

SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PhD)

Evaluation of neuromuscular blockade management
in high-risk patients

by Zoltán Szabó-Maák

Supervisor: Prof. Béla Fülesdi



UNIVERSITY OF DEBRECEN
DOCTORAL SCHOOL OF NEUROSCIENCES

DEBRECEN, 2026

Evaluation of neuromuscular blockade management in high-risk patients

By Zoltán Szabó-Maák MD

Supervisor: Prof. Béla Fülesdi MD, PhD, DSc

Doctoral School of Neurosciences, University of Debrecen

Head of the **Examination Committee:** Prof. László Csiba MD, PhD, DSc, MHAS

Members of the Examination Committee: Prof. Dániel Bereczki MD, PhD, DSc
Álmos Klekner MD, PhD, DSc

The Examination takes place at Library of the Department of Anesthesiology and Intensive Care, Faculty of Medicine, University of Debrecen on 9 November 2026 at 11:00

Head of the **Defense Committee:** Prof. László Csiba MD, PhD, DSc, MHAS

Reviewers: Prof. László Bogár MD, PhD, DSc
Judit Boczán MD, PhD

Members of the Defense Committee: Prof. Dániel Bereczki MD, PhD, DSc
Álmos Klekner MD, PhD, DSc

The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen on 9 November 2026 at 13:00

Introduction

Blocking the neuromuscular junction facilitates endotracheal intubation, reduces the risk of complications and improves mechanical ventilation. Relaxed musculature improves surgical access during all open and laparoscopic surgeries. However, in addition to the benefits, it is necessary to be aware of the risk of postoperative residual neuromuscular blockade (PRNB), which compromises patient safety, resulting in respiratory complications. According to current recommendations, extubation should only be performed if the patient's muscle strength has fully returned, confirmed by objective neuromuscular monitoring meets TOFR ≥ 0.9 criterion. Below this level, PRNB is present requiring adequate reversal.

Reversal can be performed indirectly by neostigmine, which acts through inhibition of acetylcholinesterase enzyme; this has been standard practice for decades and remains most commonly used reversal agent worldwide in routine anesthetic practice. Alternatively, steroid-structure muscle relaxants (vecuronium, rocuronium, pipecuronium) can be directly reversed with sugammadex, which is a helical cyclodextrin molecule that encapsulates relaxants. Sugammadex was developed originally for the reversal of rocuronium, and is also registered with the FDA for vecuronium, while its use for pipecuronium is off-label; however, affinity of sugammadex for pipecuronium is stronger than for the other two drugs. The use of pipecuronium—which is widely unknown and disappearing from clinical practice in the present, is being reevaluated in the context of muscle relaxation, partly due to its favorable reversal characteristics with sugammadex.

Sugammadex reverses neuromuscular blockade more rapidly and reliably, and reduces the likelihood of respiratory complications compared with neostigmine. In addition, sugammadex is also effective in antagonizing complete and deep neuromuscular blockade (DNMB), however, it is more expensive, and its routine availability is often limited. In cases of shallow and minimal blockade, reversal with neostigmine is also safe and effective when guided by objective monitoring.

Avoiding neuromuscular monitoring and inadequate reversal prolong recovery and increase risk of postoperative respiratory complications. Although these findings have been known for decades, incidence of PRNB can still reach 60% at present, suggesting that the recommendations are not implemented sufficiently.

In addition to complications of PRNB occurring in the recovery room, the link between muscle relaxation, reversal strategies and postoperative pulmonary complications (PPCs), such as postoperative pneumonia has become evident in recent years. The exact role of this association remains unclear at present presumably to the multitude of heterogeneous risk factors and patient characteristics associated with PPCs; muscle relaxation is only a single factor among many. Nevertheless, it is well established that there are high-risk groups in which this correlation is more pronounced. This includes the elderly and frail population, patients with sleep apnea, and the severely obese individuals.

Muscle relaxation has become safer and more refined over the past decade with the widespread use of sugammadex and objective neuromuscular monitoring. Respiratory complications associated with PRNB are becoming increasingly recognized among anesthesiologists, and new monitoring options have also emerged. With the spread of laparoscopy and robotic surgery, the importance of DNMB — which has not been fully utilized until recent years — is being reevaluated. In DNMB monitoring and reversal play a crucial role; however, the actual clinical significance and technique of deep blockade cannot be considered a resolved topic.

The main objective of this Ph.D. thesis is to improve patient safety and the quality of anesthetic practice by examining the performance, reversal, and monitoring of neuromuscular blockade. In the first part, I will present our own findings regarding muscle relaxation in high-risk patients, focusing on the relationship between reversal strategies of neuromuscular blockade and postoperative pulmonary complications. In the second part, I will present a new but potentially beneficial anesthesiological practice based on a study of laparoscopic surgeries in patients at high cardiac risk, in the course of which we examined the feasibility of using pipecuronium-sugammadex combination during deep neuromuscular blockade.

Objectives

1. The objective of our first study was to compare postoperative pulmonary complications in high-risk elderly patients undergoing surgery, depending on reversal with neostigmine versus sugammadex, in a multicenter, prospective, randomized, double-blind trial. Our hypothesis was that, in patients aged 75 years or older, classified as ASA 3–4, reversal of rocuronium-induced neuromuscular blockade with neostigmine versus sugammadex results in difference postoperative outcomes.
2. Our second prospective study included patients at high cardiovascular risk who required laparoscopic abdominal surgery. The objective of this study was to investigate whether deep neuromuscular blockade induced by pipecuronium can be adequately maintained during laparoscopic surgery while using low intra-abdominal pressure, and to study whether deep block maintained during the procedure can be rapidly and safely antagonized at the end of surgery with 2 mg/kg sugammadex.

Methods I.

Reversal of residual neuromuscular block with neostigmine or sugammadex and postoperative pulmonary complications: a prospective, randomised, double-blind trial in high-risk older patients

Study design: prospective, randomized, multicenter, double-blind clinical trial. The study was initiated by Prof. Thomas Ledowski (University of Western Australia, Faculty of Medicine, Perth, Australia), and among the study centers described above, the Edömér Tassonyi Neuromuscular Working Group at the Department of Anesthesiology and Intensive Care Medicine at the University of Debrecen also participated.

Registration: The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12614000108617) and approved by the institutional review boards of all participating study centres (Asan Medical Center, Seoul, Republic of South Korea on April 1, 2014; University of Malaya, Kuala Lumpur, Malaysia on May 15, 2014; University of Western Australia [UWA], Crawley, Australia on May 16, 2015; University Debrecen, Debrecen, Hungary on October 15, 2015; and Martini General Hospital, Groningen, the Netherlands on May 12, 2016).

After written informed consent, 180 ASA physical status 3 or 4 patients ≥ 75 year of age planned to undergo surgery under general anaesthesia with the use of NMBAs were included between May 2015 and March 2019. Patients were randomised to receive reversal of a rocuronium-based neuromuscular block with either sugammadex 2 mg/kg or neostigmine 0.05 mg/kg (up to a maximum dose of 5 mg) with atropine 0.015 mg/kg at the end of surgery.

Primary outcome parameter

To facilitate the comparison of postoperative pulmonary complications, we assessed differences in Pulmonary Outcome Score (POS), which was evaluated among the study groups on the 1st, 3rd, and 7th postoperative days.

The POS consists of four equally weighted components:

- Body temperature $> 38^{\circ}\text{C}$
- White blood cell count $> 11,000 / \mu\text{L}$
- Physical examination findings consistent with pneumonia
- Dyspnea

The Pulmonary Outcome Score (POS) introduced and validated by Ledowski et al. in 2014 is a scoring system derived from retrospective data designed to characterize pulmonary morbidity at population level. We defined the parameter “physical findings consistent with pneumonia” based on the definitions of the U.S. Centers for Disease Control and Prevention (CDC), without requiring radiological confirmation. We also documented cases of clinically diagnosed and radiologically confirmed pneumonia and antibiotic therapy and the results of chest X-rays or CT scans performed after the 7th postoperative day but before discharge. In the data analysis, we used the following risk factors relevant to outcomes: smoking, asthma bronchiale, and chronic obstructive pulmonary disease

Secondary outcome parameters

1. Time from skin closure to extubation
2. Time from administration of the reversal agent to extubation
3. Incidence of postoperative nausea and vomiting in PACU
4. Incidence of desoxygenation (SpO₂ <95%, <90%, <85%) with patients on 6l oxygen via Hudson mask
5. Incidence of clinically unequivocal aspiration
6. Incidence of clinical symptoms potentially associated with residual blockade (diplopia, difficulty in swallowing, feeling of general weakness) in PACU
7. Incidence of airway obstruction; need for airway aids such as oropharyngeal or nasopharyngeal tubes, incidence of re-intubation in PACU
8. Incidence of unplanned ICU admissions
9. Patient satisfaction with anaesthesia and PACU rating on 0-10 numeric rating scale (NRS) at PACU discharge and on postoperative day 3
10. Length of PACU stay and length of in-hospital stay
11. Incidence of antibiotic treatment due to airway morbidity within 7 postoperative days.
12. Incidence and results of chest x-rays or ct scans performed within 7 postoperative days
13. 30 day postoperative mortality

Inclusion criteria

Patients scheduled for elective or urgent (non-emergency) surgery ASA risk category 3 or 4, > 75 years of age, paralysed with rocuronium and extubated at the end of surgery.

Exclusion criteria

Emergency (=immediate) surgery, incapacity to consent to study participation, aspiration/significant atelectasis or active pneumonia within 7 preoperative days, planned to remain intubated at the end of surgery, all cardio-thoracic patients and all patients with significant chest trauma, contraindication to one of the study drugs or rocuronium, known severe neuropathy or myopathy affecting airway maintenance, breathing and neuromuscular monitoring, history of stroke with ongoing paresis, sepsis.

Intraoperative period

Patients received general anaesthesia using either a volatile anaesthetic- or a propofol-based maintenance and opioids per the attending anaesthetists' choice. For ethical considerations, the protocol did not prescribe a specific practice regarding intraoperative neuromuscular monitoring, and all attending anaesthetists were asked to commit to whether or not they would usually apply such monitoring during surgery, and specifically after administration of the reversal agent. Patients in both groups received rocuronium 0.6 mg/kg on induction of anaesthesia and further bolus doses of 5–20 mg at the discretion of the attending anaesthetist. To achieve a comparable depth of neuromuscular block, quantitative monitoring of the train-of-four (TOF) at the adductor pollicis brevis muscle (via supramaximal stimulation of the ulnar nerve) was used by an (unblinded) attending research assistant (not involved in postoperative data collection) with the TOF kept at two twitches towards the end of surgery and at the point of reversal. At the end of surgery, and solely at the discretion of the attending anaesthetist, the research assistant administered the study drug, leaving the clinician blinded to what reversal drug had been given. Further neuromuscular monitoring (from study drug administration until tracheal extubation) was only undertaken if the attending clinician had stated that this was the standard practice, or in case of urgent clinical requirement. The point of tracheal extubation was solely defined by the attending anaesthetist. After extubation, patients were given oxygen 6 L/min via a Hudson face mask, and discharged from the operating theatre to either the PACU or ICU. Patients for whom tracheal extubation at the end of surgery was unexpectedly impossible because of clinical requirements were subsequently excluded from further data analysis

Post-Anesthesia Care Unit (PACU) period

Following extubation, the patient was transferred to the recovery room (PACU); if the patient's condition indicated it, they were admitted to the intensive care unit. Here, oxygen was administered uniformly via a Hudson face mask at a flow rate of 6 L/min. TOF monitoring was not required in the recovery room for the purposes of the study protocol. However, if the anesthesiologist decided to continue monitoring, they were permitted to do so, and we documented the results and/or any medication administered there. We examined or calculated the following parameters:

1. Time from skin closure to extubation
2. Time from administration of the reversal agent to extubation
3. Need for anti-emetic medication (drug/dose)
4. Bradycardic episodes (HR <50 bpm) as well as tachycardic episodes (HR >100 bpm)
5. Incidence of postoperative nausea and vomiting
6. Incidence of clinical symptoms potentially associated with residual blockade (diplopia, difficulty in swallowing, feeling of general weakness)
7. Incidence of desaturation (SpO₂ <95%, <90%, <85%) with patients on 6 L/min oxygen via Hudson mask
8. Incidence of aspiration
9. Incidence of airway obstruction; need for airway aids such as oropharyngeal or nasopharyngeal tubes, incidence of re-intubation in PACU
10. Incidence of unplanned ICU admissions
11. Patient satisfaction with anaesthesia and PACU rating on 0-10 numeric rating scale (NRS) at PACU discharge
12. Length of PACU stay (from admission to fulfilling institutional discharge criteria, not until the patient is actually transferred to the ward, so "ideal" rather than "real" PACU time)
13. Opioid requirements in theatre and PACU (drug/dose)

Period in surgical ward

Patients are visited by an anaesthetist 24 h, then 48 h, then 84 h (= 7 days) after surgery. Each visit requires also a blood sample to determine the white cell count (WCC). If the patient had a WCC taken within 24 h from the visit (only for time points 48 and 84 h post surgery) this value may be used and no additional sample is required.

On each occasion the following points will be noted:

1. Pulmonary outcome score parameters:
 - a) WCC > 11000/ μ l
 - b) Patient short of breath (patient self assessment)
 - c) Auscultation and other physical examination consistent with pneumonia
 - d) Body temperature > 38 C.
2. Chest X-ray or CT taken? Not prescribed by study but results noted in CRF if studies performed.
3. Patient satisfaction with anaesthesia and PACU rating on 0-10 numeric rating scale (NRS) at PACU discharge
4. New antibiotic treatment for suspected chest infection?
5. SpO₂ on room air/4l oxygen per face mask

Further data collection

1. Length of in-hospital stay
2. 30-day mortality
3. Chest x-rays/cts done within > 7 days postoperative stay but prior to discharge?

Randomization and blinding

Randomization was carried out via a central randomization website (*Randomize.net*), which recorded the number and date of each institutional randomization. During randomization, each patient was assigned an unique identifier, and the system simultaneously assigned the patient to either the NEO or SUG study group. The randomization was performed by a research assistant, who was the only person aware of the assignment. The research assistant administered the study drug in the operating room as a reversal agent at the end of the surgery; otherwise, he did not participate in the anesthesia and did not collect any further postoperative data. The research assistant prepared the investigational drugs without the attending anesthesiologist

being present, diluting each with 5 ml of normal saline in an unlabeled syringe. The attending anesthesiologist, as well as the other investigators involved in data collection, were unaware of the specific patient group; in other words, they remained blinded until the end of the study. It was possible to inform the anesthesiologist only in the event of an emergency situation in which identifying the study medications would have been essential (for example, a severe anaphylactic reaction to the study medications). Postoperative data were collected by another research assistant, and the results of any chest X-rays and CT scans were interpreted by a radiologist. These persons were also unaware of which study group each patient belonged to.

Data collection process (Flowchart)

A total of 297 patients met the inclusion criteria; of these, 100 patients refused to give consent, in 14 cases the anesthesiologist declined to participate, in 3 cases the surgery was canceled. Following the data collection period, during the unblinding process, it was revealed that in six cases (participants 93, 94, 96, 156, 157, and 160) the randomization had been performed incorrectly. These cases were incorrectly registered on the website, without the numbers actually representing participants. Due to this randomization error, the number of enrolled patients increased to 186. By the end of the study, a total of 180 patients had been enrolled and randomized, with 93 in the SUG group and 87 in the NEO group. During patient follow-up, we lost 8 cases in the SUG group: 3 patients withdrew their informed consent, 3 patients remained intubated at the end of surgery, in 2 cases, medication errors were made (the attending anaesthesiologist used atracurium or cis-atracurium instead of rocuronium). We excluded 4 cases from the NEO group: 1 patient withdrew consent, 2 patients remained intubated, in 1 case there was a medication error (the patient received sugammadex in addition to neostigmine). The final statistical analysis included 168 cases: 83 in the SUG group and 85 in the NEO group.

Data collection and storage

All data collected during the study period were recorded both on paper, and in electronic form. Paper-based records containing patient data are retained for the period specified by the Ethics Committees. At the end of each patient's follow-up period, the electronic data were transferred in Excel format to the Central Data Processing Unit at the University of Western Australia (UWA). UWA ensures the secure storage of all electronic data for 25 years. However, the management of the original documents generated during data collection was handled by the co-investigators, specifically the current head of each individual research group.

Statistical methods

A repeated-measures power analysis was conducted during the study design, which showed that 150 subjects randomised to two groups were required with at least three observations per subject to allow a minimum difference of 5% on a symptom scale of 0–4 with $\alpha=0.05$ and power=0.87. A slightly larger sample was recruited to allow for errors in assessment of eligibility.

Description of the sample characteristics used frequency and percentage for categorical variables and mean (standard deviation [sd]) for normally distributed continuous variables, and median (inter-quartile range) for skewed continuous variables. For each subject, we determined for Days 1, 3, and 7 whether the score was higher than the preoperative score. The resulting binary variable was analysed using a mixed-effects logistic regression analysis with day interacting with treatment group as fixed effects and patient nested within centre as random effects. The Netherlands centre was removed from this specific analysis, as it had only randomised three patients, all receiving the SUG treatment. Mann–Whitney *U*-test was used to compare treatment groups for equality of length of stay.

Results I.

Demographic and intraoperative characteristics of the patient populations:

Distribution of study participants by sex was as follows: women (n=105) vs. men (n=63); the mean age (standard deviation) [range] was 80 (4) [75–91] years. All patients were classified as ASA 3. There were no differences between study groups regarding documented underlying pulmonary comorbidities, surgical characteristics, total dose of rocuronium administered during surgery, duration of anesthesia and surgery, or the time interval between skin closure and arrival in the recovery room. Extubation based on neuromuscular monitoring in SUG group was 49%, and in NEO group, 59%. Time from administration of the study drug to extubation was shorter in SUG group (SUG: 8.7 minutes (5.4) vs. NEO: 11.1 minutes (6.7), $p=0.009$). In SUG group, proportion of patients achieved TOFR >0.9 was higher (SUG: 86% vs. NEO: 60%, $p=0.007$), and incidence of TOFR <0.8 was significantly lower.

Early postoperative complications: In the recovery room, no differences were observed between treatment groups in terms of any early postoperative outcome parameters

Pulmonary outcome: The postoperative pulmonary outcome score between the two groups showed no significant difference at baseline or on postoperative Days 1, 3, and 7. However, the distribution of outcome scores on the postoperative days showed that in group NEO, more patients still showed higher scores than in group SUG, with all subjects scoring 3 or 4 found in the NEO group on postoperative Days 3 and 7.

A generalised mixed-model logistic regression analysis examining the probability of subjects in the two groups for having higher pulmonary outcome scores on postoperative Days 1, 3, and 7 (vs preoperative baseline) showed ~50% lower probability for patients in the SUG vs NEO group on Day 7. However, these results did not reach statistical significance.

Corresponding to the observed trend in improved pulmonary outcomes in SUG, this group also showed a significant difference in radiographically diagnosed cases of pneumonia within 7 postoperative days: SUG two cases (2.4%) vs NEO eight cases (9.6%); $P=0.046$. Thus, 80% of all confirmed cases of pneumonia were observed after reversal with NEO.

Length of hospital stay: No significant difference in length of hospital stay and 30 day postoperative mortality was found between groups.

Methods II.

Deep neuromuscular block with pipecuronium in patients undergoing laparoscopic surgery — A prospective case series

Study design, ethics

This single-centre, prospective, observational case-series study was approved by the local ethics committee of the University of Debrecen and the National Institute of Pharmacy (OGYÉI/3968-1/2023); written informed consent was obtained from all participating patients. The study was first registered prior to patient enrolment in the European Clinical Trials Database (registration number 2022-004114-11), and later also in the Clinical Trials Database (registration number NCT06517524, Principal investigator: Béla Fülesdi).

Data collection

The study and data collection were performed at the Clinical Centre of the University of Debrecen (Debrecen, Hungary) between March 2023 and December 2023.

Inclusion criteria

We included 10 adult New York Heart Association (NYHA) Functional Classification 3–4 surgical patients (high cardiovascular risk) who were awaiting cardiac surgery or heart transplantation, before which they underwent non-elective abdominal surgery either for tumour removal or for cholecystectomy. Age: 18–65 years, patients categorized in ASA 3, BMI 18.5–25. A scheduled laparoscopic surgery is to be performed with endotracheal intubation, patient is in supine or lateral decubitus position and one arm accessible for neuromuscular monitoring.

Exclusion criteria

Diseases affecting neuromuscular function (myopathies, severe liver and kidney failure), medications affecting neuromuscular function (magnesium, aminoglycosides), difficult airway or anticipated difficult intubation, pregnancy, breastfeeding, urgent surgery, chronic obstructive pulmonary disease, glaucoma

Intraoperative period

After intravenous (iv) midazolam (0.01-0.03 mg/kg, maximum 2 mg) premedication, anaesthetic induction was accomplished with etomidate (0.3 mg/kg), followed by intravenous administration of 2 µg/kg fentanyl and pipecuronium bromide (Arduan®, Richter Gedeon Ltd. Budapest, Hungary) in a dose of 0.09 mg/kg (2 x ED95). After tracheal intubation, sevoflurane maintenance was age-adjusted for target minimum alveolar concentration of 1–1.5%. Bolus iv fentanyl (1 mcg/kg) was used for analgesia. Additional doses of pipecuronium bromide 0.01–0.02 mg/kg were given iv when a post-tetanic count (PTC) of 4–8 was determined by a TOF-Watch SX® acceleromyograph (Organon Ireland Ltd., Dublin, Ireland). During surgery, the patient's hemodynamic parameters such as heart rate and mean intra-arterial pressure (MAP) were recorded continuously. While the upper pressure limit of intraabdominal pressure was set at 15 mm Hg, as per institutional routine, the surgeon aimed to perform the procedure using low-pressure pneumoperitoneum, defined as an intra-abdominal pressure value below 10 mm Hg.

A calibrated TOF-Watch SX® acceleromyograph was used for neuromuscular monitoring according to good clinical research standards [8], and all train-of-four (TOF) data were normalized. When the muscle response stabilized, pipecuronium was administered and the trachea was intubated once the train-of-four (TOF) count was 0. A post-tetanic count (PTC) stimulation was evaluated every 5 min throughout surgery and was used to guide administration of additional pipecuronium (0.01–0.02 mg/kg) once PTC was 4–8. Administration of sevoflurane was discontinued after deflation of pneumoperitoneum, and neuromuscular block was antagonized with 2 mg/kg iv sugammadex. Neuromuscular recovery was documented as a normalized TOF ratio ≥ 0.9 , and the endotracheal tube was removed when the patient responded to verbal commands.

Primary endpoints of the study

Maintenance of low-pressure pneumoperitoneum during laparoscopic surgery using deep neuromuscular block with pipecuronium and reversal of neuromuscular block to TOF ratio ≥ 0.9 within 3 min after administration of 2 mg/kg sugammadex.

Secondary endpoint of the study: Changes in hemodynamic parameters, requirement for hemodynamic support.

Additional endpoint of the study: Quality of the surgical field. To assess this, we used a five-point scale based on the 2017 study by Baete et al. The operating surgeon could choose from the following options regarding the field of view: 1 – very poor, 2 – poor, 3 – acceptable, 4 – good, 5 – optimal.

Results II.

Ten patients were included. Five patients underwent cholecystectomies, 3 underwent laparoscopic rectal or colon resections, and 2 underwent laparoscopic appendectomy and adrenalectomy. Surgical duration was 35–170 min, while pneumoperitoneum duration was 35–125 min.

A single dose of 0.09 mg/kg pipecuronium resulted in an onset time of 5.3 (25–75% interquartile range, IQR, of 2.3–6.3) min. A top-up dose of pipecuronium (0.01–0.02 mg/kg) was administered when recovery to PTC 4–8, TOF count = 0 was documented. This was necessary in 5 patients, 56.0 ± 28.1 min (range: 25–90 min) after the first pipecuronium dose. At administration of the top-up dose, the PTC was a median of 5.0 (range: 5–15). In these cases, the duration of pneumoperitoneum was 125, 75, 75, 35, and 45 min, respectively. After administration of the first top-up dose, deep block was maintained for 51.2 ± 19.7 min (median: 45 min, range: 45–80 min). An additional, second top-up was necessary in 4 cases because of the surgical need for longer duration of pneumoperitoneum. The administration of a third top-up dose of pipecuronium was necessary in a single patient. The duration between pipecuronium administrations was 45 min.

Using this neuromuscular blocking strategy, the depth of the neuromuscular block at the end of surgery was PTC = 0 in 5 cases, PTC = 1 in 3 cases, and PTC = 6 in 2 cases. Administration of 2 mg/kg actual body weight (ABW) of sugammadex antagonized this block in 3.5 ± 1.6 min to

TOFR ≥ 0.9 , and in 4.3 ± 1.2 min to TOFR = 1.0. No re-onset of block (“recurarization”) was observed 15 min after reversal.

Feasibility of low-pressure peritoneum during the procedure: deep neuromuscular block with pipecuronium facilitated maintenance of low-pressure pneumoperitoneum in all cases. The average intraabdominal pressure was 8.1 ± 1.1 (median: 8.0, min: 6; max: 9) mmHg during the procedure. The highest mean intraabdominal pressure during the cases that was necessary to achieve proper surgical visualization was 9.7 ± 1.1 mmHg. This highest mean intraabdominal pressure was maintained for an average duration of 6.6 ± 4.7 min. The lowest mean intraabdominal pressure was 7.2 ± 1.2 mmHg.

Intraoperative hemodynamic parameters of the patients showed negligible changes compared to baseline values. Changes in mean arterial pressure were not significantly different—either in absolute terms or as a percentage of baseline—during the various phases of surgery. Continuous noradrenaline support was required in one patient; in this case, the anesthesiologist decided to use catecholamine therapy due to hypotension that was already present before induction.

With regard to the quality of the surgical field, based on a five-point scale used in a 2017 study by Baete et al., the average score given by surgeons was 4.6 ± 0.4 , which corresponded to an “optimal” rating in 8 cases and an “acceptable” rating in 2 cases.

Discussion

The objective of my Ph.D thesis was to improve patient safety and the quality of anesthesia by examining the administration, reversal, and monitoring of neuromuscular blockade. This objective can be interpreted in the context of the clinical practice of muscle relaxation, a topic that can be summarized as follows.

Muscle relaxation is an essential component of anesthesia; however, inadequate management can lead to serious respiratory complications in both the early and late postoperative periods. The physiological and clinical rationale for muscle relaxation with PRNB, and respiratory complications directly following surgery is considered unequivocal; however, the relationship between PPC (such as postoperative pneumonia) and muscle relaxation reversal strategies has yielded conflicting results to date. The investigation of possible associations is hindered by heterogeneity in etiology, risk factors, and diagnostic criteria. Nevertheless, over the past

decade, both attitude and practice regarding relaxation have changed considerably. In fact, taking into account negative consequences of PRNB is increasingly becoming accepted as part of the general awareness of anaesthesiology. International guidelines on the safe management of muscle relaxation have been published, at the same time quantitative neuromuscular monitors and sugammadex have become more widely accessible. On the other hand, there are significant differences worldwide between countries and even among different institutions: varying monitoring and reversal practices have to be taken into account, moreover neuromuscular monitoring and sugammadex reversal are generally applied only in a minority of cases in many hospitals. Consequently, there are differences in the incidence of residual paralysis and respiratory complications, as well as in how these conditions are assessed.

A comprehensive approach in muscle relaxation, while taking into account the potential complications of PRNB, also involves the use of novel monitoring techniques and advancements in medication management. With the growing importance of laparoscopy and robotic surgery, the relevance of DNMB is becoming more evident, whereas in previous decades it was considered undesirable condition, if the issue was even mentioned. DNMB can only be carried out safely with objective monitoring and appropriate reversal with sugammadex; however, the actual clinical significance and technique of deep blockade cannot be considered a resolved topic.

Among the findings forming the basis of this PhD thesis, the first study was a multicenter, prospective, randomized, controlled trial that compared pulmonary outcomes following the reversal of neuromuscular blockade with neostigmine versus sugammadex in high-risk, elderly patients (aged 75 years or older). According to our findings, the incidence of radiologically confirmed pneumonia was significantly lower in the late postoperative period in patients receiving sugammadex. Regarding Pulmonary Outcome Score (POS), the probability of a worse postoperative outcome was shown to be lower as a trend among patients reversed with sugammadex; however, this did not reach statistical significance.

Previously, various retrospective and observational studies have shown that sugammadex provides benefits in terms of pulmonary outcomes. The present study was preceded by a retrospective investigation published by Ledowski et al. in 2014, in which they found that, among patients over 60 years of age with ASA 3-4 status, reversal with sugammadex reduced the degree of POS elevation compared with neostigmine, whereas in younger and lower-risk (ASA 1-2) populations, such a correlation could not be detected. The POS scoring system was developed and validated in this study; its introduction was intended to reduce biases due to

heterogeneous clinical presentations of PPCs and the diversity of definitions. While POS has not yet become widely adopted or externally validated, we have decided to use it based on methodological considerations. Firstly, our study was registered in 2015, prior to the consensus criteria for postoperative pulmonary complications were defined, and data collection took place between 2015 and 2019. Secondly, the four components of the POS are consistent with the generally accepted clinical criteria for pneumonia, and by integrating symptoms that correlate with each other, it attempts to mitigate biases arising from clinical diversity.

Our findings are consistent in several aspects with the results of previous studies showing the potential benefits of sugammadex. Among elderly patients, PRNB is more frequent than in younger populations, and it is more frequently associated with dysphagia and respiratory complications observed in the early postoperative period. Postoperative atelectasis and hypoventilation are also more frequent in the elderly, and together they are risk factors for the development of postoperative pneumonia. Sugammadex provides more rapid and reliable reversal in cases of deep and moderate NMB and reduces the likelihood of early respiratory complications. However, with appropriate objective neuromuscular monitoring, neostigmine is also safe, provided that extubation is performed when TOFR ≥ 0.9 . In the absence of objective monitoring, reversal with neostigmine cannot provide this condition, while even with the use of sugammadex—when reversal is performed without monitoring—several studies have reported a PRNB incidence of 4–6%.

Although sugammadex reversal is more favorable in terms of pathophysiological concerns and early complications, the results of studies evaluating its effect on pulmonary outcomes are inconsistent. This can be partly explained by the differing risk profiles of the study populations and the differences in the study designs. In the POPULAR study published in 2019, a significant association between use of intraoperative muscle relaxants and PPCs was clearly demonstrated; however, there was no difference between the groups in terms of sugammadex versus neostigmine reversal. Another contradictory finding of the study was that intraoperative monitoring did not reduce the rate of PPCs, compared to not using neuromuscular monitoring. The methodology of the study, however, has been criticized in numerous publications: only 22% of all participants were monitored, and in many cases, only those patients who were already at higher risk were chosen for monitoring; furthermore, the monitoring criteria were also not consistent. In their randomized controlled trial published in 2020, Togioka et al. also did not find significant differences in the incidence of PPCs between sugammadex and neostigmine reversal in an elderly population; however, the study was conducted in a group of

patients in relatively good condition (ASA II–III). In any case they also confirmed in this report the advantages of sugammadex regarding PRNB. In their large-scale retrospective analysis published in 2019, which reflected real-world clinical practice, Oh and colleagues found that rehospitalization within 30 days was significantly more frequent among patients reversed with neostigmine – in their interpretation of the results, they also suggest a higher rate of pulmonary complications. A meta-analysis published in 2023, which analyzed pooled data from randomized and observational studies, reports confirming findings. Here, several specific pulmonary endpoints—including pneumonia, atelectasis, the need for noninvasive ventilation, and reintubation—showed the superiority of sugammadex reversal. Our own findings are consistent with these results, as they focus specifically on an elderly, high-risk population, in which the clinical significance of the reversal strategy likely had a more pronounced impact.

In our study, reversal was uniformly performed at TOFC = 2, and further monitoring and the timing of extubation were based on the anaesthesiologist's own decision, just as they would have in the normal course of anaesthesia. The rate of objective monitoring was 49% and 59% in the two groups, respectively, which closely reflects world-wide practice in terms of both the timing of reversal and the prevalence of monitoring. The research design was intended to model real-world anesthesiological conditions. The rates of extubation with TOFR <0.9 and TOFR <0.8 were significantly lower in the sugammadex group, and the time from reversal to extubation was shorter in cases where extubation was performed based on TOF monitoring. In most cases, we used an acceleromyography for monitoring; however, it should be noted that a peripheral nerve stimulator was also possible to use. During AMG monitoring, preload and T1 normalization were not required, which reduces validity of the above data.

Although objective neuromuscular monitoring and sugammadex are becoming increasingly widespread globally, their availability often remains limited. It is common for monitoring to be omitted, for neostigmine to be used inappropriately, and for extubation to be decided based only on clinical signs. Taking all of this into account, international guidelines nonetheless strongly recommend the routine use of objective neuromuscular monitoring and emphasize that neostigmine should be administered as late as possible, when the TOFR is in the range of 0.2–0.4. It is fair to say that academic standards are much higher than what is typically found in everyday anesthesiological care, so significant progress is still needed in this area worldwide.

However, in centers where sugammadex and objective monitoring are used routinely and without restrictions, it becomes possible to achieve a more precise "fine-tuning" of

neuromuscular blockade. In these centers, the issue of PRNB is practically resolved in regards to the level of equipment and drug availability; only under such circumstances does the role of deep neuromuscular blockade ($\text{TOFC}=0$, $\text{PTC} \geq 1$) become relevant. This trend is becoming an increasingly common practice for improving the surgeon's visual field and maintaining a low-pressure pneumoperitoneum during laparoscopic and robot-assisted surgeries. The process is most advanced in the European Union and the United States, in those hospitals where sugammadex and objective monitors are available at every anesthesia station. In cases of DNMB, preventing PRNB is particularly important; in such cases, this can only be achieved with sugammadex, as reversal with neostigmine is not an option due to its pharmacological properties.

Currently, surgeries performed under deep neuromuscular blockade are carried out worldwide using a combination of rocuronium and sugammadex with objective monitoring; the dose of sugammadex required for reversal is 4 mg/kg. If the institutional equipment and individual practice do not allow for this, laparoscopic surgeries are performed under fluctuating neuromuscular blockade; unwanted diaphragmatic movements are managed on a case-by-case basis by deepening anesthesia or administering opioids. Rocuronium is administered using an infusion pump or by frequent bolus repetition.

Our observational study, which assessed the potential for deep neuromuscular blockade induced by pipecuronium, can be interpreted within this clinical context; our primary goal was to demonstrate a practical and realistic alternative to the current practice of rocuronium for neuromuscular blockade. The background to this study was provided by articles published by Tassonyi et al. in 2015 and 2018 in the journal **Anesthesia & Analgesia**, which were based on our research group's studies. These publications demonstrate the favorable pharmacological properties of pipecuronium, which is gradually falling out of clinical practice, particularly with regard to its excellent reversibility with sugammadex. These favorable properties are most prominent in surgeries requiring deep neuromuscular blockade: a lower dose of the relaxant is required, and the deep blockade tends to persist longer due to the drug's potent effect. In addition, the affinity of sugammadex for pipecuronium is four times stronger than that for rocuronium, which allows for a lower reversal dose, offering financial benefits as well. Prior to the introduction of sugammadex in 2008, pipecuronium had been phased out of routine practice mainly because of its high potency and the potential for prolonged residual blockade, since neostigmine—the only agent available at the time—was generally inappropriate for reversal. Sugammadex's stronger affinity for pipecuronium prompted a reevaluation of pipecuronium's

potential clinical applications. In the observational cohort study described in the PhD thesis, we demonstrated that pipecuronium bolus is suitable for inducing DNMB that ensures low-pressure pneumoperitoneum and good surgical visibility during laparoscopic surgery, and that this blockade can be reliably reversed with 2 mg/kg sugammadex. The case series involved patients at high cardiovascular risk, underscoring the benefits of deep NMB and a continuously low-pressure pneumoperitoneum in maintaining hemodynamic stability. Clearly, this potential benefit is not related to the type of muscle relaxant used, but rather to the fact of deep NMB; our findings regarding blood pressure changes demonstrated this during pipecuronium-induced relaxation. The literature differs regarding the criteria for defining hemodynamic instability during anesthesia. In our study, we followed the retrospective study by Senne et al., in which hemodynamic instability was defined as a change in mean arterial pressure (MAP) exceeding 30%. In another study, David et al. defined clinically relevant changes in systolic blood pressure associated with an increased cardiovascular risk as 5–10 mmHg, and changes in diastolic blood pressure as 3–5 mmHg.

In accordance with our objectives—and in contrast to previous study—we examined a smaller patient population and conducted neuromuscular monitoring and the recording of intraoperative data based on stricter criteria, following the standards of neuromuscular research. The undeniable limitations of study are the small sample size ($n = 10$) and the lack of a rocuronium control group. However, we were able to demonstrate that pipecuronium provides a sufficient duration of action in an average-length laparoscopic procedure, and that DNMB it produces is sufficient for appropriately low intra-abdominal pressure; furthermore, it can be effectively antagonized at the end surgery with 2 mg/kg sugammadex even at TOFC=0. This sample size does not allow for extrapolation to daily practice; studies with larger sample sizes that assess real-world practice are needed for different patient groups and types of surgery. However, our results are consistent with previous studies published by our working group and provide a basis for further research on pipecuronium.

In summary: The studies in this doctoral dissertation focused on the diagnosis of residual neuromuscular block and the possibilities for its reversal. In both studies, we aimed to examine high-risk patients, as the rate of perioperative complications in this population increases in parallel with severity. We demonstrated first in a prospective, randomized study that reversal with sugammadex reduces the incidence of radiologically confirmed postoperative pneumonia in a group of elderly, high-risk patients. Although a trend toward worse pulmonary outcome scores was observed with neostigmine reversal, no significant difference in this variable could be demonstrated between sugammadex and neostigmine. The study is consistent with previous findings and those from the period since then, which also confirm the benefits of reversal with sugammadex in this context. Our second study demonstrated that deep neuromuscular blockade induced by pipecuronium is adequate for maintaining a low-pressure pneumoperitoneum during laparoscopic surgery and that, despite the degree of blockade, it can be safely reversed with 2 mg/kg sugammadex even when TOFC=0. In this study, we demonstrated that pipecuronium may be a feasible alternative to the currently generally used rocuronium-sugammadex combination during surgeries requiring deep neuromuscular blockade, and we provided a basis for further research aimed at repositioning the clinical role of pipecuronium.

Original Contributions

1. In a multicenter, randomized trial, we demonstrated that, in elderly patients, reversal with neostigmine prolongs the time required for muscle strength to return to a TOFR of 0.9—a level considered safe—compared with sugammadex.
2. The study also confirmed that, in cases of reversal with neostigmine, elderly patients are at greater risk of developing radiologically confirmed pneumonia on the 7th postoperative day.
3. We confirmed that the use of 0.9 mg/kg of pipecuronium ensures a deep neuromuscular block for the duration of laparoscopic surgical procedures.
4. We have demonstrated that, by inducing a deep block with pipecuronium, intra-abdominal pressure can be maintained at a continuously low level during surgery while ensuring adequate surgical visibility.
5. In DNMB induced by pipecuronium, we confirmed the importance of low intra-abdominal pressures during laparoscopy in patients at high cardiovascular risk, as low intra-abdominal pressures help prevent the hemodynamic side effects.
6. We have demonstrated that deep pipecuronium blockade at the end of laparoscopic surgery can be reversed within a few minutes using 2 mg/kg of sugammadex.



Registry number: DEENK/192/2026.PL
Subject: PhD Publication List

Candidate: Zoltán Szabó-Maák

Doctoral School: Doctoral School of Neurosciences

List of publications related to the dissertation

1. Asztalos, L. *, **Szabó-Maák, Z. ***, Berhész, M., Kanyári, Z., Nagy, G., Pongrácz, A., Nemes, R., Brull, S. J., Fülesdi, B.: Deep neuromuscular block with pipecuronium in patients undergoing laparoscopic surgery: a prospective case series.
Anaesth. Crit. Care Pain Med. 44 (2), 1-4, 2025.
DOI: <http://dx.doi.org/10.1016/j.accpm.2025.101493>
* These authors contributed equally to this work.
IF: 4.7 (2024)
2. Ledowski, T., **Szabó-Maák, Z.**, Loh, P. S., Turlach, B. A., Yang, H. S., Boer, H. D. d., Asztalos, L., Shariffuddin, I. I., Chan, L., Fülesdi, B.: Reversal of residual neuromuscular block with neostigmine or sugammadex and postoperative pulmonary complications: a prospective, randomised, double-blind trial in high-risk older patients.
Br. J. Anaesth. 127 (2), 316-323, 2021.
DOI: <http://dx.doi.org/10.1016/j.bja.2021.04.026>
IF: 11.719

List of other publications

3. Nemes, R., Pongrácz, A., Asztalos, L., Nagy, G., **Szabó-Maák, Z.**, Fedor, M., Fülesdi, B.: Ajánlás az izomrelaxánsok biztonságos perioperatív használatára.
Orv. hetil. 166 (15), 569-577, 2025.
DOI: <http://dx.doi.org/10.1556/650.2025.33285>
IF: 0.9 (2024)
4. Asztalos, L., Kanyári, Z., **Szabó-Maák, Z.**, Farkas, O., Tóth, D., Fülesdi, B.: A mély neuromuscularis blokk szerepe a laparoszkópos műtétek során.
Orv. hetil. 165 (52), 2039-2046, 2024.
DOI: <http://dx.doi.org/10.1556/650.2024.33192>
IF: 0.9





5. Szabó-Maák, Z., Molnár, V., Kis, B., Belán, I., Fülesdi, B.: A nagyérocclusióval járó ischaemiás stroke endovascularis ellátásának anesztéziája.
Orv. hetil. 165 (51), 1999-2007, 2024.
DOI: <http://dx.doi.org/10.1556/650.2024.33186>
IF: 0.9
6. Szabó-Maák, Z., Kis, B., Oláh, L.: Az endovascularis terápia szerepe és jelentősége a stroke-ellátási láncban.
Orv. hetil. 165 (1), 14-23, 2024.
DOI: <http://dx.doi.org/10.1556/650.2024.32952>
IF: 0.9
7. Simon, É., Csipkés, C., Andraskó, D., Kovács, V., Szabó-Maák, Z., Tankó, B., Buchholz, G., Fülesdi, B., Molnár, C.: Preoperatively administered single dose of dexketoprofen decreases pain intensity on the first 5 days after craniotomy: a single-centre placebo-controlled, randomized trial.
Transl. Neurosci. 14 (1), 1-8, 2023.
DOI: <http://dx.doi.org/10.1515/tnsci-2022-0323>
IF: 1.8
8. Tassonyi, E., Asztalos, L., Szabó-Maák, Z., Nemes, R., Pongrácz, A., Lengyel, S., Fülesdi, B.: Reversal of Deep Pipecuronium-Induced Neuromuscular Block With Moderate Versus Standard Dose of Sugammadex: a Randomized, Double-Blind, Noninferiority Trial.
Anesth. Analg. 127 (6), 1344-1350, 2018.
DOI: <http://dx.doi.org/10.1213/ANE.00000000000003719>
IF: 3.489
9. Nemes, R., Fülesdi, B., Pongrácz, A., Asztalos, L., Szabó-Maák, Z., Lengyel, S., Tassonyi, E.: Impact of reversal strategies on the incidence of postoperative residual paralysis after rocuronium relaxation without neuromuscular monitoring: a partially randomised placebo controlled trial.
Eur. J. Anaesth. 34 (9), 609-616, 2017.
DOI: <http://dx.doi.org/10.1097/EJA.0000000000000585>
IF: 3.958
10. Asztalos, L., Szabó-Maák, Z., Gajdos, A., Nemes, R., Pongrácz, A., Lengyel, S., Fülesdi, B., Tassonyi, E.: Reversal of Vecuronium-induced Neuromuscular Blockade with Low-dose Sugammadex at Train-of-four Count of Four: a Randomized Controlled Trial.
Anesthesiology. 127 (3), 441-449, 2017.
DOI: <http://dx.doi.org/10.1097/ALN.0000000000001744>
IF: 6.523





**UNIVERSITY of
DEBRECEN**

**UNIVERSITY AND NATIONAL LIBRARY
UNIVERSITY OF DEBRECEN**

H-4002 Egyetem tér 1, Debrecen

Phone: +3652/410-443, email: publikaciok@lib.unideb.hu

11. Végh, T., **Szabó-Maák, Z.**, Szatmári, S., Hallay, J., László, I., Takács, I., Fülesdi, B.: A normokapniás és a permisszív hiperkapniás tüdőprotektív egytűdős lélegeztetés hatása az artériás oxigén tenzióra.
Anaesthesiol. Intenzív Ther. 40 (4), 194-200, 2010.

Total IF of journals (all publications): 35,789

Total IF of journals (publications related to the dissertation): 16,419

The Candidate's publication data submitted to the Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

17 April, 2026

