moderate NMB level as target objective;
4) Bolus only as the administration method to maintain profound NMB;
5) Use of other NMBA to maintain profound NMB.

8.1.3 EXCLUDED STUDIES

Author	Year	Motif
Boon M.	2013	Study protocol
Kim H.	2009	Not profound NMB target
Kopman A.	2005	Not profound NMB target
Liu Y.	2017	Not profound NMB target
Lee J.	2016	Case-report
Van Brantegem E.	2014	Insufficient data reported
Yamamoto S.	2015	Unfit comparative group assignment
Rex C.	2009	Unfit comparative group assignment
Smetana K.	2017	Review
Soto-Mesa D.	2015	Not profound NMB target
Veelo D.	2015	protocol
Lee H.	2015	Unfit comparative group assignment
Nonaka T.	2013	Unfit comparative group assignment
Georgiev S.	2011	Not profound NMB target
Makri I.	2011	Review

8.1.4 INCLUDED STUDIES CHARACTERISTICS

8.1.4.1 Participants and surgery profile

AUTHOR (year)	Sample size	Age (y)	BMI (kg/m^2)	ASA	Surgical procedure
Baete S. (2017)	30/30	41/42	40/41	I-III	Laparoscopic surgery
Yoo Y. (2015)	34/32	63.9/61.5	23.6/24.4	I-II	Laparoscopic surgery
Madsen M. (2017)	65/63	63/65	26/25	I-III	Upper laparotomy
Kim M. (2016)	30/31	57.1/56.8	23.0/24.2	I-III	Laparoscopic surgery
Martini C. (2014)	12/12	53.5/55*	25.9/25.8	I-III	Laparoscopic surgery
Staehr-Rye A. (2014)	25/23	45.25/47.5*	26.75/26.25*	I-II	Laparoscopic surgery
Kim H. (2019)	28/28	57/50.25*	24/23*	I-III	Robotic gastrectomy
Mekawy N. (2012)	40/0	N/A/	29.8/-	I-II	Endoscopic sinus surgery

Data reports mean parameters for deep/moderate NMB. Abbreviations: N/A – Not available or no answer. *Calculated based on the formulas presented by Hozo S. et al. [38].

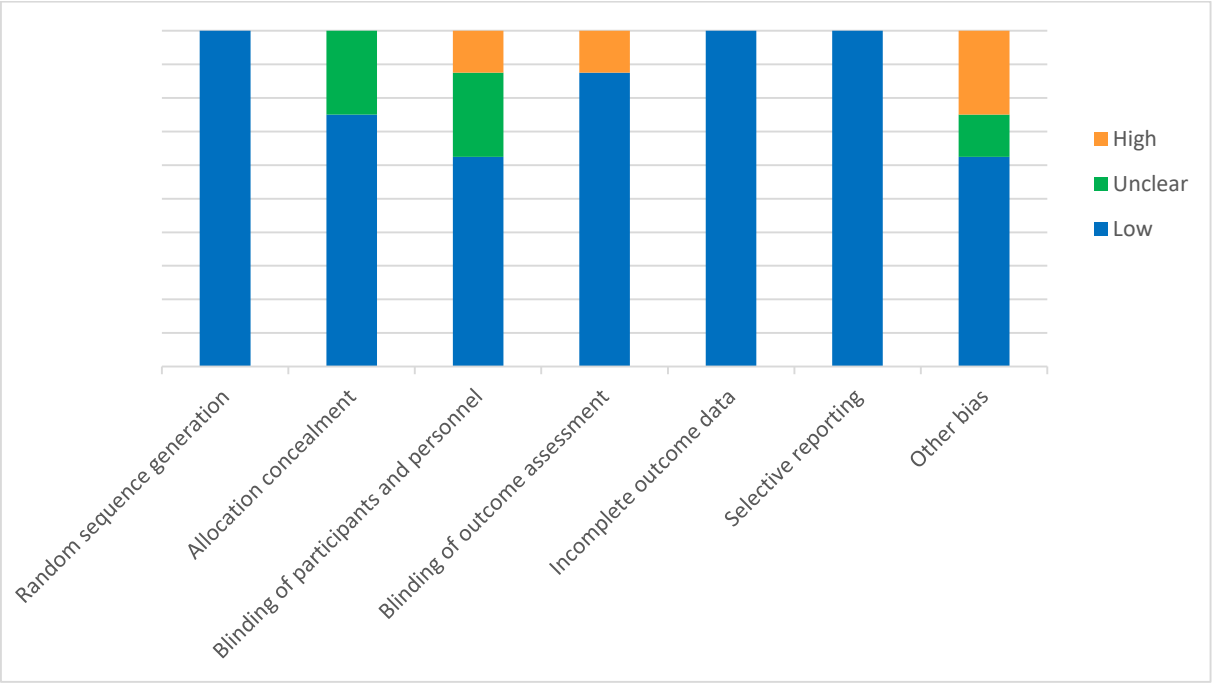
8.1.4.2 Intervention and outcome characteristic

AUTHOR (year)	RESEARCH TYPE	INTERVENTION									COMPARISON	OUTCOME	
		Rocuronium administration			Monitoring					Sugammadex reversal			
		Induction dose (mg/kg)	Initial infusion rate (mg/kg/h)	Adjustments	Device	Nerve	CAL	PTC target	Stimuli interval (min)	Time point	Amount (mg/kg)		Primary	Secondary and other
Baete S. (2017)	Randomized trial	0.6	0.6	Target titrated	TOF Watch®-SX	Ulnar	yes	1-2	5	End of surgery	4	Moderate vs. Deep NMB	SRS; IAP; duration of surgery	Postoperative pulmonary function; the need for postoperative respiratory support; Administered rocuronium (mg/kg), remifentanil and propofol; time from TOFR >90% to pulmonary function tests
Yoo Y. (2015)		1	0.6	Target titrated		Fascial	yes	1-2	15	End of surgery	N/A	Moderate vs. Deep NMB	IOP	SRS; IAP; Administered rocuronium (mg); postoperative pain; postoperative respiratory events;
Madsen M. (2017)		0.6	N/A	Add bolus		Ulnar	yes	0-1	3-5	End of anesthesia	4-16	Moderate vs. Deep NMB; bolus vs. infusion	SRS	Surgical rating score at surgical instances, need for intervention; operating time, wound dehiscence or infections; adverse events
Kim M. (2016)		0.6	N/A	Target titrated		Ulnar	N/A	1-2	N/A	End of surgery	2-4	Moderate vs. Deep NMB	IAP	Surgical conditions (5-stage satisfaction scale); perioperative respiratory and cardiovascular parameters; postoperative recovery profiles; pain and nausea intensity; Administered rocuronium (mg);
Martini C. (2014)		1	0.6	Add bolus + adjust infusion rate		Ulnar	yes	1-2	15	End of surgery	4	Moderate vs. Deep NMB	SRS	Level of agreement between anesthesiologists and surgeon on surgical conditions; effects on hemodynamic variables; time to TOF.0.9 (min); relevant variables in the PACU; Administered rocuronium (mg)
Staehr-Rye A. (2014)		0.3+0.7	0.3-0.4	Target titrated		Ulnar	yes	0-1	3-4	End of surgery	2-8	Moderate vs. Deep NMB	Surgical conditions	Time of surgery, the proportion of procedures completed with IAP of 8 mm Hg; pain; postoperative consumption of analgesics; antiemetics; incidence and time of postoperative events; Administered rocuronium (mg);
Kim H. (2019)		1	0.3	Add bolus + adjust infusion rate		Ulnar	yes	1-2	10	End of surgery	4	Moderate vs. Deep NMB	Quality of recovery post-op. day 1	Quality of recovery postoperative day 2; intraoperative hemodynamics and respiratory data; Postoperative pain, nausea, vomiting, and medication use; administered rocuronium (mg);
Mekawy N. (2012)		0.6	0.6-0.9	Target titrated	TOF guard	Ulnar	yes	1-2	N/A	*T2*	4	Conventional vs. Sugammadex reversal	Recovery profile	Postoperative Respiratory System Evaluation Score; Administered rocuronium (mg); Reversal recovery time (min)

Abbreviations: NMB - Neuromuscular blockade; PTC – Post-tetanic count; CAL – Monitor device calibration; SRS – Surgical Rating Scale; NRS – numeric rating scale (0-100) IAP – Internal Abdominal Pressure; IOP - Intra Ocular Pressure; N/A – Not available or no answer.

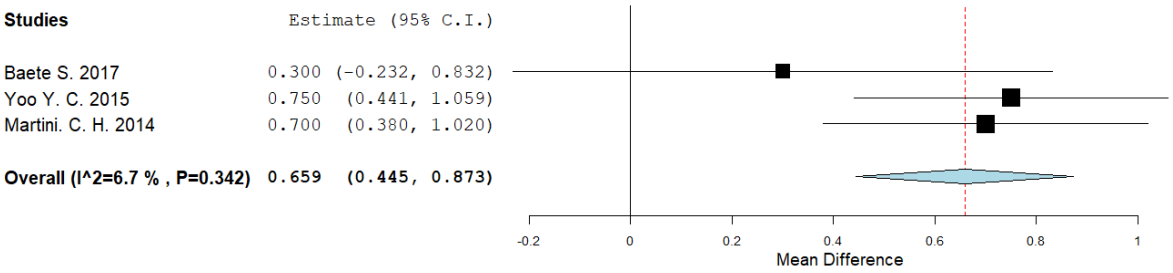
8.1.5 RISK OF BIAS AND QUALITY ASSESSMENT

AUTHOR	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Baete S.	Low	Low	Low	Low	Low	Low	Low
Yoo Y.	Low	Low	Low	Low	Low	Low	Low
Madsen M.	Low	Low	Unclear	Low	Low	Low	High
Kim M.	Low	Low	Low	Low	Low	Low	High
Martini C.	Low	Unclear	Low	Low	Low	Low	Low
Staehr-Rye A.	Low	Low	High	Low	Low	Low	Low
Kim H.	Low	Low	Low	Low	Low	Low	Low
Mekawy N.	Low	Unclear	Unclear	High	Low	Low	Unclear

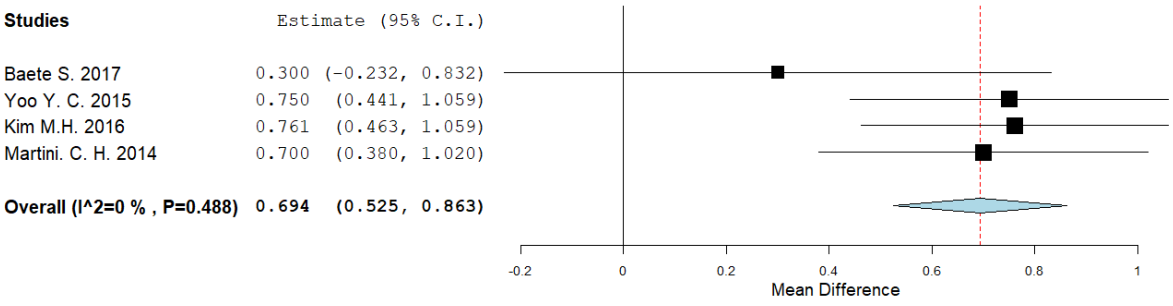


8.1.6 SURGICAL CONDITIONS SENSITIVITY ANALYSIS

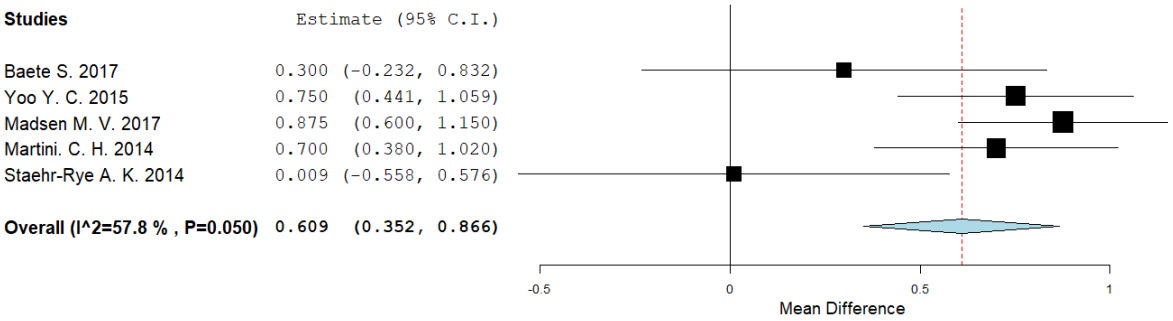
8.1.6.1 Studies with the lowest risk of other bias are included



8.1.6.2 Studies with target PTC 1-2 are included



8.1.6.3 Studies with PTC measurements equal or inferior to 15 minutes are included



8.2 QUESTIONNAIRE TO NMB MONITOR USERS

8.2.1 QUESTIONNAIRE

CURRENT PRACTICE

1. WHAT ARE THE NMB DEVICES YOU USE?

❑ TOF-Watch ®

❑ TOFscan®

❑ Other_____

2. HOW MANY AVAILABLE NMB DEVICES ARE IN THE SERVICE YOU WORK? _____

3. HOW OFTEN DO YOU USE NMB MONITORING?

❑ 0 % (Never)

❑ < 25 % (Rarely)

❑ 25-50 % (Sometimes)

❑ > 50 % (Often)

❑ 100 % (Always)

4. WHAT YOU THINK ARE THE MAIN BENEFITS OF USING NMB MONITORING?

_____
_____

5. WHAT YOU THINK ARE THE MAIN ISSUES OF USING NMB MONITORING?

_____
_____

6. WHICH STIMULATION PATTERNS YOU COMMONLY USE?

❑ Single Twitch

❑ Train-of-four – TOF

❑ Tetanic stimulation

❑ Post tetanic count – PTC

❑ DBS

7. WHICH MONITORING SITES YOU CONSIDER?

❑ adductor pollicis

❑ orbicularis oculi

❑ corrugator supercilii

❑ Great toe

❑ Other_____

8. HOW OFTEN DO YOU INDUCE DEEP NMB?

❑ 0 % (Never)

❑ < 25 % (Rarely)

❑ 25-50 % (Sometimes)

❑ > 50 % (Often)

❑ 100 % (Always)

9. HOW OFTEN DO YOU USE ROCURONIUM AS A MUSCLE RELAXANT AGENT?

❑ 0 % (Never)

❑ < 25 % (Rarely)

❑ 25-50 % (Sometimes)

❑ > 50 % (Often)

❑ 100 % (Always)

10. HOW MANY TIMES YOU USE ROCURONIUM AS A MUSCLE RELAXANT AGENT VIA INFUSION?

❑ 0 % (Never)

❑ < 25 % (Rarely)

❑ 25-50 % (Sometimes)

❑ > 50 % (Often)

❑ 100 % (Always)

11. WHAT DO YOU CONSIDER FOR ROCURONIUM DOSE REFERENCE?

❑ ED_{95}

❑ Personal experience

❑ Other _____

12. DO YOU USE MONITOR RESPONSES AS GUIDANCE FOR ROCURONIUM DOSAGE?

_____

_____

13. WHAT ARE THE BASIS OF NMBA DOSAGE REGULATIONS IN DEEP NMB?

_____

_____

14. HOW OFTEN DO YOU USE SUGAMMADEX AS A REVERSAL AGENT?

❑ 0 % (Never)

❑ < 25 % (Rarely)

❑ 25-50 % (Sometimes)

❑ > 50 % (Often)

❑ 100 % (Always)

15. HOW OFTEN YOU DETECT POST-OPERATIVE COMPLICATIONS RESULTING FROM INCOMPLETE REVERSAL?

❑ 0 % (Never)

❑ < 25 % (Rarely)

❑ 25-50 % (Sometimes)

❑ > 50 % (Often)

❑ 100 % (Always)

16. HOW OFTEN YOU DETECT POST-OPERATIVE COMPLICATIONS RESULTING FROM INCOMPLETE REVERSAL AFTER DEEP NMB?

❑ 0 % (Never)

❑ < 25 % (Rarely)

❑ 25-50 % (Sometimes)

❑ > 50 % (Often)

❑ 100 % (Always)

MARKET

17. DO YOU KNOW OTHER/NEW NMB MONITORING SYSTEMS?

❑ _____ ❑ _____❑ _____

18. DO YOU FIND ANY MAJOR ISSUES IN THE PRODUCT YOU USE? WHICH?

_____
_____

19. HOW OFTEN DO YOU RECOGNIZE TOF MEASUREMENT ERROR?

❑ 0 % (Never)

❑ < 25 % (Rarely)

❑ 25-50 % (Sometimes)

❑ > 50 % (Often)

❑ 100 % (Always)

20. DO YOU RECOGNIZE BENEFITS OF AN ADVISORY SYSTEM, COUPLING INFUSION AND MONITORING, FOR PERSONALIZED ROCURONIUM ADMINISTRATION DURING DEEP NMB?

❑ Yes

❑ No

Which?_____
_____
_____

21. DO YOU KNOW A METHOD TO DO SO? WHICH?

_____
_____

22. WHAT ARE THE MAIN FLAWS IN THE CLOSED-LOOP SYSTEMS YOU KNOW?

_____
_____

23. WHAT ARE THE MAIN FEATURES YOU WOULD NEED FOR A SYSTEM OF THIS KIND?

_____

_____

OUR PROPOSAL

■ Study of the deep neuromuscular block monitoring and drug administration during surgery, for the development of an advisory system for the anesthesiologist, coupling appropriate stimulation monitoring with personalized rocuronium dosages to maintain a safe and stable degree of NMB (1-2 PTC).

24. DO YOU SEE USEFULNESS IN SUCH A PRODUCT?

❑ Yes

❑ No

25. DO YOU HAVE ANY SUGGESTION OF SPECIFICATIONS TO BE ADDED?

_____

_____

26. DO YOU THINK THIS SYSTEM WOULD BE APPEALING TO USE?

❑ Yes

❑ No

27. WOULD SUCH A SYSTEM INCREASE THE USE OF DEEP NMB?

❑ Yes

❑ No

28. HOW MUCH WOULD BE THE COST OF SUCH SYSTEM? ❑ _____

29. OTHER OBSERVATIONS:

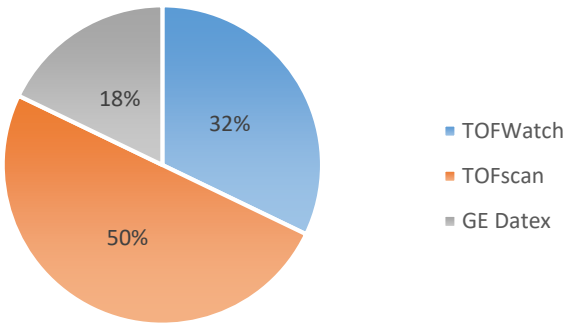
_____

_____

8.2.2 RESULTS ANALYSIS

CURRENT PRACTICE

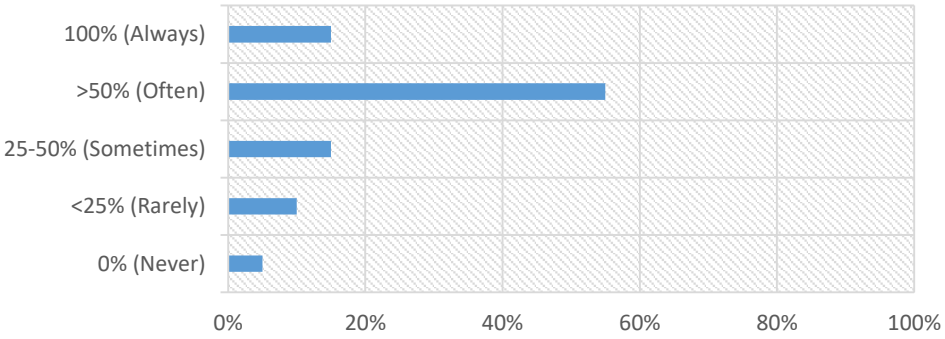
1. WHAT ARE THE NMB DEVICES YOU USE?



2. HOW MANY AVAILABLE NMB DEVICES ARE IN THE SERVICE YOU WORK?

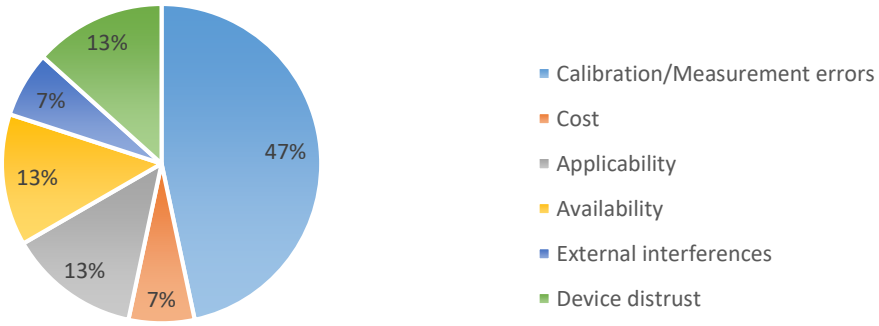
10.65 (2.5)

3. HOW OFTEN DO YOU USE NMB MONITORING?

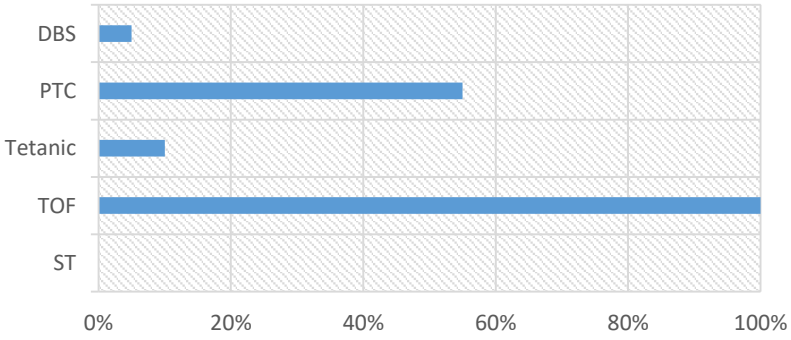


4. WHAT YOU THINK ARE THE MAIN BENEFITS OF USING NMB MONITORING?

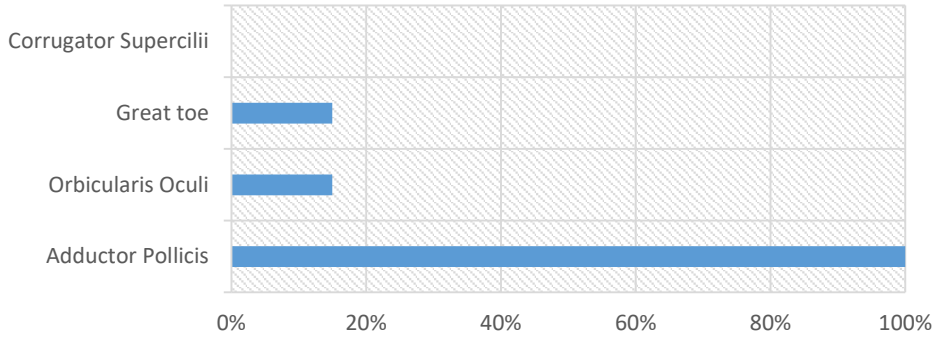
5. WHAT YOU THINK ARE THE MAIN ISSUES OF USING NMB MONITORING?



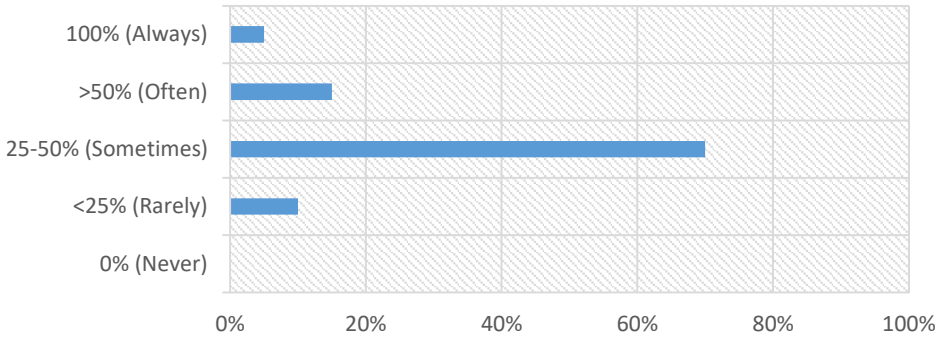
6. WHICH STIMULATION PATTERNS YOU COMMONLY USE?



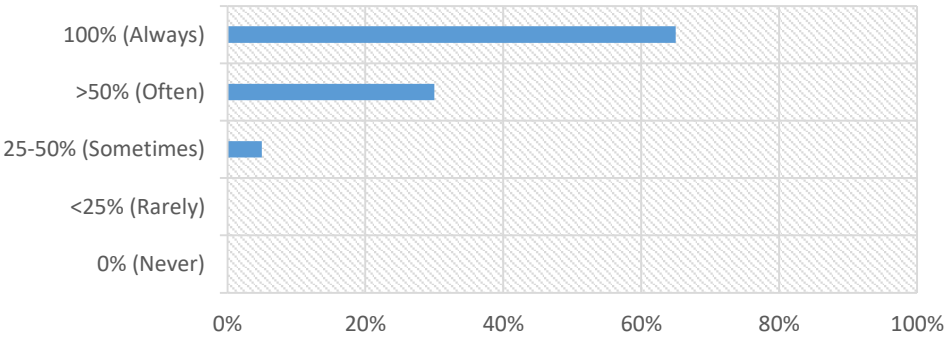
7. WHICH MONITORING SITES YOU CONSIDER?



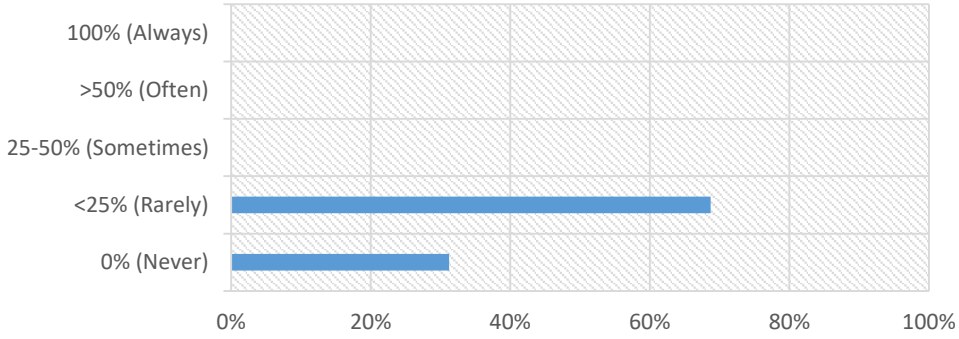
8. HOW OFTEN DO YOU INDUCE DEEP NMB?



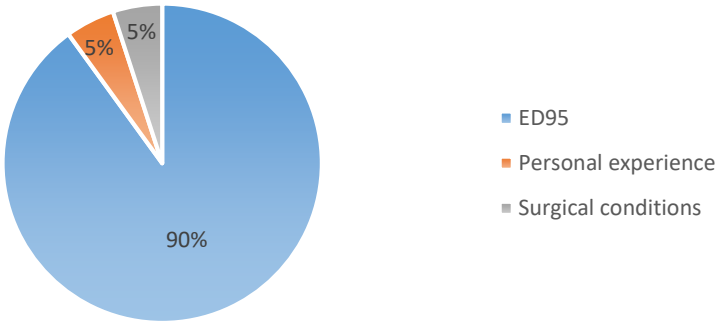
9. HOW OFTEN DO YOU USE ROCURONIUM AS A MUSCLE RELAXANT AGENT?



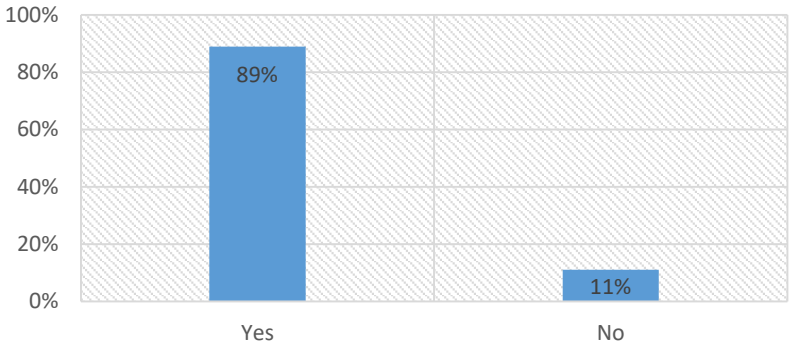
10. HOW MANY TIMES YOU USE ROCURONIUM AS A MUSCLE RELAXANT AGENT VIA INFUSION?



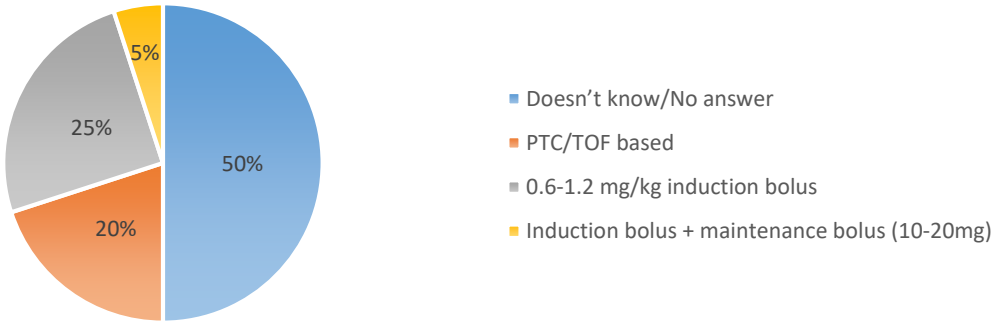
11. WHAT DO YOU CONSIDER FOR ROCURONIUM DOSE REFERENCE?



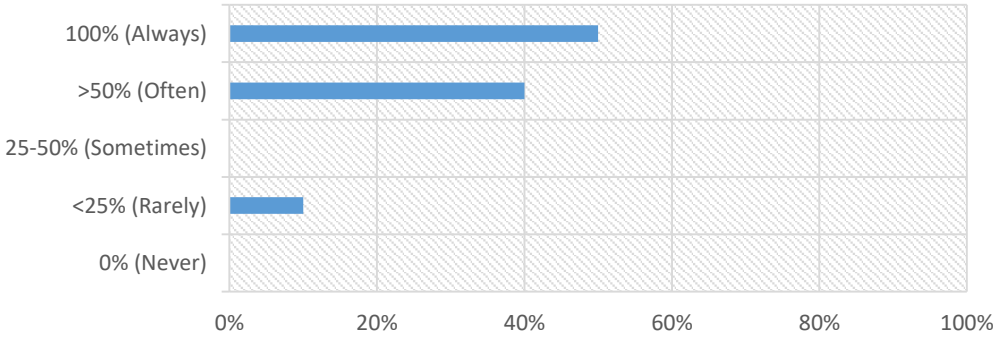
12. DO YOU USE MONITOR RESPONSES AS GUIDANCE FOR ROCURONIUM DOSAGE?



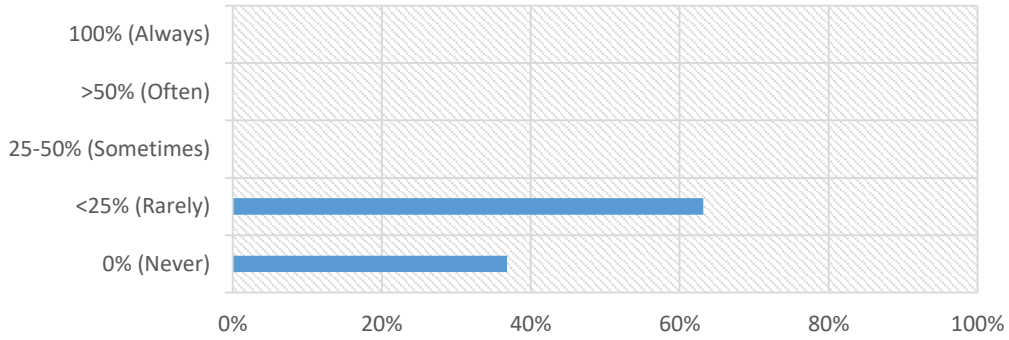
13. WHAT ARE THE BASIS OF NMBA DOSAGE REGULATIONS IN DEEP NMB?



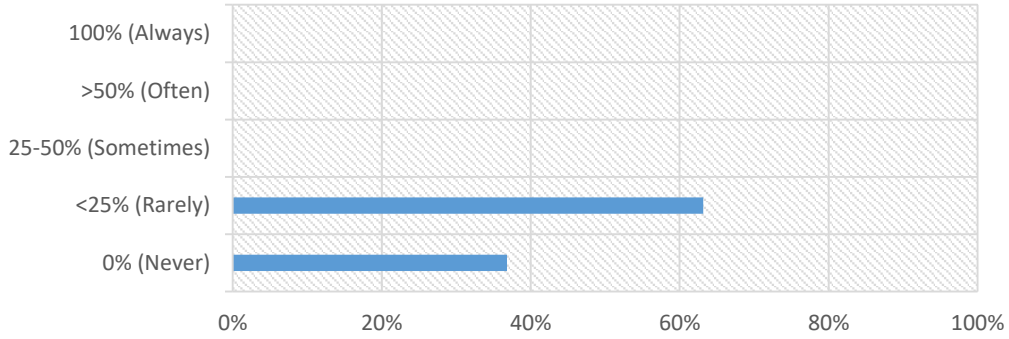
14. HOW OFTEN DO YOU USE SUGAMMADEX AS A REVERSAL AGENT?



15. HOW OFTEN YOU DETECT POST-OPERATIVE COMPLICATIONS RESULTING FROM INCOMPLETE REVERSAL?

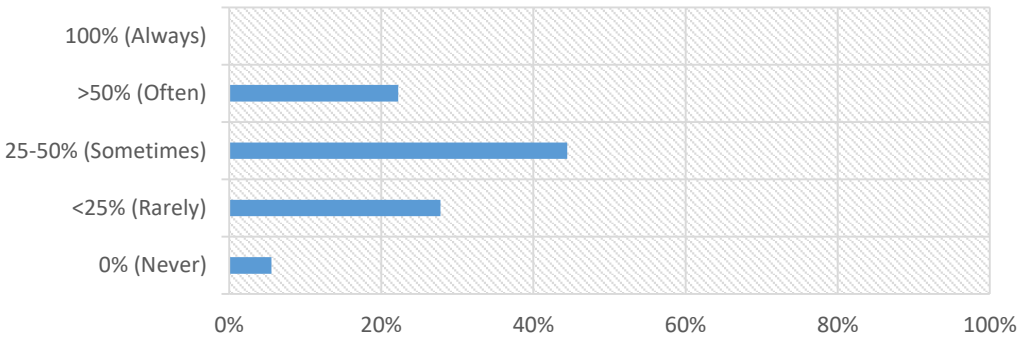


16. HOW OFTEN YOU DETECT POST-OPERATIVE COMPLICATIONS RESULTING FROM INCOMPLETE REVERSAL AFTER DEEP NMB?

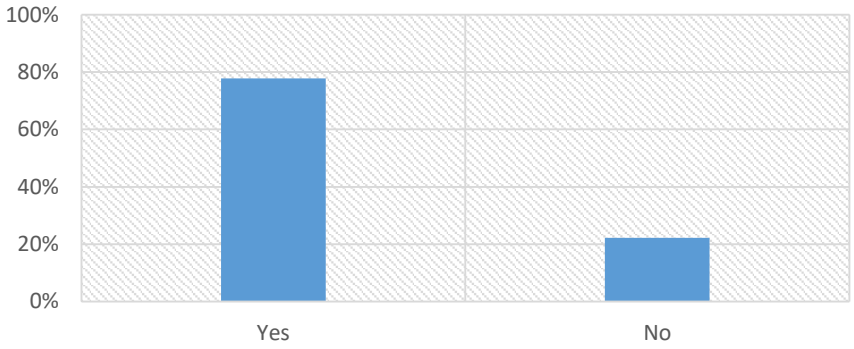


MARKET

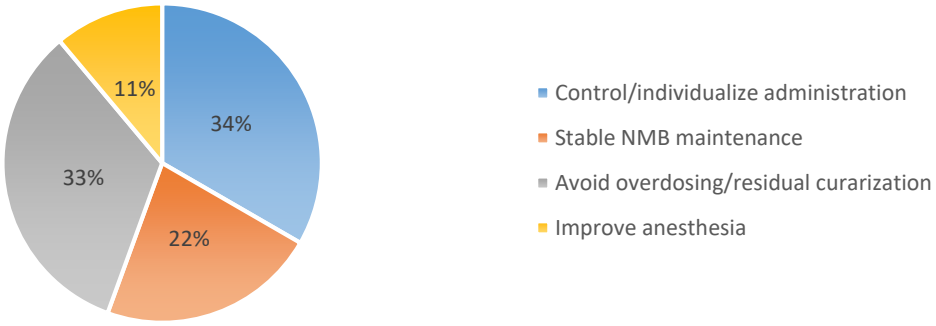
17. DO YOU KNOW OTHER/NEW NMB MONITORING SYSTEMS?
    - ✓ TOF cuff
    - ✓ EMG
18. DO YOU FIND ANY MAJOR ISSUES IN THE PRODUCT YOU USE? WHICH?
    - ✓ Reliability
    - ✓ Calibration
    - ✓ Device fragility
19. HOW OFTEN DO YOU RECOGNIZE TOF MEASUREMENT ERROR?



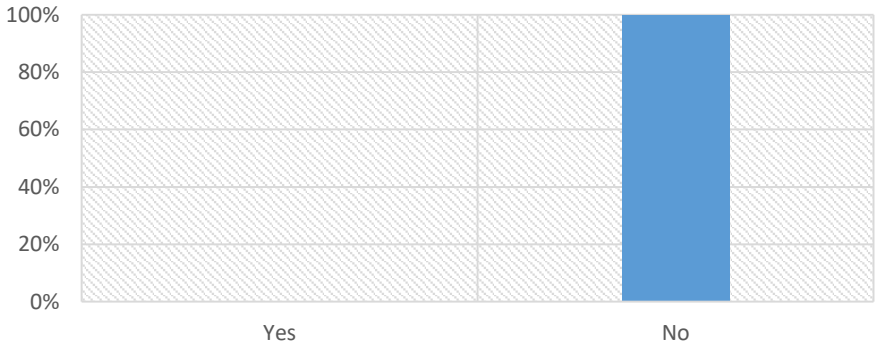
20. DO YOU RECOGNIZE BENEFITS OF AN ADVISORY SYSTEM, COUPLING INFUSION AND MONITORING, FOR PERSONALIZED ROCURONIUM ADMINISTRATION DURING DEEP NMB?



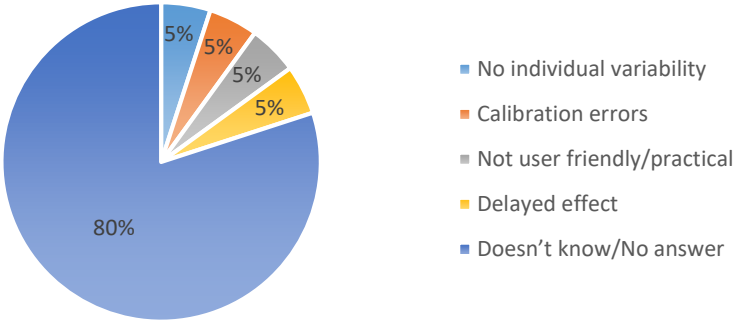
Which?



21. DO YOU KNOW A METHOD TO DO SO? WHICH?



22. WHAT ARE THE MAIN FLAWS IN THE CLOSED-LOOP SYSTEMS YOU KNOW?



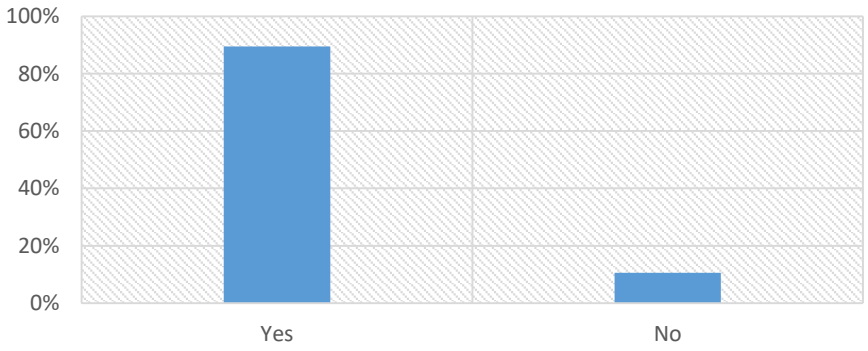
23. WHAT ARE THE MAIN FEATURES YOU WOULD NEED FOR A SYSTEM OF THIS KIND?

- ✓ User friendly
- ✓ Easy applicability
- ✓ Reliability

OUR PROPOSAL

■ Study of the deep neuromuscular block monitoring and drug administration during surgery, for the development of an advisory system for the anesthesiologist, coupling appropriate stimulation monitoring with personalized rocuronium dosages to maintain a safe and stable degree of NMB (1-2 PTC).

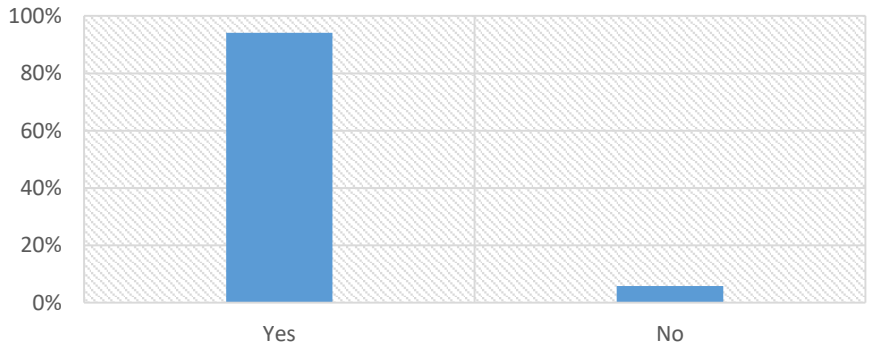
24. DO YOU SEE USEFULNESS IN SUCH A PRODUCT?



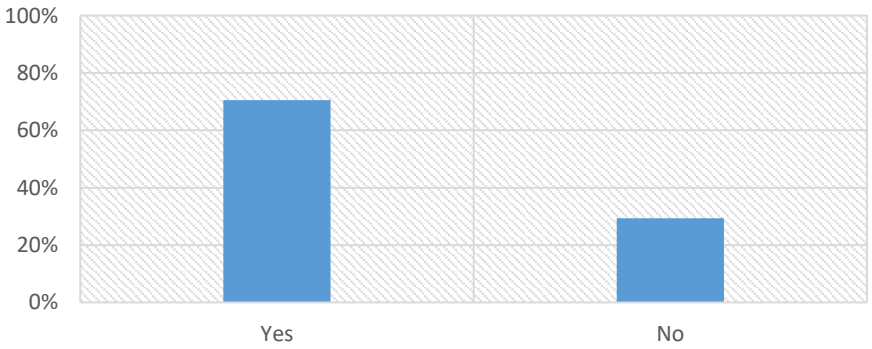
25. DO YOU HAVE ANY SUGGESTION OF SPECIFICATIONS TO BE ADDED?

- ✓ User friendly
- ✓ Automatic NMB measurements
- ✓ Portability

26. DO YOU THINK THIS SYSTEM WOULD BE APPEALING TO USE?



27. WOULD SUCH A SYSTEM INCREASE THE USE OF DEEP NMB?



28. HOW MUCH WOULD BE THE COST OF SUCH SYSTEM?

- ✓ 100-2500€/system
- ✓ 10-20€/patient

8.3 INVESTIGATION PROJECT PROPOSAL

8.3.1 CLINICAL PROTOCOL

Protocolo Clínico

DESENVOLVIMENTO DE UM SISTEMA DE ACONSELHAMENTO AO ANESTESISTA PARA APERFEIÇOAR O RELAXAMENTO NEUROMUSCULAR PROFUNDO POR INFUSÃO DE ROCURÓNIO

1. Introdução

A anestesia geral é habitualmente descrita como envolvendo três componentes principais: hipnose (inconsciência e ausência de memória), analgesia (anti-nocicepção ou ausência de dor) e imobilidade (geralmente referida como relaxamento muscular), os quais ocorrem como resultado da acção de fármacos. No caso da imobilidade, é obtida essencialmente à custa da administração de fármacos relaxantes musculares (curarizantes).

Relaxamento muscular e bloqueio neuromuscular, no contexto da anestesiologia, são sinónimos, pelo que ambas as expressões são utilizadas indiferentemente, quer na clínica quer em terminologia científica.

O estudo clínico que nos propomos realizar tem que ver com a componente "relaxamento muscular", dando continuidade a uma actividade de investigação nesta área com grande tradição no Serviço de Anestesiologia do CHP, como adiante se explica. O estudo foi concebido com o sentido de conseguir avanços nesta área da anestesiologia, e tem por objectivo principal desenvolver um sistema de aconselhamento ao anestesista que proporcione uma optimização do bloqueio neuro-muscular profundo, uma modalidade de relaxamento muscular cuja utilização se encontra em crescimento por oferecer vantagens em vários tipos de procedimentos cirúrgicos.

1.1. Relaxamento muscular e sua monitorização

O relaxamento muscular é essencial para permitir proceder à intubação da traqueia, um requisito habitual na anestesia geral, uma vez que a "profundidade" anestésica, proporcionada pelos anestésicos gerais e pelos opióides (que são o anti nociceptivo mais usual), provocam acentuada depressão respiratória ou mesmo apneia, tornando necessário o uso de ventilação artificial mecânica, a qual por regra se faz após colocação de um tubo na traqueia, operação que implica um grau acentuado de relaxamento muscular de modo a provocar a abertura das cordas vocais e assim permitir a passagem de um tubo até à traqueia. Para isso, na indução da anestesia e após o doente estar inconsciente, administra-se uma dose considerável de um relaxante muscular, de modo a que em cerca de 90 segundos se produza abertura das cordas vocais que permita a introdução do referido tubo traqueal. O efeito deste fármaco também facilita a manobra de ventilação manual através de uma máscara facial, à qual se procede durante o tempo que medeia entre a perda de consciência e a redução da capacidade ventilatória, e a instalação do relaxamento muscular produzido pelo fármaco dito curarizante. Em média este intervalo de tempo é inferior a dois minutos.

Uma vez realizada a intubação da traqueia e iniciada a ventilação mecânica, e enquanto se mantêm a administração de um anestésico geral que assegura a hipnose e a de um opióide que proporcione anti nocicepção, tira-se partido do efeito ainda presente da dose dita de intubação do relaxante muscular, para proporcionar relaxamento muscular que permita a execução da cirurgia, já que na maioria dos casos é muito importante que o cirurgião encontre a musculatura da zona cirúrgica bem relaxada e que o doente se mantenha imóvel, isto é, sem a ocorrência de movimentos que pudessem resultar de

uma reacção a um nível de anestesia insuficiente, ou a reflexos espinhais ou ocorrência de tosse por reacção reflexa à presença do tubo traqueal. Durante o decurso de uma cirurgia, os fármacos relaxantes musculares são por norma usados para proporcionar relaxamento muscular que facilite a cirurgia, o que acontece através da administração de doses repetidas, nomeadamente quando a duração da cirurgia excede uns meros 30 minutos, tempo provável de duração do relaxamento muscular produzido pela dose de intubação.

Os relaxantes musculares foram introduzidos na clínica em 1942. Nessa época eram usados exclusivamente no interesse da cirurgia e não da anestesia. Usavam-se com o objectivo de proporcionar algum relaxamente muscular que facilitasse a cirurgia, mas em doses reduzidas de modo a não comprometer a ventilação. Nessa época os doentes eram mantidos em ventilação espontânea, já que não era rotina a intubação traqueal nem a ventilação automática. Assim os relaxantes musculares eram administrados pelos anestesistas, mas no interesse da cirurgia, situação que se veio a alterar com a introdução do laringoscópio, intubação traqueal e ventilação mecânica, hoje usuais.

Assim, embora durante a realização da cirurgia o grau de relaxamento muscular seja sobretudo do interesse do cirurgião, é ao anestesista que compete decidir da administração do relaxante muscular e é o anestesista que monitoriza o seu efeito. Tal faz-se sobretudo recorrendo a monitores específicos do relaxamento muscular, ou da transmissão neuro-muscular, vulgarmente designados por "neuroestimuladores". Consiste essa monitorização na utilização de um monitor específico, por vezes incorporado como módulo no monitor multi-modular da anestesia, que permite a aplicação de um estímulo eléctrico sobre um nervo periférico, por norma o nervo cubital ao nível do pulso, e a consequente avaliação da resposta a esse estímulo ao nível de um músculo enervado por esse nervo, por norma o músculo adutor do polegar. Tradicionalmente a estimulação faz-se com a aplicação de uma salva de 4 estímulos de uma intensidade entre 25 e 70 mAmp, em 2 segundos (Train of Four ou TOF), repetidos de forma automática, ao longo de todo o procedimento, a intervalos de 12 ou mais segundos. A resposta ao nível do músculo pode ser avaliada por vários métodos, nomeadamente pela detecção do movimento do polegar, da aceleração desse movimento ou pela simples medição da actividade eléctrica ao nível do adutor do polegar evocada pela estimulação (electromiografia ou EMG).

No CHP a monitorização do grau de relaxamento muscular através de neuro-estimuladores, a que chamamos monitorização do bloqueio neuro-muscular, ou BNM, ou monitorização do TOF, é realizada em todos os procedimentos em que se administra um fármaco relaxante muscular. No CHP estão disponíveis vários monitores. Estes monitores implicam o uso de apenas um tipo de consumíveis que são eléctrodos cutâneos, os mesmos que se usam no ECG. A monitorização do grau de relaxamento através de um neuroestimulador é complementada com a avaliação de outros parâmetros clínicos, nomeadamente a presença de movimentos (espontâneos ou reflexos), pela presença de movimentos respiratórios (detectados facilmente nas curvas de capnografia, fluxo e pressão das vias áreas) e ainda pela avaliação que o cirurgião faz da qualidade do relaxamento dos músculos das estruturas do local do corpo onde intervêm.

Na monitorização do BNM utilizando o TOF, a cada sequência de 4 estímulos ocorre uma avaliação quantitativa das respostas. A monitorização inicia-se antes de administrar o relaxante, de modo a obter uma referência, situação em que se observam, ao nível do músculo ou do movimento do dedo, quatro respostas iguais entre si, isto é, não só estão presentes 4 respostas, como a razão entre a 4ª e a 1ª é de 100%, já que são iguais. À primeira das quatro respostas, designada por T1, atribui-se um valor de 100%. Em todas as medições subsequentes a primeira resposta a cada TOF é comparada

com a referencia, de modo que o monitor proporciona sempre uma quantificação de T1 como percentagem em relação à referencia. Por regra, com a dose dita de intubação traqueal, desparecem todas as 4 respostas ao TOF. Algum tempo após uma dose de intubação começa a observar-se o reaparecimento de respostas: primeiro apenas uma e pequena, depois duas, depois três e finalmente as quatro, embora ainda com a primeira resposta muito maior do que a quarta. A partir do momento em que estão presentes 4 repostas, a razão entre a 1ª e a 4ª, TOF ratio, é usada para avaliar da "profundidade" do BNM. O valor de T1 tambem permite uma avaliação do BNM, embora o TOF ratio seja mais valorizado. A recuperação do bloqueio neuromuscular é traduzida por um aumento progressivo do TOF ratio, que acaba por atingir 100%, ainda que para tal, por vezes, seja necessário administrar um antagonista dos relaxantes musculares.

Para a maioria dos procedimentos cirúrgicos foi consensual, ao longo das últimas três décadas, que a ocorrência de 2 respostas ao TOF seria compatível com "relaxamento cirúrgico" adequado [1]. Ainda que fosse eventualmente possível optimizar as condições cirúrgicas suprimindo todas as repostas ao TOF, tem sido entendido como correcto permitir que se verifiquem até duas repostas, já que dessa forma se torna mais fácil obter uma recuperação do relaxamento no momento do despertar. Isto porque o consenso era, e permanece, que para realizar a extubação traqueal, e permitir o despertar, é mandatório ter um TOF ratio igual ou superior a 90%.

No final dos procedimentos cirúrgicos (ou diagnósticos) pretende-se, por regra, que o doente recupere a consciência e a ventilação espontânea, de modo a que possa ser removido o tubo traqueal e que possa assim comunicar oralmente e reassumir um adequado contacto com o ambiente que o/a rodeia, o chamado "despertar". Todavia, este despertar implica que tenha ocorrido uma recuperação da transmissão neuro-muscular, de modo a que não haja limitação da capacidade respiratória e da capacidade de efectuar movimentos, abrir os olhos, deglutir, tossir e comunicar oralmente. Esta recuperação é crucial, sendo bem conhecidas as implicações de uma recuperação incompleta, a qual, para além de grande desconforto para o doente, está associada a maior morbilidade e mortalidade pós-operatórias.

A recuperação de uma situação em que só estivessem presentes 2 respostas ao TOF para um TOF ratio de 90%, é obtida através da administração de um antagonista dos relaxantes musculares. A administração do antagonista é realizada sempre que no final da cirurgia o TOF ratio é inferior a 90% e precede o despertar do doente. Pode acontecer que no final da cirurgia o TOF haja recuperado espontaneamente acima de 90%, dispensando-se nessa situação, e apenas nessa, a administração de um antagonista. Se no pós-operatório, após a remoção do tubo traqueal, o TOF for inferior a 90%, ocorre uma situação a que se chama "bloqueio neuromuscular residual". A ocorrência deste bloqueio residual está bem estudada, sabendo-se ter uma incidência de cerca de 25% e estar associada a um aumento significativo da morbilidade e do tempo de internamento [1], [2][15, 22,23,24].

Assim, temos que o relaxamento muscular é um efeito obtido através da administração, pelo anestesista, de fármacos relaxantes musculares, que o relaxamento muscular é usado para proporcionar condições que permitam a intubação da traqueia na indução da anestesia e o relaxamento muscular ou imobilidade durante procedimentos cirúrgicos ou diagnósticos. O nível do relaxamento muscular é monitorizado com equipamento apropriado, neuroestimuladores, os quais permitem também garantir que antes do despertar do doente já não exista bloqueio neuro-muscular residual. O correcto manuseio do relaxamento muscular enquanto componente da anestesia geral, deve implicar sempre o uso de um neuroestimulador de modo a monitorizar quantitativamente e ao longo de todo o procedimento, o nível de relaxamento [49, 52].

1.2 Perspectivas do anestesista e do cirurgião relativamente ao relaxamento muscular

A análise do papel do relaxamento muscular no contexto de uma cirurgia, implica a noção de que o efeito dos relaxantes musculares interessa tanto aos anestesistas como aos cirurgiões. Na perspectiva do anestesista o relaxamento muscular visa proporcionar condições para a intubação traqueal e para a ventilação mecânica. Na do cirurgião importa sobretudo poder operar sem que a contracção dos músculos ou a ocorrência de movimentos perturbem ou dificultem ou mesmo impossibilitem a boa execução técnica. A realidade na prática clínica é que, com frequência, surgem situações em que o anestesista e o cirurgião divergem na avaliação de se o nível de relaxamento ou de bloqueio é o ideal ou óptimo. Não é surpresa que para o cirurgião a tendência seja para desejar um nível de relaxamento ou de imobilidade tão acentuado quanto possível e que para o anestesista, o nível existente, não muito profundo, seja desejável. Isto porque a acção dos anestesistas está fundada no consenso de que a presença de duas respostas ao TOF é suficiente para proporcionar "relaxamento cirúrgico adequado", e ainda porque o anestesista, conhecedor das complicações associadas a BNM residual, tem sempre a preocupação de garantir uma recuperação total do bloqueio NM antes de despertar o doente, sendo que quanto menos profundo for o grau de relaxamento, mais fácil será a sua recuperação e mais rápido o processo de despertar. A preocupação do anestesista envolve ainda o factor tempo e o interesse em reduzir o intervalo de tempo entre duas cirurgias, para isso contribuindo quer uma rápida instalação do BNM quer a sua rápida reversão. Neste cenário, foi acontecendo, ao longo dos anos, uma tendência por parte do anestesista, para procurar obter "relaxamento muscular" e, essencialmente, imobilidade, à custa de ir aumentando as doses do hipnótico e do opióide, abstendo-se de aumentar as doses de relaxante muscular. Aumentar a dose do relaxante torna claramente mais difícil reverter o seu efeito no momento de despertar. Em contrapartida, os modernos hipnóticos (sevoflurano, desflurano, propofol) e os modernos opioides (remifentanil), pela propriedade de terem semi-vidas muito curtas, permitem compatibilizar doses altas durante a cirurgia com concentrações reduzidas no momento do despertar, de modo a que este não seja retardado por o doente ter recebido doses mais elevadas. Todavia, existe hoje forte evidência de que a profundidade anestésica dita "excessiva", que pode facilmente resultar desta prática, pode estar relacionada com aumento da morbilidade e, mais do que isso, aumento da mortalidade ao fim de um ou mais anos após a cirurgia [19]. A "profundidade" da anestesia é hoje facilmente quantificada através de monitores próprios que utilizam índices derivados do electroencefalograma (EEG), já que tanto os hipnóticos como os opioides actuam sobretudo no cérebro, alterando o EEG. O monitor da profundidade anestésica mais usado na clínica é o BIS [18]. O monitor do BIS capta o EEG através de um sensor colocado na testa, processa esse EEG e proporciona um índice que varia entre 100 (indivíduo acordado) e zero (coma profundo), sendo que anestesia geral adequada corresponde a um valor de BIS entre 40 e 60. A ocorrência de BIS inferior a 40 tem sido associada a aumento da mortalidade pós-operatória [19][20], pelo que hoje em dia não é visto como uma prática segura "abusar" do uso de hipnóticos e opioides, nomeadamente para "compensar" um relaxamento muscular menos profundo e desse modo tentar minimizar a probabilidade de movimento durante a cirurgia ou tentar obter "relaxamento" cirúrgico. Acresce que por vezes o índice BIS não reflecte adequadamente o nível de hipnose por estar "contaminado" pela actividade eléctrica proveniente da electromiografia dos músculos frontais. Activiadde essa captada pelo sensor do BIS e que pode ser indistinguível de actividade eléctrica com origen cortical, já que para frequências de actividade electrica de 30hHz, a origem tanto pode ser cortical como muscular [50]. O ensaio clínico por nós recentemente concluído [25], mostrou que nos doentes submetidos a BNM profundo a actividade electromiografica captada pelo BIS era menor e que esses doentes necessitaram de menos quantidade de propofol para manter anestesia adequada (dados ainda não publicados).

Assim, durante décadas, vem subsistindo no ambiente das salas de operações, um cenário em que se torna difícil conciliar interesses contraditórios: o anestesista a pretender o menor grau de BNM possível e o cirurgião referindo dificuldades em operar com o nível de relaxamento muscular proporcionado pelo anestesista. E como é do lado do anestesista que estão os instrumentos implicados no BNM, isto é a administração dos fármacos e a monitorização do seu efeito, a tendência tem sido no sentido de prevalecer a opinião do anestesista. A agravar este quadro, acontece que na prática clínica, os neuroestimuladores usados para monotorização do BNM recorrem à estimulação do nervo cubital e à avaliação da resposta evocada no dedo polegar, sendo bem sabido que existe uma enorme diferença entre o pequeno músculo adutor do dedo polegar, aliás denominado adutor curto, e os músculos de maior tamanho, nomeadamente os do abdómen, região lombar, membros inferiores e diafragma. A monitorização do BNM no adutor do polegar, não reflecte o que se passa nos músculos das estruturas onde o cirurgião actua. E ainda que há décadas os tratados de anestesia afirmem e mostrem, através de figuras e números bem explícitos, ser enorme a dimensão da diferença na resposta ao BNM, nomeadamente na sua recuperação, entre o adutor do polegar e o diafragma [1], os anestesistas manifestam tendência a persistir "amarrados" aos seus dogmas ou aos hábitos de uma prática transmitida ao longo de gerações que faz prevalecer a avaliação do TOF no polegar e a sua fácil objectivação, leia-se quantificação, desvalorizando a avaliação subjectiva feita pelo cirurgião. Não é invulgar que num cenário em que o cirurgião "se queixa" de ter dificuldade em operar e sugere ser o relaxamento muscular insuficiente, depararmo-nos com uma atitude de alguma sobranceria por parte do anestesista, atribuindo essa dificuldade a uma eventual inabilidade do cirurgião, ilibando assim de responsabilidades a anestesia. Neste cenário não é difícil que na "disputa" entre anestesista e cirurgião, quem saia a perder seja... o doente.

Esta eventual contradição entre anestesista e cirurgião na avaliação da adequação do nível de relaxamento muscular, não tem sido fácil de sanar. Isto porque a comunicação entre as duas partes nem sempre é eficaz [13] os cirurgiões não dominam a monitorização do BNM nem a sua linguagem e a ciência que lhes é subjacente. Naturalmente começam a surgir iniciativas no sentido de conhecer melhor a posição de cirurgiões e anestesistas e de procurar o envolvimento mútuo e consensos [56]. Um estudo reente [25], questionou cirurgiões e anestesistas sobre como avaliavam as condições de relaxamento muscular durante cirrugias laparoscópicas, revelando uma significativa discordância na avaliação, sendo que os anestesistas avaliavam as condições como mais favoráveis do que os cirurgiões, um resultado que confirma que, apesar do conhecimento da fisiologia, farmacologia e monitorização do BNM ser um atributo dos anestesistas, a avaliação clínica que empregam na prática não é sensível aos interesses do cirurgião, da cirurgia e, em última análise, do doente. Outro factor importante que vem contribuindo para perpetuar a contradição entre anestesista e cirurgião é ausência de um árbitro, isto é, da inexistência de uma opinião imparcial.

Felizmente que, recentemente, dois factos vieram suprir a necessidade de recorrer a um árbitro, permitindo alterar este paradigma. Esses dois factos são: o rápido crescimento de técnicas cirúrgicas laparoscópicas [57] e o surgimento, na prática clínica, de um novo antagonista dos relaxantes musculares, ou mais exactamente de um dos relaxantes existentes, o sugamadex [58]. A cirurgia laparoscópica, amplamente utilizada por cirurgiões gerais, torácicos, urologistas e ginecologistas, beneficia muito de um nível de relaxamento muscular muito profundo, pelo menos muito mais profundo do que o que existe quando se observam duas respostas no TOF. Ao mesmo tempo que a cirurgia começou a usar técnicas que beneficiam de BNM profundo, a anestesia passou a poder dispor de um maior à vontade em proporcionar esse BNM profundo, dada a possibilidade de proceder à sua rápida e completa reversão recorrendo ao inovador sugamadex. Assim, recente e simultaneamente, alguns procedimentos cirúrgicos passaram a justificar relaxamento muscular profundo e a anestesia passou a poder proporcionar com segurança esse nível de bloqueio. O

sugamadex veio possibilitar a reversão quase imediata do BNM, seja qual for o seu grau de profundidade. A introdução do Sugamadex em Portugal aconteceu em 2011, sendo que nessa altura a sua utilização seguiu recomendações especiais [21].

1.2. Importância do BNM profundo

Presentemente, BNM profundo é utilizado com frequência em cirurgia laparoscópica. O primeiro ensaio clínico que comparou BNM profundo com não profundo em cirurgia laparoscópica foi publicado em 2013 [44]. Nesses procedimentos é necessário insuflar a cavidade abdominal com gás, sendo muito importante minimizar a pressão intra-abdominal daí resultante, o que se consegue através de BNM profundo. Recentemente foram publicados estudos clínicos que demonstram a superioridade do bloqueio profundo em diversos tipos de cirurgia laparoscópica em ensaios que randomizam doentes para bloqueio profundo versus bloqueio não-profundo, comparando a avaliação da qualidade das condições cirúrgicas ou do relaxamento muscular efectuada pelos cirurgiões, os valores de pressão intra-abdominal, a dor pós-operatória, entre outros [4], [5][27 a 31, 33 a 37, 39 e 40]. Metanálises recentes comprovam a superioridade do BNM profundo na cirurgia laparoscópica [54, 55].

Para além da cirurgia laparoscópica, usa-se BNM profundo em cirurgias em que qualquer movimento por parte do doente seria perigoso, como certas cirurgias cerebrais, em procedimentos não cirúrgicos realizados sob anestesia geral em que a imobilidade é vital, como a embolização de aneurismas cerebrais, ou ainda em cirurgias não laparoscópicas, mas que envolvem zonas com músculos e estruturas sensíveis, como seja a cirurgia do ráquis em doentes neurocirúrgicos [38, 41].

BNM profundo é definido como o bloqueio, ou ocupação dos receptores pelo relaxante muscular, que resulta em TOF de zero e na ocorrência de 1 a 2 contagens pós-tetancias ou PTC após um estímulo tetânico de 50Hz [53]. Utiliza-se esta definição, porque se após uma estimulação tetância de 50Hz o número de contagens for zero, fica-se sem saber se o bloqueio é excessivamente profundo, isto é, se tardaria muito tempo até surgir uma PTC e porque se o número de PTC for superior a 2, existe maior probabilidade de o bloqueio recuperar e de vir a surgir uma resposta ao TOF.

A ocupação de receptores por um relaxante muscular ao nível da placa motora está claramente relacionada com o tipo de respostas obtidas com os neuroestimuladores, de modo que um bloquio profundo consiste na ocupação de mais de 99% dos receptores. Esta técnica, PTC, a contagem do número de respostas a uma sequência de estímulos simples aplicados um a cada segundo após um tétano de 50Hz, passou a ser usada na avaliação de bloqueio profundo porque os neurosteimuladores existentes incluiam, e incluem, a possibilidade de realizar estímulos tetânicos de 50Hz e contagem de PTC, uma opção introduzida nos anos 1980 com o objectivo de melhor avaliar a recuperação do BNM e assegurar o controlo do processo de reversão do BNM. Assim, quando a anestesia começou a poder proporcionar aos doentes e aos cirurgiões BNM profundo com segurança por dispor de sugamadex, dispunha já, nas salas de operações, de monitores capazes de quantificar rigorosamente BNM profundo. A introdução de sugamadex e o consequente uso, com mais frequência, de BNM profundo, não dispensam a monitorização do BNM, antes reforçam a sua necessidade e importância [49].

O uso mais frequente de BNM profundo não está, todavia, a ser acompanhado de desenvolvimentos no modo de o proporcionar, seja no que respeita à administração do relaxante muscular, seja no que respeita à monitorização: BNM profundo envolve por um lado o modo como o relaxante é administrado e por outro o modo como o BNM é monitorizado. O relaxante é quase sempre o

rocurónio, por ser o que permite a reversão com sugamadex. Isto porque manter BNM profundo no tipo de cirurgias referido, implica ter no final do procedimento um nível de BNM ainda profundo, já que a fase de encerramento nesses procedimentos não demora mais do que escassos minutos, não permitindo tempo suficiente para a recuperação espontânea do BNM uma vez suspensa a administração do relaxante. Assim, é oportuno e importante acompanhar o interesse clínico pelo BNM profundo, por um aperfeiçoamento no modo de o proporcionar.

1.3. Importância da variabilidade inter-individual e a variedade no modo de administrar BNM

O uso de BNM profundo vem colocar novos desafios quer à administração do rocurónio quer à monitorização do seu efeito. Um dos desafios resulta da variabilidade inter-individual na reposta ao rocurónio. Tal como com outros fármacos, existe uma grande variabilidade inter-individual na acção do rocurónio [51], o que aumenta as exigências com a administração e monitorização. No que respeita a estes dois aspectos, os estudos clínicos que avaliam do benefício de BNM profundo, são omissos ou pouco explícitos na informação sobre como é administrado o rocurónio e como é monitorizado o BNM ou ainda sobre como se vai ajustando a dose de rocurónio em função dos resultados da monitorização. Afirmam, o que é óbvio, que BNM profundo implica ter de zero a duas contagens pós-tetânicas (PTC), mas não explicam qual a frequência com que é realizada a avaliação de PTC. A maior parte dos estudos utilizam como monitor do BNM o aparelho TOF-Watch, o único validado para ensaios clínicos [53], mas esse monitor não permite a aplicação de estímulos tetânicos e contagens PTC de forma programada automática, obrigando a que o anestesista accione manualmente essa estimulação de cada vez que pretende uma avaliação de PTC. Assim, permanece pouco clara e indefinida a frequência com que se devem realizar avaliações de PTC quando se pretende BNM profundo. Por outro lado, quando a contagem de PTC fornece o resultado de zero, não é possível saber se o nível e BNM está muito próximo, em tempo, de proporcionar o surgimento de uma contagem de PTC ou distante desse momento. Quanto ao rocurónio, não está claro nem consensual qual o modo ideal de administração no contexto de BNM profundo. Após a dose inicial de intubação é necessário não permitir que o BNM recupere acima do nível de bloqueio profundo, nomeadamente a ponto de surgir resposta ao TOF, sendo que tal tanto pode ser obtido à custa de doses (bolus) suplementares, como de uma infusão contínua. Os ensaios clínicos que aplicam BNM profundo dedicam pouca importância ao modo de administração do rocurónio. Assim, podemos afirmar que permanecem como questões em aberto a de quando iniciar a administração suplementar e a de como o fazer, se em bolus repetidos, se por infusão. Na prática clínica o anestesista tem dificuldade em aplicar avaliação de PTC a intervalos regulares, já que tal não é feito de forma automática, e tem tendência a proporcionar BNM profundo à custa de bolus repetidos de rocurónio. Com esta prática é difícil assegurar estabilidade do BNM profundo e manter, ao longo do procedimento, uma a duas respostas de PTC.

Um dos aspectos ainda pouco abordados é o da avaliação do BNM com PTC nos minutos subsequentes à dose de intubação. O anestesista tende a assumir que após a dose de intubação ocorre bloqueio profundo de duração prolongada, não sendo habitual avaliar o nível de BNM com PTC nos primeiros 15 ou 30 minutos após a dose inicial. Dados preliminares de um ensaio clínico por nós realizado no qual após a dose de intubação aplicamos estimulação tetânica e avaliação de PTC a cada cinco minutos, revelam uma variabilidade grande na resposta a uma mesma dose de intubação (0,6mg/kg). Após o bólus inicial, o aparecimento de PTC=1 tardou em média 12,5 minutos, sendo que o desvio padrão foi de 5,2 minutos, traduzindo grande variabilidade. O mesmo se verificou para o aparecimento da primeira contagem de TOF, que foi de 35±17,4 minutos, de novo uma grande variabilidade. Houve doentes que não chegaram a atingir PTC de zero e outros que permaneceram longos minutos com PTC de zero. Nestes casos a avaliação de PTC foi realizada a cada 5 minutos

após a dose de intubação, com TOF Watch, e durante todo o procedimento. Os doentes randomizados para receber bloqueio profundo com perfusão de rocurónio iniciada quando PTC>0, tiveram em média 22,2±6,8 períodos de 5 minutos com TOF=0, mas desses em apenas 15,7±6,5 períodos de 5 minutos ocorreu PTC de 1 a 2 o que quer dizer que em 20% do tempo o nível e BNM não foi mantido como pretendido, isto é, com PTC de 1 ou 2 (ver tabela em anexo). Estes resultados preliminares revelam a utilidade da avaliação de PTC a intervalos regulares, neste caso de 5 minutos, demonstram grande variabilidade individual na resposta ás mesmas doses de rocurónio e mostram que mesmo com o cuidado de ajustes a cada 5 minutos o anestesista não consegue assegurar o nível adequado de BNM profundo em 20% do tempo do procedimento. Assim, verifica-se ser pertinente e oportuno desenvolver métodos de administração de rocurónio para BNM profundo que incorporem a avaliação frequente de PTC a intervalos fixos e a quantificação de como cada doente responde à dose de intubação para individualizar e optimizar a administração de rocurónio de modo a manter o nível desejado de PTC.

Actualmente a experiência clínica já adquirida com a utilização de BNM profundo e reversão com sugamadex, permite constatar, como acima se pretende demonstrar, que há grande margem para aperfeiçoar a obtenção de BNM profundo, mas permite também, questionar o paradigma actual da anestesia e admitir que imobilidade durante a cirurgia deva ser assegurada através de BNM profundo. Indo um pouco mais além, pode ser legítimo propor que um nível de BNM ainda mais profundo do que o BNM de 1 a 2 PTC, possa ser mais adequado em grande parte dos procedimentos, por proporcionar melhor garantia de condições ideias de relaxamento dos músculos do local onde o cirurgião intervém ou por minimizar os riscos de ocorrência de movimento em procedimentos em que tal possa colocar o doente em perigo. Esta hipótese é reforçada pela possibilidade de o BNM profundo poder estar associado a menor consumo de anestésicos gerais e a menor incidência de efeitos hemodinâmicos adversos, como hipotensão arterial, um resultado proporcionado pelo ensaio clínico que concluímos recentemente.

Se podemos admitir como hipótese que o BNM profundo ou mesmo BNM intenso possa passar a ser o desejável no contexto de uma anestesia geral, permanecem, todavia, questões em aberto. Bloqueio intenso é o que acontece quando após um tétano de 50Hz o número de PTC é zero. Bloqueio intenso pode, teoricamente, proporcionar uma maior garantia de imobilidade e de relaxamento total dos músculos abdominais e diafragma, minimizando, ou abloindo mesmo, a possibilidade de movimentos reflexos, nomeadamente de tosse em reacção à presença do tubo traqueal. Todavia, não existe ainda uma forma de monitorizar o BNM quando após um estímulo tetânico de 50Hz, proporcionado pelos monitores actualmente comercializados, ocorre total ausência de respostas pós-tetânicas, isto é zero PTC. Dado o interesse pelo BNM intenso (zero PTC) e dada a possibilidade das vantagens que pode oferecer, faz sentido investigar formas de quantificar BNM intenso.

Após a dose inicial de intubação acontece com frequência que o doente não tem qualquer resposta na estimulação pós-tetânica (PTC de zero), o que corresponde a uma fase de bloqueio intenso. Tal ocorrência não coloca problemas, uma vez que é transitória e ocorre numa faze do procedimento em que o despertar do doente ainda está distante. Assim, faz sentido tirar partido da ocorrência furtuita de bloqueio intenso, para investigar formas de o avaliar. De notar que nem em todos os doentes ocorre BNM intenso após a dose de intubação. Nos doentes em que ocorrer BNM intenso, uma forma de obter uma avaliação do nível de BNM poderia passar pela utilização de um estímulo tetânico mais intenso do que 50Hz. O monitor TOF Watch permite aplicar uma estimulação de 100Hz, mas esse modo de estimulação não é todavia seguido, automaticamente, de estímulos de 1Hz, tal como no tétano de 50Hz, o qual é seguido automaticamente de 15 estímulos simples de 1Hz, contabilizando, também automaticamente, o número de respostas presentes, o qual pode ir de zero a 15. Na nossa

prática, pudemos verificar que usando o TOF Watch, a aplicação de um estímulo tetânico de 100Hz pode ser seguida de até 60 estímulos simples de 1Hz, embora tal função não seja automática, tendo que que ser activada manualmente pelo utilizador após cada estimulação de 100Hz. Usando esta técnica já nos foi possível verificar que quando se observa a ocorrência de zero respostas após um tétano de 50Hz, ocorrem respostas após um tétano de 100Hz. Através de software adequado, TOF Link, é possível registar o número de respostas que se seguem a um tétano de 100Hz. Assim, faz todo o sentido tirar partido dos períodos em que a dose de intubação de rocurónio resulte em zero contagens de PTC, para estudar o que acontece com a aplicação de um estímulo tetânico de 100Hz através do monitor TOF Watch, seguido de estimulação com estímulos simples de 1Hz e registo das respostas com o software TOF Link.

1.4 Contributos do Serviço de Anestesiologia do CHP para avanços e boas práticas no BNM

O serviço de anestesiologia do CHP é uma referência nacional no que respeita ao bloqueio neuro-muscular. Tal está bem patente na investigação realizada ao longo dos últimos 15 anos e que incluiu o desenvolvimento de um sistema automático, Hipocrates [14], para obter relaxamento muscular com TOF de 10% através de infusão do relaxante muscular atracurio, o estudo Inspire I [15], o ensaio que avaliou a qualidade de recobro comparando sugamadex com neostigmina [16], o ensaio clínico que comparou BNM profundo e BNM standard avaliando o consumo de anestésicos (Registo ClinicaTrials NCT02484651)[25] (já concluído, tendo sido o primeiro ensaio clínico de iniciativa do investigador no CHP) e ainda o estudo Inspire II (Registo ClinicaTrials NCT03417804)[26], presentemente em fase de recrutamento de doentes. Isto, para além de uma pratica clinica diária de rigor na administração de relaxantes, antagonistas e monitorização do BNM, que constituem uma verdadeira referência a nível nacional em sintonia com os principais centros mundiais da anestesiologia no que respeita a avanços no conhecimento e aplicação de relaxamento muscular.

Um dos factores que tem contribuído para o desempenho do Serviço de Anestesiologia do CHP nesta área é a colaboração, desde há cerca de 30 anos, com matemáticos da Faculdade de Ciências e engenheiros da Faculdade de Engenharia, com grande conhecimento da anestesiologia e do ambiente do bloco operatório e com uma vasta experiência, nas áreas da anestesiologia, na utilização de sensores e de monitores, na análise e processamento de sinal, na aquisição e tratamento de dados, na análise estatística, no desenho de estudos, na modelação farmacocinética/farmacodinâmica e no desenvolvimento de controladores aplicados à optimização da administração de fármacos e de sistemas de aconselhamento ao anestesista.

Em face dos avanços recentes na cirurgia e na anestesia que tornam oportuno e viável a utilização de relaxamento profundo e tirando partido do saber adquirido em relaxamento muscular pelo Serviço de Anestesiologia do CHP e ainda da colaboração estreita com matemáticos e engenheiros, pensamos ter toda a oportunidade realizar um estudo que permita avançar ainda mais no modo de administração de relaxantes musculares, eventualmente contribuindo, no futuro, para melhor segurança dos doentes cirúrgicos.

O estudo que agora pretendemos levar a cabo tem por objectivo desenvolver um método mais avançado de administração de rocurónio para BNM profundo, aplicando avaliação de contagens pós-tetânicas a cada 3 minutos, combinando esta avaliação frequente com a individualização da administração subsequente à dose de intubação e o aperfeiçoamento da administração, especificamente através do desenvolvimento de um sistema de aconselhamento ao anestesista. Os objectivos específicos são detalhados mais adiante.

O método de obtenção de relaxamento muscular profundo que nos propomos criar será desenvolvido a partir da avaliação, doente a doente, do modo como cada um responde à dose de intubação de rocurónio, utilizando esse dado para definir a taxa de administração de rocurónio em infusão contínua durante a manutenção. Isto monitorizando o BNM com TOF-Watch, avaliando contagens pós tetânicas (50Hz) rigorosamente a cada três minutos, com aplicação de estimulação de 100Hz sempre que a estimulação precedente com 50Hz revele ausência de PTC.

Um tema pertinente ao desenhar o presente estudo é o da frequência da avaliação de PTC. A contagem de PTC foi introduzida na prática clinica como forma de calcular, perante ausência de respostas ao TOF, o intervalo de tempo provável até que surgisse a primeira resposta ao TOF. Foram criadas tabelas que, em função do número de PTC, estimavam esse tempo. Como o inicio da utilização intencional de BNM profundo, a modalidade PTC passou a ser utilizada como método para avaliar o nível de BNM através do número de contagens por tetânicas presentes. Relativamente à frequência da avaliação de PTC, teoricamente poder-se-ia dizer que quanto mais frequentes, melhor. Todavia a própria natureza da avaliação de PTC faz com que após uma aplicação se tenha que respeitar um intervalo de tempo que permita que o aumento temporário de acetilcolina na placa motora causado pela estimulação tetânica se dissipe. Esse intervalo parece ser de 90 segundos. Portanto a frequência de estimulação terá que ser superior a 90 segundos. Nos monitores como o TOF Watch, a aplicação de uma avaliação de PTC é seguida de um período de tempo em que o monitor fica inibido de executar nova PTC. Apenas um dos monitores disponíveis no mercado oferece a possibilidade de realizar automaticamente avaliações de PTC repetidas. Trata-se do monitor TOF-Scan da IDMED, em uso no nosso hospital, que permite a estimulação automática e repetida, a cada 5 minutos, com tétano de 50Hz e avaliação de PTC, através da aplicação de 10 estímulos simples de 1Hz. Trata-se, nesse monitor, do modo "auto-pilot". No ensaio clínico por nós efectuado comparando bloqueio profundo com bloqueio standard, a monitorização do BNM foi com o monitor TOF Watch. Nesse ensaio aplicamos estimulação de 50Hz a cada 5 minutos, mas manualmente. Um alarme alertava os investigadores, a cada 5 minutos, para realizarem uma avaliação de PTC (ver anexo).

Para o presente estudo propormo-nos realizar PTC a cada 3 minutos, de modo a obter um controlo mais apertado através de avaliações mais frequentes. Os monitores actualmente comercializados, impõem, após uma avaliação de PTC, um período de inibição da estimulação que vai de um a dois minutos. Isto porque se sabe que a mobilização de acetilcolina à placa motora que ocorre com uma estimulação tetânica, altera temporariamente as condições ao nível da placa motora, enviesando avaliações realizadas pouco tempo depois. É aliás esse o principio que permite obter respostas após um tétano, PTC, quando antes do tétano, e para o mesmo tipo de estimulação, não ocorre qualquer resposta. Assim, avaliar PTC a intervalos de 3 minutos parece-nos ser um bom compromisso entre aguardar o tempo suficiente para a normalização da acetilcolina e realizar avaliações com uma frequência superior a 5 minutos, proporcionando assim a possibilidade de um controlo mais fino do nível de bloqueio profundo, o qual, como se explicou, se baseia na presença de 1 a 2 PTC. Um estudo recente [59], comparou a avaliação de PTC a cada 3 minutos numa mão com a estimulação com TOF a cada 15 segundos na outra mão, concluindo que a realização de PTC a cada 3 minutos não altera o BNM nem os resultados da monitorização. Neste estudo iremos ainda aproveitar o facto de no CHP existirem outros monitores do BNM para os utilizar em simultâneo com TOF Watch, tal como explicado adiante.

O estudo a levar a cabo compreende três fases:

1. Administração de rocurónio para bloqueio neuro-muscular profundo através de um bolus inicial numa dose habitual (1mg/kg), perfusão de rocurónio do modo usual a partir do

momento em que ocorrer recuperação do BNM, monitorização com TOF Watch e reversão do BNM com sugamadex, em tudo seguindo um protocolo que se distingue da prática usual apenas na frequência de monitorização do BNM, repetindo a avaliação de PTC a intervalos fixos de três minutos.

2. Análise dos resultados obtidos na fase 1, nomeadamente doses de rocurónio e efeito produzido, avaliando especialmente o modo como o TOF desce nos cerca de 120 segundos iniciais após a dose de intubação até ao seu desaparecimento e o modo como ocorre a recuperação até ter PTC=2 após esse bolus. Desenvolver, com base nesta informação, um algoritmo para administração de rocurónio destinado a obter bloqueio profundo, isto é, bloqueio com 1 a 2 PTC, método baseado na aplicação de estimulação tetânica e PTC a cada três minutos. Criar um sistema de aconselhamento a utilizar em tempo real, sob supervisão do anestesista, destinado a aperfeiçoar a estabilidade do BNM profundo.
3. Administração de rocurónio para bloqueio neuro-muscular profundo com um bolus inicial na dose usada na fase 1, monitorização do BNM igual à fase 1 e administração de rocurónio com base no sistema de aconselhamento desenvolvido na fase 2. O sistema funciona sob supervisão do anestesista responsável pelo caso que a qualquer momento pode assumir o controlo directo da administração de rocurónio. Este sistema incorporará informação obtida pelo modo como cada doente responde à dose inicial de intubação, na tentativa de individualizar a administração de rocurónio. Esta fase destina-se a avaliar o desempenho do sistema de aconselhamento. Para tal regista-se o número de medições em que o número de PTC foi de zero ou superior a 2, comparando-o com o registado nos doentes da fase 1.

2. Objetivos

Assim, os objectivos específicos do estudo são:

1. Analisar a resposta individual a uma dose de intubação de 1mg/kg de Rocurónio (Fase 1)
2. Desenvolver um algoritmo que utilize, doente a doente, a informação relativa ao modo como respondeu à dose da intubação, para determinar a taxa de infusão de Rocurónio, criando um sistema de aconselhamento ao anestesista que, a cada 3 minutos, recebe informação do número de PTC obtidas e sugere eventuais alterações na taxa de infusão (Fase 2)
3. Avaliar o desempenho do algoritmo/sistema de aconselhamento através da análise do número de períodos de 3 minutos em que o número de PTC é inferior a zero ou superior a 2 e comparando esse número com o registado nos doentes da Fase 1 em que a infusão de rocurónio foi efectuada sem usar o sistema de aconselhamento. Contabilizar ainda o número de procedimentos da Fase 3 em que o anestesista responsável tenha optado por abandonar o sistema de aconselhamento por entender que o desempenho deste não era adequado (Fase 3)
4. Avaliar a utilidade de PTC após estimulação de 100Hz como método de quantificar bloqueio intenso, isto é, mais do que profundo, isto sempre que em resposta ao tétano de 50Hz o número de PTC seja zero

Um objectivo claramente secundário será comparar os resultados da monitorização do BNM quando mais do que um monitor for usado. Como pelo menos em cada doente será usado o TOF Watch e o sistema de monitorização do BNM instalado em todos os monitores multi-modulars de anestesia do CHP (Aysis – General Electric), pelo menos esses serão comparados. Nos casos em que o anestesista entenda usar mais algum dos monitores disponíveis, nomeadamente o TOF Scan, será realizada uma comparação com o TOF Watch.

3. Critérios de Inclusão

Considerando a variabilidade da farmacodinâmica do rocurónio (EC50 e EC90) em adultos, que é de 30% [16], e analisando os estudos para o desenvolvimento dos modelos PK-PD do Rocurónio, estima-se que os dados de 30 doentes seriam adequados para a recolha da Fase 1. No entanto, considerando que o presente estudo é observacional, entendemos adequado aumentar o número de doentes de modo a aumentar a significância estatística da amostra e sua representatividade, pelo que na Fase 1 serão recolhidos dados de 40 doentes. Na Fase 3, para analisar o desempenho do sistema de aconselhamento serão recolhidos dados de 20 doentes.

Serão incluídos pacientes adultos, com idades entre 18 e 90 anos, de ambos os sexos, ASA I a III, com cirurgia programada no bloco operatório de Neurocirurgia do HSA-CHP ou na sala D do bloco operatório central, em que o médico anestesista responsável tenha optado por anestesia geral com bloqueio neuromuscular profundo com rocurónio.

O estudo tem caracter observacional e não envolve qualquer randomização.

Diariamente, após a confirmação da aplicação de BNM profundo indicada pelo anestesista responsável, os investigadores verificam se o/os doentes em causa reúnem critérios para inclusão no estudo. Em caso afirmativo, no dia anterior à cirurgia, um dos investigadores aborda o doente selecionado de modo a obter o seu consentimento informado para o estudo e para procede à sua pesagem numa balança de bio impedância. Havendo mais do que um doente a ser operado em simultâneo, e como a logística do estudo não permite incluir mais do que um doente em simultâneo, selecciona-se apenas um doente, utilizando como critério escolher em primeiro lugar o que estiver marcado para a sala 1 do bloco de neurocirurgia, em segundo lugar o da sala 2 e em terceiro lugar o da sala D. Nessa eventualidade apenas se obtém consentimento informado por parte do doente efectivamente selecionado.

Como se pode ver pelo protocolo a seguir descrito, o estudo não implica alterações à prática clínica habitual, no que respeite aos fármacos administrados, respectivas doses, monitorização e reversão do seu efeito. Apenas introduz monitorização mais frequente do BNM. Essa monitorização, todavia, é realizada com os monitores usados diariamente no CHP, aprovados para uso clínico e sempre usando modalidades de monitorização permitida pelos monitores. O sistema de aconselhamento ao anestesista a ser utilizado na fase 3 em momento algum substitui o anestesista e não implica qualquer sistema de automação nem actuação sobre o paciente.

Por forma a assegurar a confidencialidade da identidade do paciente para cada um será criado um código o qual passará a ser usado em todos os dados recolhidos.

Este estudo não apresenta custos acrescidos para o CHP, uma vez que todos os dispositivos, monitores ou fármacos fazem parte da rotina habitual ou do equipamento da equipa de investigação do Centro de Investigação Clínica em Anestesiologia, tendo ido adquiridos ao abrigo de projectos anteriores.

4. Critérios de Exclusão

Excluem-se pacientes com IMC superior a 35 kg/m2, complicações neuromusculares ou relacionadas a sensibilidade ao rocurónio, comorbilidades cardiovasculares, hepática ou renal graves e idades inferiores a 18 ou superiores a 90 anos.

5. Procedimento

Os doentes seguem a rotina habitual do bloco operatório, com realização de check-list de admissão, protocolo de cirurgia segura, monitorização standard e protocolo anestésico usual.

O estudo seguirá, para as fases 1, 2 e 3 o seguinte protocolo:

FASE 1:

i) Monitorização do BNM com o monitor TOF-Watch e ainda o monitor modular do sistema ASYS disponível em todas as salas de operações. O monitor TOF-Scan (também disponível no CHP) ou o monitor TOF-Cuff, caso possa ser disponibilizado pelo distribuidor já que não está disponível no CHP), poderão ser adicionados, caso o anestesista responsável pelo caso o pretenda. Todavia, a avaliação do BNM erá realizada sempre em função do TOF-Watch
ii) Calibração dos monitores de BNM após o doente estar inconsciente (é o procedimento usual)
iii) Administração de dose de intubação de rocurónio de 1mg/kg
iv) Estimulação a cada 3 minutos, com estímulo tetânico e avaliação de contagens pós tetânicas
v) Na eventualidade de 9 minutos após a dose de intubação não ter produzido BNM profundo (PTC menor ou igual a 2), administrar bolus adicional de rocurónio de 0,3mg/kg (1xED95)
vi) Permitir a recuperação do BNM até ter uma contagem pós tétano de 50Hz
vii) Quando obtidas pelo menos duas contagens pós tétano de 50hz em pelo menos duas avaliações sucessivas, iniciar perfusão contínua de rocurónio a 10ug/kg/min (trata-se da dose recomendada).
viii) Manter a estimulação a cada 3 minutos e tentar manter uma a duas contagens PTC através de ajustes manuais no ritmo de infusão de rocurónio efectuadas pelo anestesista responsável pelo caso.
ix) Suspender a perfusão de rocurónio quando o cirurgião iniciar o encerramento
x) Administrar sugamadex para reversão do bloqueio de acordo com as recomendações para cálculo da dose
xi) Iniciar o despertar do doente apenas quando TOF superior a 90%
xii) Quando a estimulação com 50Hz resultar em zero contagens pós-tetânicas, a estimulação seguinte, três minutos depois, será com 100Hz, seguida de estímulos simples a 1Hz (até se observar ausência de resposta), sendo que três minutos depois a estimulação será de novo com 50Hz, isto até que três estimulações de 50Hz resultem todas em pelo menos uma PTC

FASE 2

i) Através dos dados obtidos na fase 1 procede-se ao estudo analítico e posteriormente ao desenvolvimento de um algoritmo de personalização do bloqueio neuromuscular profundo para incorporar num sistema de aconselhamento ao anestesista.

FASE 3

i) Igual a fase 1
ii) Igual a fase 1
iii) Igual a fase 1
iv) Igual a fase 1
v) Igual a fase 1
vi) Igual a fase 1

vii) Quando obtidas pelo menos duas contagens pós tétano de 50hz em pelo menos duas avaliações sucessivas, iniciar infusão de rocurónio de acordo com o sistema de aconselhamento desenvolvido na FASE 2. A cada 3 minutos o sistema recebe o resultado do neuroestimulador TOF Watch (número de PTC), aplica o algoritmo desenvolvido na Fase 2 e exibe, no écran do computador, uma informação ao anestesista que sugere uma taxa de infusão de rocurónio em ug/kg/min, competindo ao anestesista a validação e consequente implementação desta sugestão, alterando a taxa de infusão na seringa infusora de rocurónio. Ao longo da infusão, e em função dos dados da monitorização do BNM, o sistema vai sugerindo ao anestesista, quer a administração de pequenos bolus, a paragem temporária da infusão (ou taxa de infusão de zero ug/kg/min) ou a alteração (subida ou descida) da taxa de infusão. Perante cada sugestão do sistema de aconselhamento, competirá ao anestesista a sua validação e implementação. A seringa infusora de rocurónio está ligada ao computador de modo a que a taxa de infusão seja continuamente gravada para posterior análise.

viii) Manter a estimulação a cada 3 minutos e manter a infusão de rocurónio de acordo com as indicações (se aceites pelo anestesista responsável) do sistema de aconselhamento.

ix) Igual a fase 1

x) Igual a fase 1

xi) Igual a fase 1

xii) Igual a fase 1

A obtenção do consentimento informado será realizada por um dos médicos que são investigadores no estudo. A condução da anestesia dos doentes a incluir no estudo será da responsabilidade do anestesista destacado para o caso, o qual não será necessariamente investigador no estudo. O anestesista responsável pelo caso trabalha habitualmente nas salas onde será realizado o estudo, utiliza habitualmente rotinas como as que fazem parte do estudo no que respeite ao BNM e estará familiarizado com o protocolo do estudo, fruto de um contacto prévio, aceitando colaborar. Em cada caso estará presente a investigadora Mafalda Couto que se responsabilizará pela supervisão da execução do protocolo no que inclui a monitorização do BNM, administração do rocurónio e a recolha de dados do estudo. Em qualquer momento o anestesista responsável pode, se o entender necessário, interromper a execução do protocolo.

A administração de anestésicos gerais, analgésicos, ou de qualquer outro fármaco que não o rocurónio fica a cargo do anestesista responsável pelo caso, o qual supervisiona a administração do rocurónio de acordo com o presente protocolo, seja na Fase 1 seja na Fase 3 de acordo com as sugestões do sistema de aconselhamento. A investigadora Mafalda Couto estará presente para assegurar a disponibilização dos monitores do BNM, as ligações dos monitores e seringa infusora ao computador que regista os dados da infusão de rocurónio, e ainda a aplicação da estimulação a cada três minutos como preconizado, recorrendo a um relógio com alarme de modo a garantir a aplicação atempada dos estímulos.

Os dados disponibilizados pelo monitor multimodular AYSIS, nomeadamente o BNM por electromiografia, serão recolhidos de modo contínuo através do software Rugloop[II] (Demed Engineering, Belgium), habitualmente utilizado para a recolha de dados em estudos clínicos no bloco operatório de neurocirurgia e instalado num computador dedicado. Este software também recolhe dados do sistema de perfusão dos fármacos anestésicos utilizado diariamente no bloco operatório de neurocirurgia, sistema Fresenius Base Primea - Orchestra. Estes dados são transferidos e tratados usando o software LABGRAB, instalado num computador dedicado. O monitor TOF Watch é

conectado ao mesmo computador através do software TOFLink (disponível no CHP) para registo da monitorização do BNM. Uma seringa Alaris será utilizada para a infusão de rocurónio, sendo a seringa conectada ao mesmo computador para registo dos dados da infusão de rocurónio, sendo que a velocidade de infusão será sempre ajustada pelo anestesista responsável pelo caso. Os dados colectados por outros monitores de BNM eventualmente utilizados, TOF Scan e ou TOF Cuff, no caso de não haver software de interface específicos para a transferência de dados, serão registados manualmente.

O desenvolvimento do sistema de aconselhamento será executado pela investigadora Mafalda Couto, sob supervisão da Professora Catarina Nunes (Coordenadora do Centro de Investigação Cínica em Anestesiologia do CHP e do Mestrado de Estatística, Matemática e Computação pela Universidade Aberta) e do Professor Joaquim Gabriel Mendes (Professor integrado no grupo de Automação, Instrumentação e Controlo na Faculdade de Engenharia da Universidade do Porto).

Espera-se que a monitorização de PTC a cada 3 minutos, a utilização de estimulação de 100Hz quando ocorrer PTC de zero após 50Hz e o desenvolvimento de um modo de obtenção de BNM profundo que simultaneamente individualize e automatize a administração de rocurónio, possam constituir um avanço importante num dos componentes fundamentais da anestesia geral, com larga aplicabilidade clínica. As suas vantagens potenciais são:

a) aumento da segurança do doente por maior garantia de imobilidade durante a cirurgia
b) melhores condições para o cirurgião por BNM profundo de uma forma estável
c) melhor controlo da profundidade do componente hipnótico da anestesia geral
d) menor consumo de anestésicos gerais com menor incidência de hipotensão arterial e menor utilização de fármacos vasoactivos em anestesias gerais simples, isto é sem uso de técnicas combinadas
e) poder controlar BNM intenso, isto é, BNM com zero PTC após estimulação de 50Hz, através da implementação de um novo método de monitorização do BNM

Estes benefícios deverão ser investigados e verificados posteriormente em estudos futuros, a fim de provar o conceito desenvolvido e eventualmente progredir para a criação de um dispositivo médico com automação da administração de rocuronio, não fazendo parte dos objectivos do presente estudo.

6. Tratamento dos dados

Os dados obtidos, doses de rocurónio e monitorização do BNM, serão analisados offline. Os dados recolhidos para análise avaliados ao longo do tempo são os volumes e velocidades de administração de Rocurónio, os estímulos aplicados pelo neuroestimulador TOF Watch (padrão, intensidade, frequência, etc.) os intervalos de tempo de estímulos e os valores das respostas (nomeadamente contagens e amplitude de cada resposta de PTC). O software Matlab será usado para análise avançada de dados e pós-processamento. Será produzido um ficheiro Excel por paciente com os dados do rocurónio e da monitorização.

Prevê-se a apresentação de resultados através de comunicações científicas nas áreas da engenharia e da anestesiologia. Prevê-se a publicação de artigos científicos em revistas internacionais, um mais técnico na área da engenharia e um com os resultados clínicos numa revista de anestesiologia.

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8.3.2 INFORMED CONSENT

DEFI
centro hospitalar do Porto
DEPARTAMENTO DE ENSINO, FORMAÇÃO E INVESTIGAÇÃO

TERMO DE CONSENTIMENTO INFORMADO

DESENVOLVIMENTO DE UM SISTEMA DE ACONSELHAMENTO AO ANESTESISTA PARA APERFEIÇOAR O RELAXAMENTO NEUROMUSCULAR PROFUNDO POR INFUSÃO DE ROCURÓNIO

Eu, abaixo-assinado, fui informado/a de que o Estudo de Investigação acima mencionado tem que ver com um dos aspectos da anestesia geral a que vou ser submetido/a, que é o relaxamento muscular. Foi-me explicado que para a minha cirurgia é benéfico que os músculos estejam muito bem relaxados, o que se designa como relaxamento profundo. O medicamento relaxante muscular que me vai ser administrado é o que se usa habitualmente. Chama-se rocurónio e será usado nas doses habituais. O anestesista, como habitualmente nestas anestesias, irá usar um dispositivo (monitor do relaxamento muscular), que mede a contracção de um dos músculos do dedo polegar, para avaliar, a cada 3 minutos, o nível de relaxamento muscular, de modo a que se mantenha profundo.

O estudo de investigação tem por objectivo desenvolver um sistema de aconselhamento ao anestesista para aperfeiçoar o relaxamento muscular profundo. Neste estudo os investigadores vão utilizar, na sala de operações, um computador que fica ligado ao monitor que mede o relaxamento muscular eàseringa que administra o medicamento rocurónio. Os dados do monitor e da seringa serão continuamente gravados para poderem ser analisados. Os investigadores vão desenvolver um algoritmo (equações matemáticas) que irão permitir analisar a cada 3 minutos o nível de relaxamento muscular e apresentar, no ecrã do computador, qual a dose de rocurónio entendida como ideal naquele momento. Essa dose é apresentada ao anestesista, o qual decide se a aceita ou não.

O procedimento anestésico segue a rotina habitual para o tipo de cirurgia a que vai ser submetido/a. Não são usados medicamentos novos, nem doses diferentes das habituais, nem procedimentos que alterem a duração da anestesia ou da cirurgia, nem qualquer intervenção desagradável ou dolorosa. Em qualquer momento é o seu anestesista que decide qual a melhor dose do medicamento rocurónio, não existindo um sistema automático, nem controlo por um computador. Será o médico, com base nos seus conhecimentos e experiencia e análise da situação, que terá a última palavra. Seguindo ou não a dose aconselhada. A utilidade do sistema de aconselhamento será avaliada no final do estudo analisando se o aconselhamento do sistema foi aprovado pelo anestesista resultando num nível estável de relaxamento muscular profundo. No final da cirurgia será administrado o medicamento sugamadex para obter uma rápida recuperação da força muscular proporcionando um despertar rápido e seguro. Trata-se do procedimento habitual neste tipo de anestesia. Este medicamento é administrado diariamente a muitos doentes sujeitos a cirurgia neste hospital.

Foi-me garantido que todos os dados relativos à identificação dos participantes neste estudo são confidenciais e que será mantido o meu anonimato.

Sei que posso recusar-me a participar ou interromper a qualquer momento a participação no estudo, sem nenhum tipo de penalização por este facto.

Compreendi a informação que me foi dada, tive oportunidade de fazer perguntas e as minhas dúvidas foram esclarecidas.

Aceito participar de livre vontade no estudo acima mencionado.

Também autorizo a divulgação dos resultados obtidos no meio científico, garantindo o anonimato.

Nome do Participante no estudo: _____

Data	Assinatura
___/___/_____	_____

Nome do Médico Responsável: _____

Data	Assinatura
___/___/_____	_____

centro hospitalar do Porto
DEFI
DEPARTAMENTO DE ENSINO, FORMAÇÃO E INVESTIGAÇÃO

INFORMAÇÃO AO DOENTE

DESENVOLVIMENTO DE UM SISTEMA DE ACONSELHAMENTO AO ANESTESISTA PARA APERFEIÇOAR O RELAXAMENTO NEUROMUSCULAR PROFUNDO POR INFUSÃO DE ROCURÓNIO

A cirurgia a que vai ser submetido será realizada sob anestesia geral. Para isso o seu anestesista vai usar medicamentos que produzem 3 efeitos: inconsciência (vulgarmente referido como "dormir"), analgesia (ou ausência de dor) e imobilidade, ou relaxamento muscular.

O estudo que estamos a realizar incide apenas sobre o relaxamento muscular. Na cirurgia a que vai ser submetido será administrado um medicamento chamado rocurónio cujo efeito é relaxar os músculos. No caso da sua cirurgia é importante que os músculos estejam muito bem relaxados de modo a que o cirurgião possa ter as melhores condições para operar e que não ocorram movimentos, nomeadamente os chamados movimentos reflexos, isto é, não-intencionais. Para isso a dose do medicamento rocurónio será adequada para proporcionar o que se chama "bloqueio neuro muscular profundo" ou "relaxamento muscular profundo". Para avaliar se o relaxamento muscular é de facto profundo o anestesista utiliza um dispositivo (monitor) que a cada três minutos mede o grau de relaxamento muscular. Esta medição é realizada numa das mãos, avaliando o relaxamento de um dos músculos que move o dedo polegar. O medicamento rocurónio, as doses em que é administrado, o dispositivo que mede o grau de relaxamento muscular e o nível profundo de relaxamento muscular fazem parte da prática clínica habitual para a cirurgia a que vai ser submetido.

O que se pretende com este estudo é registar, ao longo de todo o procedimento, as quantidades de rocurónio administradas e os valores obtidos pela medição do nível de relaxamento muscular. Esse registo será feito com recurso a um computador que se ligaàseringa que administra o rocurónio e ao monitor do bloqueio neuro-muscular.

Com este estudo pretende-se obter dados de cada doente que permitam avaliar o modo como cada um respondeàdose inicial de rocurónio, a qual se sabe variar de doente para doente, tal como acontece com todos os medicamentos. Em cada doente, este medicamento vai sendo doseado pelo anestesista de modo a obter o nível desejado de relaxamento profundo. A dose eficaz para tal também varia de doente para doente, sendo necessário ir ajustando a dose em função das medições efectuadas pelo monitor do relaxamento muscular.

Numa primeira fase do estudo vamos gravar os dados de cada doente. Numa segunda fase vamos analisar esses dados de modo a desenvolver um algoritmo (um conjunto de fórmulas matemáticas) que possa permitir orientar a administração de rocurónio em novos doentes. Numa terceira fase iremos utilizar um sistema de apoioàdecisão do anestesista com o qual pretendemos aperfeiçoar o relaxamento profundo, isto é adequar as doses do medicamento rocurónio para obter um relaxamento profundo que seja estável. Este sistema de aconselhamento funciona com um computador presente na sala de operações que a cada 3 minutos vai recebendo os dados do monitor de relaxamento muscular e sugerindo ao anestesista o que se calcula ser a dose ideal. Assim, nessa fase, a cada 3 minutos o sistema aconselha ao anestesista a dose de rocurónio. Compete ao anestesista, em função da sua avaliação clínica e com base nos seus conhecimentos e experiência, aceitar e implementar esse aconselhamento. Ao analisar os resultados iremos verificar a utilidade do sistema, verificando se de facto o aconselhamento foi aceite pelo anestesista e resultou em estabilidade do relaxamento muscular profundo.

Ao participar neste estudo vai receber o medicamento habitualmente usado para obter relaxamento muscular, nas doses habituais. No final da cirurgia será administrado o medicamento sugamadex, nas doses habituais, o qual reverte o relaxamento muscular, permitindo que desperte rápida e confortavelmente. Em relação ao que é usual haverá duas diferenças: os dados do

medicamento e do monitor serão gravados e, na terceira fase do estudo, estará disponível um computador que para além da recolha dos dados vai auxiliando o anestesista aconselhando a melhor dose de rocurónio, sempre tendo em conta o modo como esse doente reagiuàdose inicial, a qual será a mesma para todos os doentes.

Este estudo é apenas observacional de recolha de dados e de aconselhamento ao anestesista e não interfere com a prática clínica habitual ou com o procedimento anestésico ou cirúrgico. Não são usados medicamentos novos, nem doses não habituais nem o participante é sorteado para receber um determinado tratamento.

Todos os dados relativos à identificação dos participantes neste estudo são confidenciais e será mantido o anonimato. O doente pode recusar-se a participar ou interromper a qualquer momento a participação no estudo, sem nenhum tipo de penalização por este facto. A divulgação dos resultados obtidos será feita apenas no meio científico, garantindo o anonimato.

Muito obrigado por aceitar participar.

Identificação e contacto do Investigador Principal:

Pedro Amorim
Médico Anestesiologista e Chefe de Serviço
Serviço de Anestesiologia do Centro Hospitalar do Porto
Telefone: 222077500 (extensão 1280 ou 1250 ou 1895)
Email: u03189@hgsa.min-saude.pt
Serviço de Anestesiologia do CHP na internet: http://www.anestesiologiachp.com/index.php

8.3.3 ACCEPTANCE LETTER

DESENVOLVIMENTO DE UM SISTEMA DE ACONSELHAMENTO AO ANESTESISTA PARA APERFEIÇOAR O RELAXAMENTO NEUROMUSCULAR PROFUNDO POR INFUSÃO DE ROCURÓNIO

209-18 (184-DEFI/183-CES) Projeto de investigação

Data de Receção no Secretariado de Estudos da Investigação (GCI): 15/10/2018
Data de Receção no Gabinete Coordenador da Investigação (GCI): 16/10/2018

Investigador Principal/ Responsável no Centro Hospitalar do Porto (CHP):
Pedro Amorim – Médico Anestesista, Assistente Graduado Sénior, Serviço de Anestesiologia, Departamento de Anestesiologia, Cuidados Intensivos e Emergência (DACIE) do CHP.

Outros Investigadores:
Catarina S. Nunes – Professora Auxiliar da Universidade Aberta e Investigadora Principal do Centro de Investigação Clínica em Anestesiologia do CHP;
Mafalda A. S. Couto – Aluna de Doutoramento da Faculdade de Engenharia da Universidade do Porto, Investigadora do Centro de Investigação Clínica em Anestesiologia do CHP;
Humberto Machado – Médico Assistente Graduado Sénior de Anestesiologia do CHP; Professor Catedrático Convidado do ICBAS/ UP;
Simão Esteves – Médico Assistente Graduado Sénior de Anestesiologia do CHP.

Resumo do Estudo:

- **Local do estudo no CHP:** Serviço de Anestesiologia, DACIE.
- **Desenho do estudo**: institucional, clínico, descritivo, observacional, transversal e prospetivo.
- **Objetivo primário** (seção 1.4): Desenvolver um método mais avançado de administração de rocurónio para BNM (bloqueio neuromuscular) profundo, aplicando avaliação de contagens pós-tetânicas (PTC) a cada 3 minutos, combinando esta avaliação frequente com a individualização da administração subsequente à dose de intubação e o aperfeiçoamento da administração, especificamente através do desenvolvimento de um sistema de aconselhamento ao anestesista.
- **Objetivos específicos** (seção 2):
  1) Analisar a resposta individual a uma dose de intubação de 1 mg/kg de rocurónio (**Fase 1**).
  2) Desenvolver um algoritmo que utilize, doente a doente, a informação relativa ao modo como respondeu à dose da intubação, para determinar a taxa de infusão de rocurónio, criando um sistema de aconselhamento ao anestesista que, a cada 3 minutos, recebe informação do número de PTC obtidas e sugere eventuais alterações na taxa de infusão (**Fase 2**).
  3) Avaliar o desempenho do algoritmo/ sistema de aconselhamento através da análise do número de períodos de 3 minutos em que o número de PTC é inferior a zero ou superior a 2 e comparando esse número com o registado nos doentes da Fase 1 em que a infusão de rocurónio foi efetuada sem usar o sistema de aconselhamento. Contabilizar ainda o número de procedimentos da Fase 3 em que o anestesista responsável tenha optado por abandonar o sistema de aconselhamento por entender que o desempenho deste não era adequado (**Fase 3**).
  4) Avaliar a utilidade de PTC após estimulação de 100Hz como método de quantificar bloqueio intenso, isto é, mais do que profundo, isto sempre que em resposta ao tétano de 50Hz o número de PTC seja zero.
- **Objetivo secundário** (seção 2): Comparar os resultados da monitorização do BNM quando mais do que um monitor for usado (*TOF Watch* vs. sistema de monitorização do BNM instalado em todos os

monitores multi-modulars de anestesia do CHP – *Asys* da *General Electric*; ou *TOF Watch* vs. *TOF Scan* quando este último for usado).

- **Participantes em estudo** (seção 3):
  Critérios de inclusão (secção 3): Pacientes adultos, com idades entre 18 e 90 anos, de ambos os sexos, ASA I a III, com cirurgia programada no bloco operatório de Neurocirurgia do HSA-CHP ou na sala D do bloco operatório central, em que o médico anestesista responsável tenha optado por anestesia geral com BNM profundo com rocurónio.
  Critérios de exclusão (seção 4): Pacientes com IMC superior a 35 kg/m^2, complicações neuromusculares ou relacionadas a sensibilidade ao rocurónio, comorbilidades cardiovasculares, hepática ou renal graves e idades inferiores a 18 ou superiores a 90 anos.
- **Tamanho da amostra** (secção 3): fase 1 – 40 doentes; fase 3 – 20 doentes.
- **Duração do estudo**: início – 01/10/2018; conclusão – 31/12/2019. Prazo a cumprir – 15 meses.
- **Metodologia**: O estudo envolve a recolha de dados (clínicos) dos participantes, no âmbito da sua cirurgia programada a ser realizada sob anestesia geral com BNM profundo com rocurónio, de acordo com o procedimento habitual de rotina adotado no CHP, na tentativa de desenvolver um sistema de aconselhamento ao anestesista para aperfeiçoar o relaxamento muscular profundo.
  - O recrutamento dos doentes e a recolha de dados clínicos a partir dos processos clínicos e registos dos monitores serão realizados pela equipa investigadora, no âmbito do seguimento clínico habitual do CHP.
  - Foi enviado o folheto informativo sobre o estudo para os doentes e o consentimento informado.
  - Após a confirmação da aplicação de BNM profundo indicada pelo médico anestesista responsável envolvido e o cumprimento dos critérios de inclusão, o doente selecionado será convidado a participar no estudo no dia anterior à cirurgia por um dos elementos da equipa investigadora, dando o seu consentimento e sendo pesado numa balança de bioimpedância. No caso de serem selecionados 2 doentes a serem operados em simultâneo, e dado que não é possível incluir mais do que um doente, serão utilizados os seguintes critérios: em primeiro lugar será selecionado o doente que irá ser operado na sala 1 do bloco de neurocirurgia, em segundo lugar o que vai ser operado na sala 2 e em terceiro lugar o da sala D.
  - O procedimento de anestesia a ser aplicado seguirá a rotina habitual para o tipo de cirurgia a que o participante será submetido (não serão introduzidas alterações quanto aos fármacos administrados e respetivas doses, tipo de monitorização e reversão do seu efeito). Será apenas realizada uma monitorização mais frequente do BNM, utilizando os monitores usados diariamente no CHP. Poderá também ser usado equipamento da equipa de investigação do Centro de Investigação Clínica em Anestesiologia, adquiridos ao abrigo de projetos anteriores.
  - O anestesista responsável pela cirurgia será convidado a colaborar no estudo, usando habitualmente o procedimento de anestesia a ser testado no estudo e estando a par do mesmo.
  - A investigadora Mafalda Couto estará presente para disponibilização dos monitores do BNM, as ligações dos monitores e seringa infusora ao computador que regista os dados da infusão de rocurónio, bem como para garantir a aplicação atempada dos estímulos a cada 3 minutos.
  - Os dados de BNM registados pelos diferentes monitores (*Aysis*, *TOP Watch*, *TOF Scan* ou *TOF Cuff*), bem como os dados do sistema de perfusão dos fármacos anestésicos, incluindo o rocurónio (sistema *Fresenius Base Primea*), serão recolhidos utilizando diferentes softwares (*Ruglood*, *TOFLink*, *LABGRAB*) para o computador, ou manualmente, quando não existirem.
  - O desenvolvimento do sistema de aconselhamento será realizado pela Investigadora Mafalda Couto sob supervisão da Prof. Catarina Nunes e do Prof. Joaquim Gabriel Mendes da FEUP.

- Não foi enviado um formulário para registo dos dados a serem colhidos, mas foram indicadas as variáveis a serem analisadas ao longo do tempo: volumes e velocidades de administração de rocurónio, estímulos aplicados pelo neuroestimulador *TOF Watch* (padrão, intensidade, frequência, etc), intervalos de tempo de estímulos e valores das respostas (contagens e amplitude de cada resposta PTC).
- O software *Matlab* será usado para análise de dados e será produzido um ficheiro Excel por paciente com os dados do rocurónio e da monitorização.
- São garantidas a proteção da identidade dos participantes e a confidencialidade dos dados recolhidos (atribuição de um código utilizado em todos os dados recolhidos).
- Foi referida a criação de uma base de dados anonimizada.

Aspetos Financeiros:

É referido que "Este estudo não apresenta custos acrescidos para o CHP, uma vez que todos os dispositivos, monitores ou fármacos fazem parte da rotina habitual ou do equipamento da equipa de investigação do Centro de Investigação Clínica em Anestesiologia, tendo sido adquiridos ao abrigo de projetos anteriores."

Requisitos Preenchidos:

☑ Pedidos de autorização dirigidos ao Conselho de Administração, Comissão de Ética para a Saúde e Departamento de Ensino, Formação e Investigação.
☑ Termo de Responsabilidade do Investigador Principal/ Responsável no CHP (Dr. Pedro Amorim).
☑ Autorização do Diretor do DACIE do CHP (Dr. António Marques).
☑ Autorização do Diretor do Serviço de Anestesiologia do CHP (Prof. Doutor Humberto Machado).
☑ Termo de Consentimento Informado e documento informativo para o doente.
☑ Lista de variáveis a serem colhidas.

APRECIAÇÃO e PARECER FINAL do GABINETE COORDENADOR DE INVESTIGAÇÃO do CHP:

A proposta de investigação "*Desenvolvimento de um sistema de aconselhamento ao anestesista para aperfeiçoar o relaxamento neuromuscular profundo por infusão de rocurónio*" foi avaliada pelo Gabinete Coordenador de Investigação, não tendo suscitado dúvidas ou questões a esclarecer.

Estritamente no que se refere à componente científica do projeto de investigação, **PARECER FAVORÁVEL pelo Gabinete Coordenador de Investigação**.

O Gabinete Coordenador de Investigação dá por concluída a análise do processo, sendo enviado ao Investigador Principal o Parecer elaborado para conhecimento.

O processo será enviado para a Comissão de Ética para avaliação dos aspetos éticos, nomeadamente o termo de consentimneto informado e o documento informativo sobre o estudo para o participante.

Deve ser aguardada a comunicação da autorização institucional para a realização do estudo.

Centro Hospitalar do Porto, 14 de novembro de 2018

_____

Márcia Oliveira, Gabinete Coordenador de Investigação

_____

Isabel Fonseca, Responsável pela área da Análise Científica dos Estudos de Investigação, DEFI/ Gabinete Coordenador de Investigação

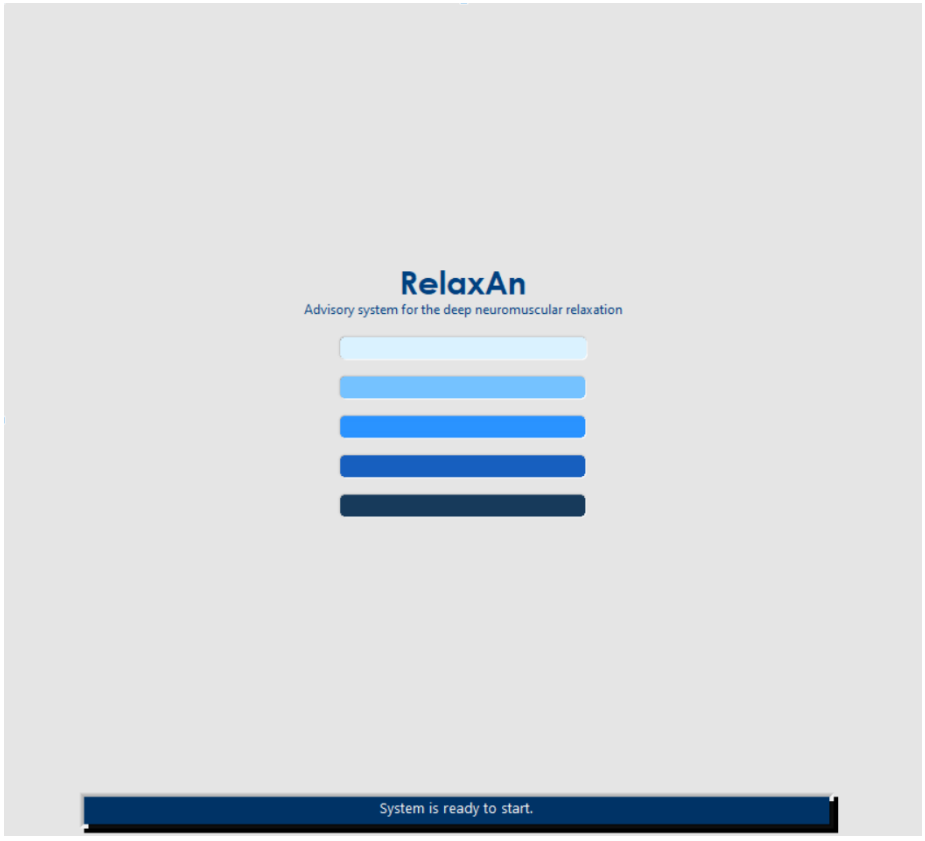
8.4 USER INTERFACE FOR RelaxAn

8.4.1 PRESENTATION PAGE

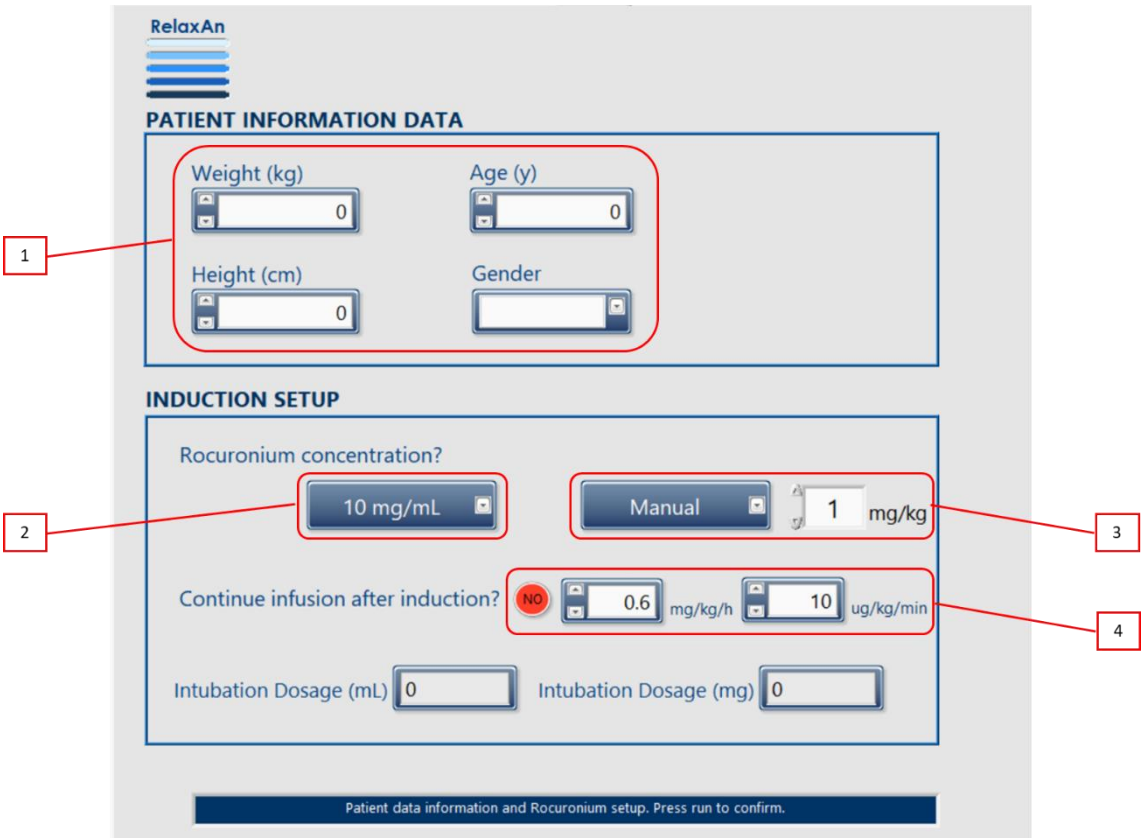
8.4.2 SYRINGE CONFIGURATION PROCESS


RelaxAn
Advisory system for the deep neuromuscular relaxation
Rocuronium Infusion Pump verified!


RelaxAn
Advisory system for the deep neuromuscular relaxation
Configuration complete.



8.4.3 PATIENT INFORMATION AND INDUCTION SETUP



1. Boxes for patient data insertion regarding weight (kg), age (year old), height (cm) and sex (female/male)
2. Selection of the dilution of the rocuronium drug:

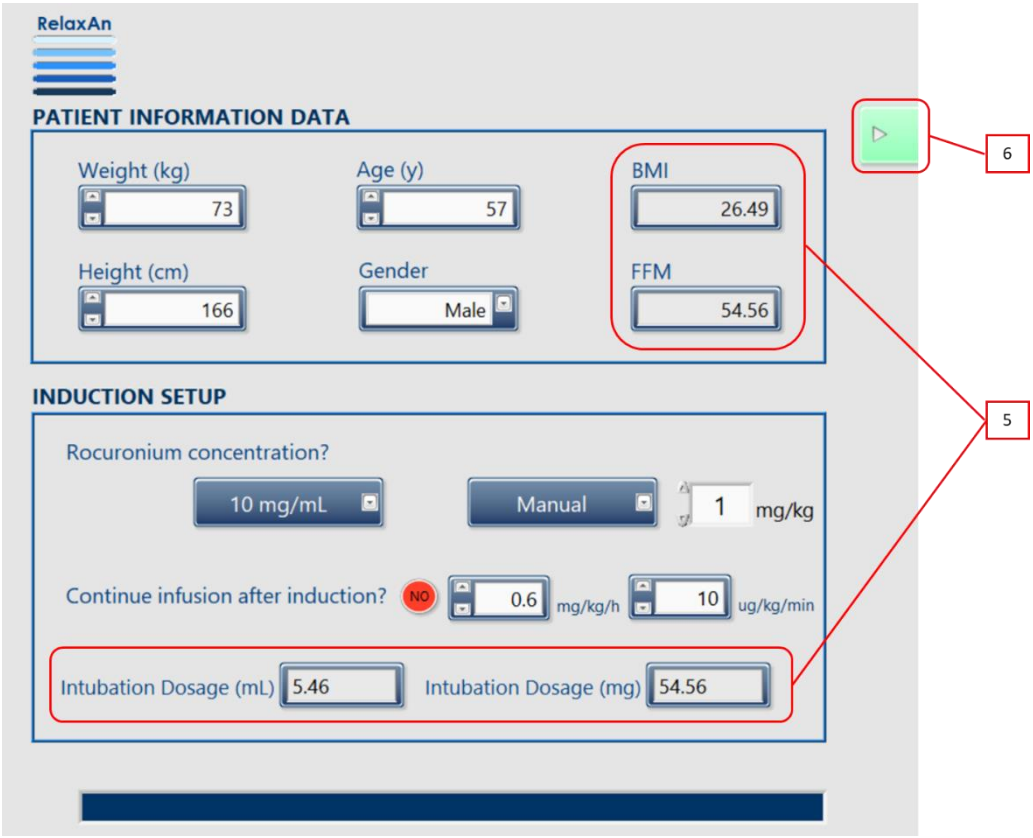
   ✓ 10 mg/mL
   5 mg/mL
3. Selection of induction bolus dose:

   1 ED95
   2 ED95
   ✓ Manual

   Manual option refers to customized dose in mg/kg (FFM)
4. After induction bolus parameters:

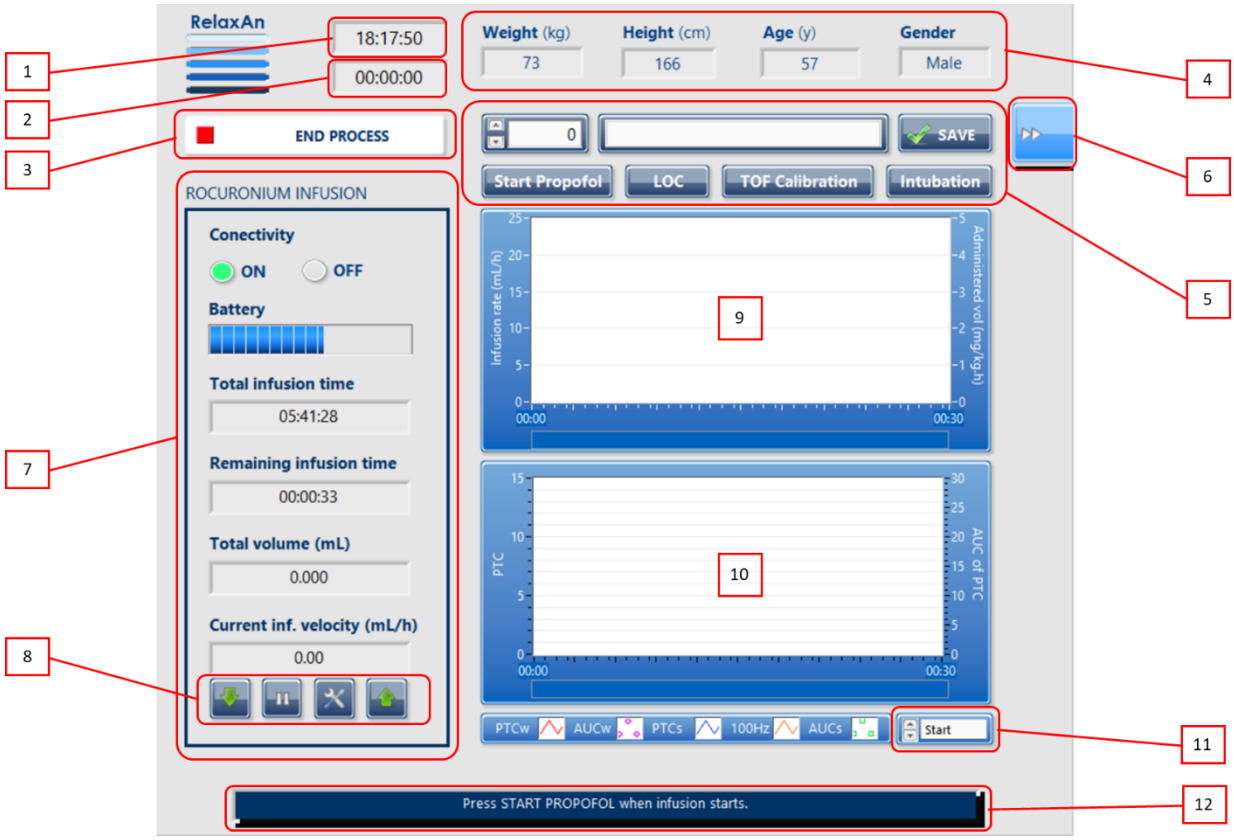
   NO or YES selects if rocuronium infusion starts after the induction bolus

   Selection of the starting infusion rate in µg/kg/min.

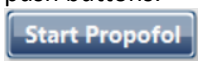


5. After the filling of the patient and induction setup data, automatic calculation of BMI (kg/m^2), FFM (kg), Intubation dosage (mL and mg) are visible in the display.
6. Run button to confirm selected parameters and advance.

8.4.4 REAL-TIME DATA DISPLAY FOR THE CLINICAL STUDY



1. Current time (HH:MM:SS).
2. Timer, starting when "Start Propofol" is pushed, corresponding to the initiation of anesthesia (HH:MM:SS).
3. Stop the program (stops ongoing processes and closes the window).
4. Patient data display (weight, height, age, and sex).
5. Events registry. For easy-use, the main stages of the anesthesia process are directly recorded with individual push buttons:

   Records Propofol infusion initiation;

   Records Loss-of-consciousness detection;

   Records TOF-Watch® SX calibration;

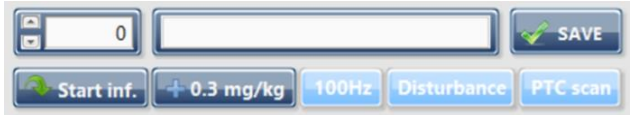
   

   Records intubation completion.

   Other details during the process can be added in the empty boxes (numerical and string) and press 

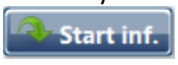
   button.

   After intubation is indicated and recorded, push-buttons are substituted by additional ones:

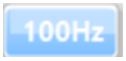
   If 

   was selected in the induction setup (previous page) infusion starts immediately after the initial bolus, else if 

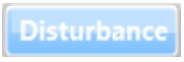
   was selected, continue infusion will initiate after pushing the 

   button, at the previously defined rate;

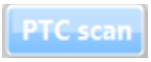
additional 0.3 mg/kg (FFM) bolus in case the initial bolus is to achieve deep NMB;



recording of 100 Hz PTC stimuli measurements;

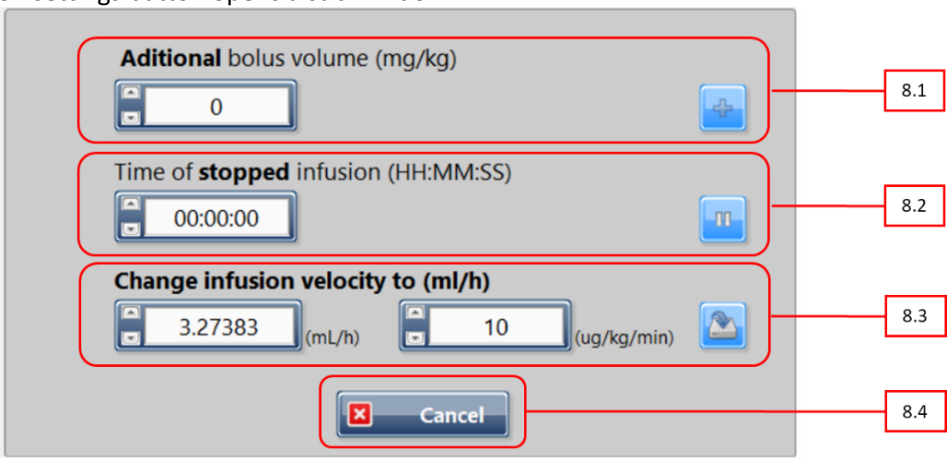


recording of visually detected disturbance during an NMB evaluation;

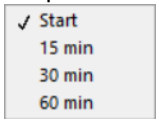


recording of measurements in TOFscan® after visual assessment (corrected measurement to fit comparison with TOF-Watch® SX).

6. Start rocuronium infusion of induction bolus (only visible after TOF-Watch® SX calibration button is pushed and validated in 6).
7. Display of syringe data and infusion details:
   ON/OFF Connectivity between PC and syringe pump;
   Current battery voltage;
   Total infusion time since rocuronium induction bolus (HH:MM:SS);
   Current remaining infusion time available (HH:MM:SS);
   Total volume of rocuronium administered, including induction bolus (mL);
   Current infusion rate (mL/h);
   Rocuronium infusion adjustments.
8. Rocuronium adjustment buttons:
    and  directly decrease/increase rocuronium infusion rate in 10 %, respectively;
    and  directly pauses/resumes the rocuronium infusion;
    infusion settings button opens a sub-window:

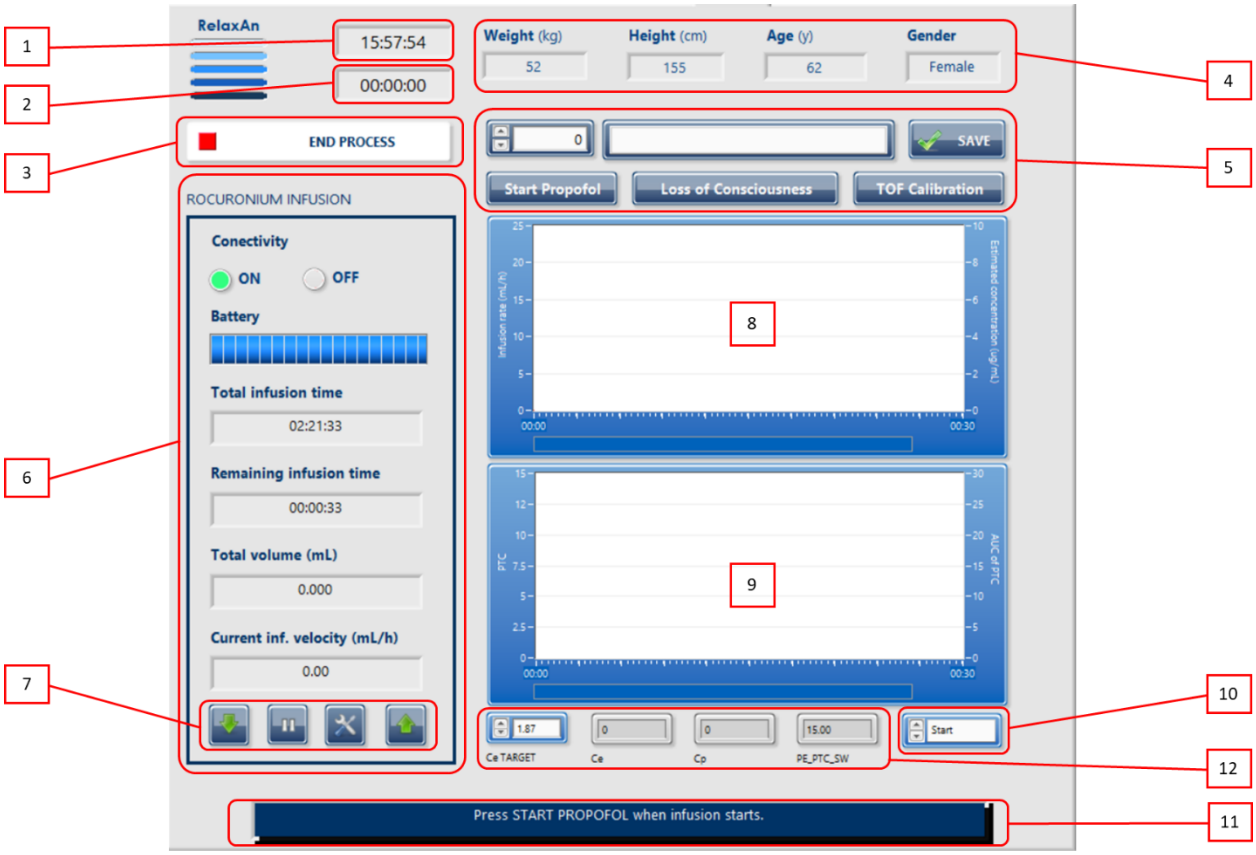


   8.1. Custom additional bolus (in mg/kg FFM) after pressing  ;
   8.2. Custom duration to stop infusion (in HH:MM:SS format) after pressing  ;
   8.3. Custom adjustment of the infusion rate (in ml/h or µg/kg/min) after pressing  ;
   8.4. Cancel any configuration and closes the sub-window.
9. Graphic visualization of rocuronium infusion rate (ml/h) and total volume administered (mg/kg/h) throughout the procedure.
10. Graphic visualization of PTC monitoring responses of both TOF-Watch® SX and TOFscan®, respective AUC of each PTC measurement, and the 100 Hz PTC responses added in 5 throughout the procedure.
11. Graphics time scale selector (since the start of the procedure, last 15, 30 or 60 minutes):

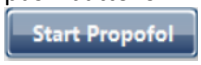


12. Display of relevant messages and alarm information for guidance and support during the procedure.

8.4.5 REAL-TIME DATA DISPLAY FOR THE RelaxAn CLOSED-LOOP CONTROL



1. Current time (HH:MM:SS).
2. Timer, starting when "Start Propofol" is pushed, corresponding to the initiation of anesthesia (HH:MM:SS).
3. Stop the program (stops ongoing processes and closes the window).
4. Patient data display (weight, height, age, and sex).
5. Events registry. For easy-use, the main stages of the induction process are directly recorded with individual push-buttons:



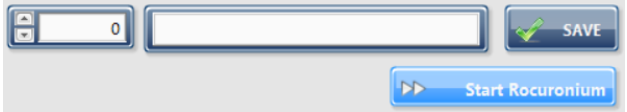
Records Propofol infusion initiation;

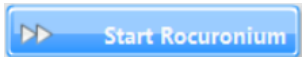
Records Loss-of-consciousness detection;

Records TOF-Watch® SX calibration;

Other details during the process can be added in the empty boxes (numerical and string) and press 

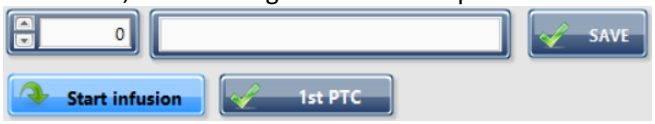
button. After calibration is indicated and recorded, these push-buttons are substituted by:



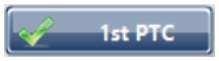


starts rocuronium infusion of induction bolus.

After induction bolus is administered, a new change on the visible push button occurs:

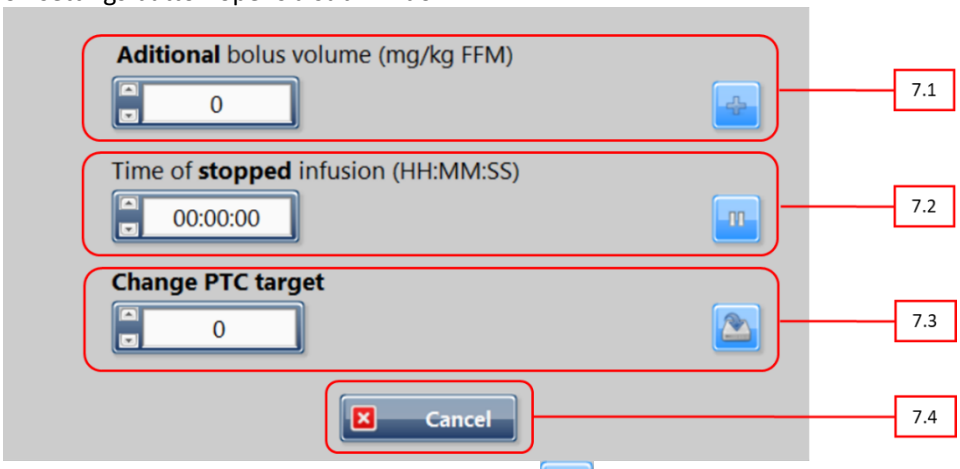


Starts continuous infusion of rocuronium, which after user validation is controlled considering the NMB monitoring feedback.

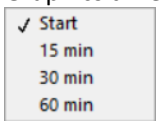


Records the time interval since initial bolus until the de detection of the first PTC recovery (recording can be repeated and restored in case of an error in NMB monitoring evaluation)

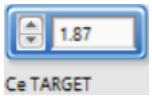
6. Display of syringe data and infusion details:
   ON/OFF Connectivity between PC and syringe pump;
   Current battery voltage;
   Total infusion time since rocuronium induction bolus (HH:MM:SS);
   Current remaining infusion time available (HH:MM:SS);
   Total volume of rocuronium administered, including induction bolus (mL);
   Current infusion rate (mL/h);
   Rocuronium infusion adjustments.
7. Rocuronium adjustment buttons:
    and  directly decrease/increase Ce_{target} (µg/mL) in 10 %, respectively;
    and  directly pauses/resumes the continuous rocuronium infusion;
    infusion settings button opens a sub-window:



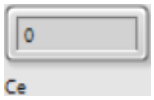
   7.1. Custom additional bolus (in mg/kg of FFM) after pressing  ;
   7.2. Custom duration to stop infusion (in HH:MM:SS format) after pressing  ;
   7.3. Custom adjustment of the PTC_{target} after pressing  , which recalculates for the Ce_{target} (µg/mL);
   7.4. Cancel any configuration and closes the sub-window.
8. Graphic visualization of the rocuronium infusion rate (ml/h) and of the estimated *Cp* (µg/mL) and *Ce* (µg/mL) throughout the procedure.
9. Graphic visualization of PTC monitoring responses of TOF-Watch® SX, respective AUC of each PTC measurement, and the predicted PTC effect based on the parameters estimated for the mean SW PK-PD model, during the procedure.
10. Graphics time scale selector (since the start of the procedure, last 15, 30 or 60 minutes):



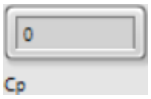
11. Display of relevant messages and alarm information for guidance and support during the procedure.
12. Current estimated values of:



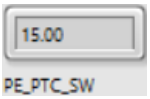
target *Ce* (µg/mL) to guide the rocuronium infusion control;



estimated rocuronium effect-site concentration (µg/mL) based on the SW PK model;



estimated rocuronium plasma concentration (µg/mL) based on the SW PK model;



estimated PTC effect, based on the mean parameters of SW PK-PD model (determined in section 4.2).

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8.5 AREA UNDER THE CURVE OF PTC

Section of the PTC measurements and respective AUC_{PTC} for a case example, showing the increasing of AUC_{PTC} to precede the recovery of the following PTC measurements.

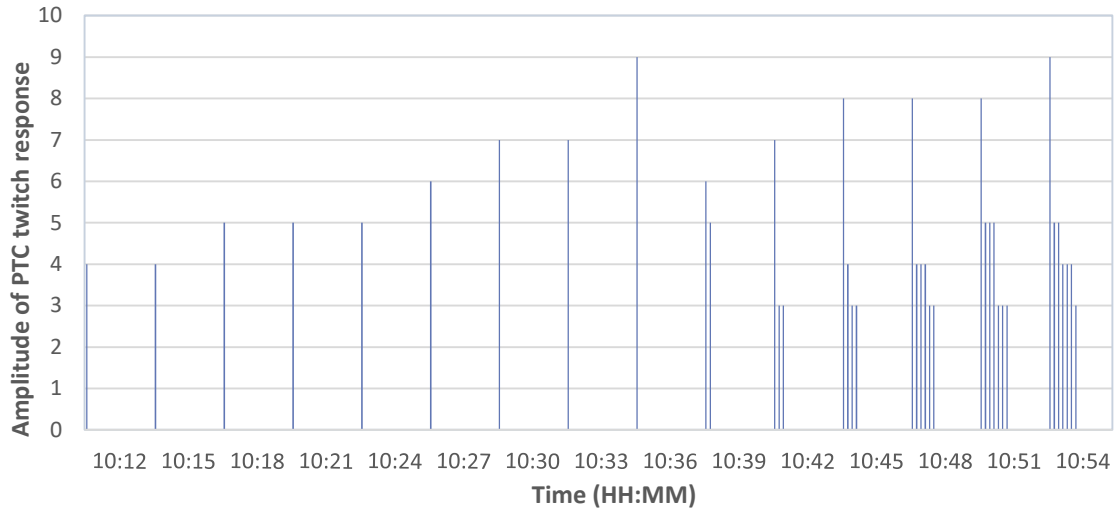


Figure 8.1 - Illustration of the twitch amplitude after the tetanic stimuli, in the PTC evaluation along the time, of a case example.

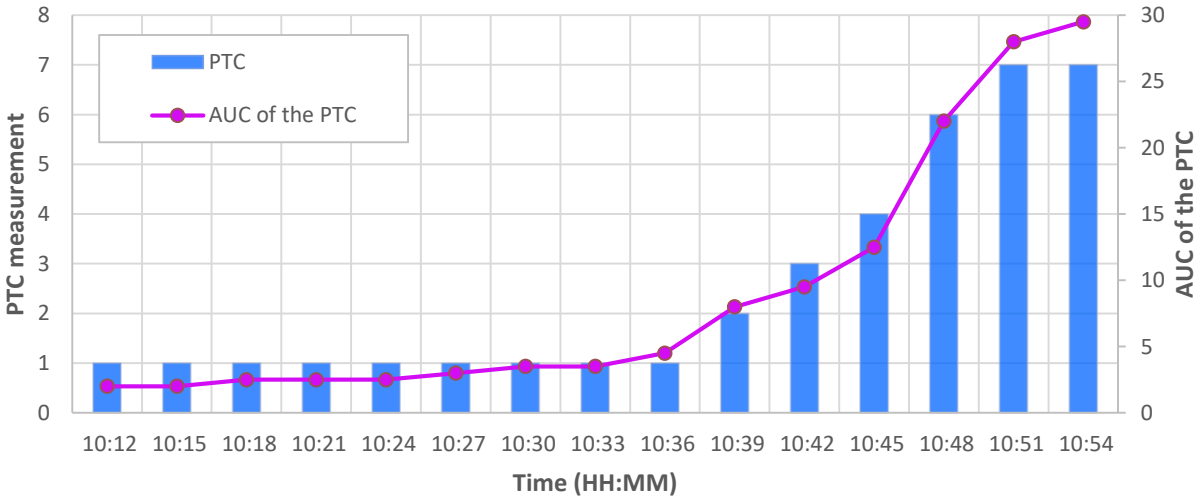


Figure 8.2 - Illustration of the of PTC measurements and respective AUC of each PTC along the time, of a case example.

From the obtained results, it is possible to observe that for a while the PTC response is 1, which could be interpreted as steady-state of the maintenance of the NMB degree. Additional information from the assessment of the AUC of the same PTC measurements indicates an increase in the magnitude of response is building up. Not long after, the following measurements showed an increase in the total of responses to the PTC, deviating rapidly and significantly from the desired 1-2 PTC target. In that sense, when aiming for a deep NMB of 1-2 PTC, the AUC_{PTC} data calculated provides an earlier indication of possible deviations that can be anticipated, and that allow to act on the amount/rate of rocuronium being used, thus, suppressing any major unbalances on the maintenance of the desired NMB degree.

8.6 FUZZY SYSTEM DESIGNER REPORT

Input variables

Name	Range	Number of membership functions
AUC_input	0 -> 300	6
PTC_input	0 -> 15	6

Output variables

Name	Range	Number of membership functions
Output_sets	0 -> 4	6

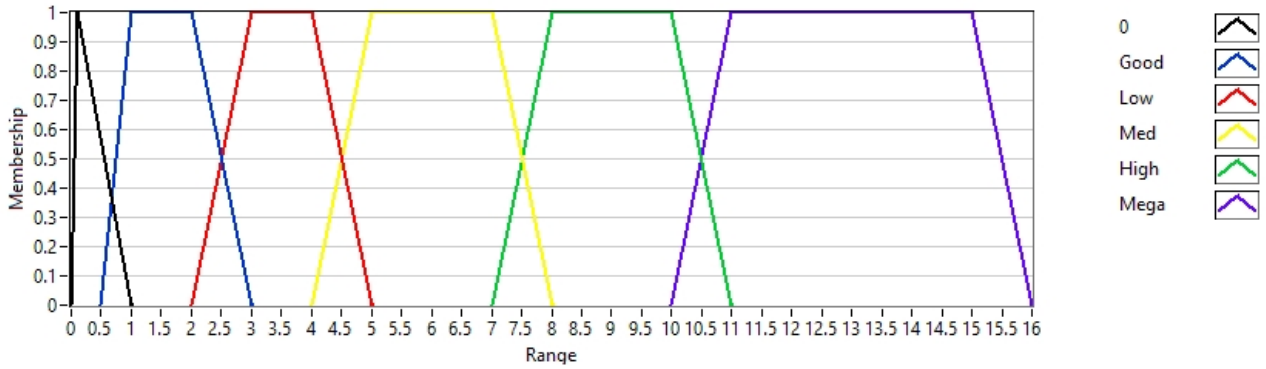
Defuzzification method

Center of Area

Input membership functions

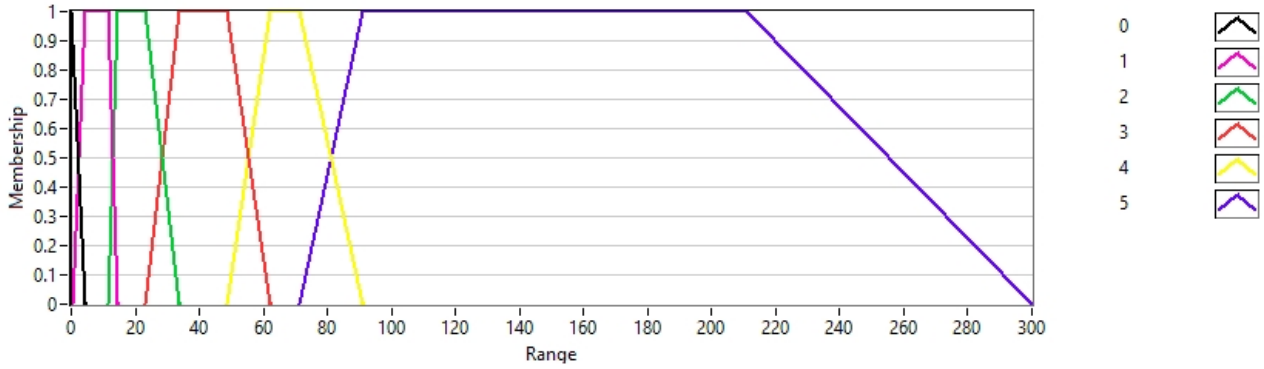
PTC_input

Membership function	Shape	Points
Null	Triangle	0 ; 0.1 ; 1
Good	Trapezoid	0.49 ; 1 ; 2 ; 3
Low	Trapezoid	2 ; 3 ; 4 ; 5
Mid	Trapezoid	4 ; 5 ; 7 ; 8
High	Trapezoid	7 ; 8 ; 10 ; 11
Huge	Trapezoid	10 ; 11 ; 15 ; 16



AUC_input

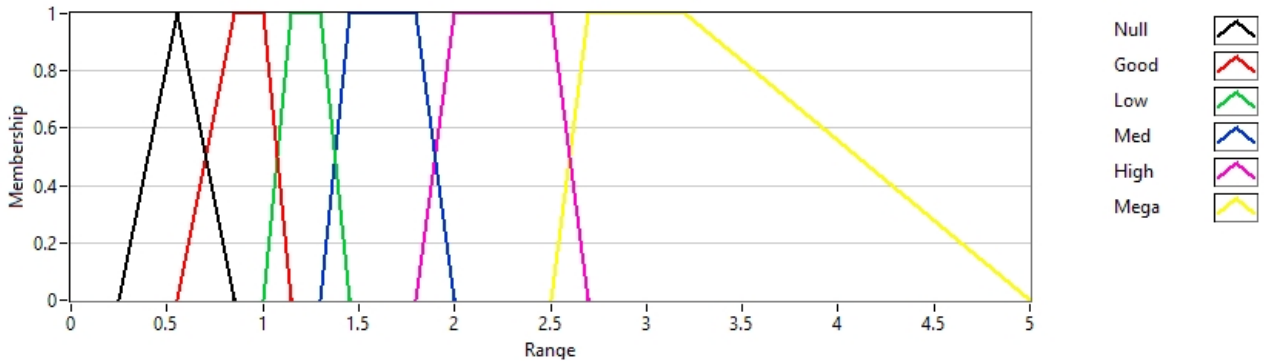
Membership function	Shape	Points
0	Triangle	0 ; 0.1 ; 4.12
1	Trapezoid	0.69 ; 4.12 ; 11.37 ; 14.67
2	Trapezoid	11.37 ; 14.67 ; 23.29 ; 33.72
3	Trapezoid	23.29 ; 33.72 ; 48.75 ; 62.05
4	Trapezoid	48.75 ; 62.05 ; 71.5 ; 91.12
5	Trapezoid	71.5 ; 91.12 ; 211 ; 300



Output membership functions

Output_sets

Membership function	Shape	Points
Null	Triangle	0.25 ; 0.55 ; 0.85
Good	Trapezoid	0.55 ; 0.85 ; 1 ; 1.15
Low	Trapezoid	1 ; 1.15 ; 1.3 ; 1.45
Mid	Trapezoid	1.3 ; 1.45 ; 1.8 ; 2
High	Trapezoid	1.8 ; 2 ; 2.5 ; 2.7
Huge	Trapezoid	2.5 ; 2.7 ; 3.2 ; 5



Rules

1. IF 'AUC_input' IS '0' OR 'PTC_input' IS 'Null' THEN 'Output_sets' IS 'Null' connective: OR (Maximum) ; implication: Minimum ; degree of support: 1.00

2. IF 'AUC_input' IS '1' OR 'PTC_input' IS 'Good' THEN 'Output_sets' IS 'Good' connective: OR (Maximum) ; implication: Minimum ; degree of support: 1.00

3. IF 'AUC_input' IS '2' OR 'PTC_input' IS 'Low' THEN 'Output_sets' IS 'Low' connective: OR (Maximum) ; implication: Minimum ; degree of support: 1.00

4. IF 'AUC_input' IS '3' OR 'PTC_input' IS 'Mid' THEN 'Output_sets' IS 'Mid' connective: OR (Maximum) ; implication: Minimum ; degree of support: 1.00

5. IF 'AUC_input' IS '4' OR 'PTC_input' IS 'High' THEN 'Output_sets' IS 'High' connective: OR (Maximum) ; implication: Minimum ; degree of support: 1.00

6. IF 'AUC_input' IS '5' OR 'PTC_input' IS 'Huge' THEN 'Output_sets' IS 'Huge' connective: OR (Maximum) ; implication: Minimum ; degree of support: 1.00