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Review paper

# Postoperative residual curarization as a complication after general anesthesia

*Paweł Radkowski*[1,2,3], *Justyna Dawidowska-Fidrych*[4], *Radosław Fidrych*[5], *Iwona Podlińska*[1], *Oliwia Mandziuk-Radkowska*[6], *Marcin Mieszkowski*[1,2]

[1] *Department of Anesthesiology and Intensive Care, WSS Hospital, Olsztyn, Poland*
[2] *Department of Anaesthesiology and Intensive Care, Faculty of Medicine, Collegium Medicum, University of Warmia and Mazury in Olsztyn, Poland*
[3] *Hospital zum heiligen Geist in Fritzlar, Germany*
[4] *Pro-Medica Hospital, Ełk, Poland*
[5] *Independent Non-Public Health Care Institution Pro Vita, Ełk, Poland*
[6] *Klinikum Lippe, Detmold, Germany*

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Abstract

Introduction: **Postoperative residual curarization (PORC) is a common complication** but rarely taken into account during the postoperative period. PORC is associated with an increased risk of morbidity and mortality in anesthetized patients. Even small degrees of residual muscle relaxation of the transverse striated muscles can have serious clinical consequences for patients including a decline of upper respiratory tract function or swallowing disorders.

Aim: The aim of the work is to discuss the problem of PORC, its risk factors and diagnosis, as well as to identify the most common errors, which can be made even by experienced anesthesiologists and can lead to an increased risk of developing this life-threatening complication.

Material and methods: This work is based on the available literature and the authors' experience.

Results and discussion: **PORC caused by non-depolarizing neuromuscular blocking agents is a known problem** in daily clinical practice. The effects of PORC significantly increase the risk of respiratory complications (hypoxia, pulmonary edema, atelectasis and pneumonia). Patients can report discomfort even with a small degree of residual muscle block above a train of four (TOF) ratio of 0.8. Complete recovery of neuromuscular function does not occur until the TOF ratio is greater or equal to 0.9.

Conclusions: The primary strategy to avoid residual neuromuscular block and to improve the safety precautions of patients undergoing anesthesia is not by means of clinical evaluation but consistent monitoring of neuromuscular conduction and extubating the patient when the TOF ratio more than 0.9.

*Corresponding author: Paweł Radkowski, Department of Anaesthesiology and Intensive Care, Regional Specialist Hospital in Olsztyn, Żołnierska 18, 10-561 Olsztyn, Poland. Tel.: +48 882 815 714. E-mail address: pawelradkowski@wp.pl.*

## 1. INTRODUCTION

Postoperative residual curarization (PORC) is an important factor which increases morbidity and mortality in anesthetized patients during the postoperative period.[1] PORC is perceived as uncomfortable to patients and can also lead to life threatening conditions such as: aspirations, obstruction of the upper respiratory tract occur quite often and can lead to serious pulmonary complications. Also, the need for oxygen is significantly increased in the postoperative stage.[2,3] The effects of residual neuromuscular block are observed not only when extubating patients in the operating room, but also in the recovery room.[4] The above-mentioned complications can lead not only to a longer duration of hospitalization, but also to an increase in the cost of treatment as well as patient morbidity and mortality. The results of many studies in recent years show how important the PORC poses in the daily work of the anesthesiologist.[5,6] This is also an important problem in Poland, where many patients affected by this complication are still being met mainly due to lack of neuromuscular conduction monitoring. PORC not only prolongs the extubation time in the operating room but above all poses a life threatening risk to the patient. Residual muscle paralysis is a result of incomplete reversal of muscle relaxation and is caused by persistent presence of high concentration of muscle relaxant at the neuromuscular junction. This effect depends primarily on the dose of the administered drug.

The most common technique for assessing the degree of muscle relaxation and neuromuscular conduction is by train of four (TOF). This method involves sending a series of four electrical pulses every 0.5 s in 10 s intervals, through electrodes attached to an easily accessible peripheral nerve. The muscle response to the stimulation described above is evaluated. On this basis, the TOF ratio is calculated, i.e. the ratio of 4th to the 1st response (T4/T1). Based on current knowledge, patients can be safely extubated once the TOF ratio over 0.9 whereas a TOF ratio less than 0.9 is predictive of striated muscle relaxation. There is a new type of neuromuscular monitor, easier to use TOF-Cuff. It is a modified non-invasive blood pressure cuff that incorporates stimulating electrodes in its inner surface and is based on the stimulation of the peripheral nerve in the arm.[7,8]

## 2. AIM

The aim of the work was to discuss the problem of PORC, its risk factors and diagnosis, as well as to identify the most common errors that can lead to an increased risk of developing this life-threatening complication.

## 3. MATERIAL AND METHODS

The work is based on the available literature and the authors' experience.

## 4. RESULTS AND DISCUSSION

PORC is a potentially life-threatening complication of non-depolarizing muscle relaxant use in anesthesia. The first studies emerged in the 1970s in Australia, almost 30 years since the first use of curare. The first description of PORC in literature was made in 1979 by Viby Mogensen.[9] In turn, in a study conducted by Cooper et al. in 1989, it was found that approximately 50% of all complications that caused patients to be transferred to the intensive care unit (ICU) were related to residual muscle relaxation of the striated muscles.[10] Berg's study from the 1990s shows that the administration of long-acting non-depolarizing muscle relaxants significantly contributes to postoperative respiratory complications especially after abdominal procedures. In this analysis, PORC and its effect on postoperative complications were more common in patients who received a long acting non-depolarizing muscle relaxant.[11] In a 2016 Australian study, more than 30% of patients reported PORC in the recovery room. Age and abdominal surgery lasting more than 90 minutes were associated with an increased risk of residual neuromuscular block.[12] PORC is much more common after the use of long acting non-depolarizing muscle relaxants (pancuronium) than intermediate acting non-depolarizing muscle relaxants (atracurium, rocuronium, vecuronium).[13–16] A 2001 study found that after the administration of intermediate-acting non-depolarizing muscle relaxants residual muscle block is common in patients during the postoperative period in the recovery room: 39% of patients who received rocuronium during anesthesia had a TOF ratio of less than 0.8 in the recovery room, 52% after administration of atracurium and 64% after myorelaxation caused by vecuronium.[17] Other studies in 2003 show that even two hours after a single dose of a long-acting non-depolarizing drug, more than 30% of patients do not achieve a TOF ratio of 0.9.[18] Another 2010 study also shows that 2 h after administrating a single dose of atracurium, 8% of patients have significant residual muscle relaxation, even though one third of atracurium is eliminated regardless of organ function (Hoffman elimination).[19] A 2015 study showed that the risk of respiratory complications increases with an increase in the dose of the non-depolarizing muscle relaxant administered during general anesthesia. However, the use of neostigmine without monitoring the reversal of the neuromuscular block also led to an increase in respiratory complications.[20]

### 4.1. Neuromuscular function

Neuromuscular conduction block is a reversible phenomenon caused by drugs that prolong the depolarization of chemically sensitive ion channels of the postsynaptic receptor of the end plate (depolarizing block) or by blocking acetylcholine access to the postsynaptic receptor (non-depolarizing block). The main place of action of non-depolarizing muscle relaxants are in postsynaptic receptors, which are responsible for stimulating muscle fibers.[21]

A study conducted by Patton and Waud in 1967 showed that neuromuscular block only occurs when 70% of acetylcholine receptors are blocked by a transverse striated non-

depolarizing muscle relaxant.[22] Muscle strength decreases according to the 'all or nothing' principle. As a result, clinical aspects of resolution of the effects of non-depolarizing muscle relaxants arise. When 70%–75% of acetylcholine receptors on the motor plate are occupied by non-depolarizing muscle relaxants, a gradual return of muscle strength is observed. Therefore, 25% of the initial dose of the non-depolarizing muscle relaxant for the repeated dose is needed. Noteworthy is the fact that a full motor response can be preserved when 70% of acetylcholine receptors are still blocked (i.e. the TOF ratio can be 0.9–1.0!). Complete neuromuscular blockade occurs when 90% of the receptors are taken. Table 1 shows muscle strength depending on the percentage of receptors occupied in the neuromuscular junction, as well as the moment when it is possible to effectively reverse the neuromuscular block with neostigmine or sugammadex and return responses in TOF stimulation. Table 2 shows clinical consequences of residual neuromuscular blockade.

**Table 1. Muscle strength depending on the percentage of acetylcholine receptors occupied in the neuromuscular junction, the moment when it is possible to effectively reverse neuromuscular blockade with neostigmine or sugammadex and return responses in TOF stimulation.**

| Percentage of occupied acetylcholine receptors, % | 0 | 70 | 75 | 90 | | | 100 |
|---|---|---|---|---|---|---|---|
| Amplitude contraction, % | 100 | 100 | | 25 | 20 | 10 | 0 |
| Muscle strength | normal | impaired | | paralytic | | | |
| Reversal of the neuromuscular block | | | neostygmine | | | | |
| | | | | sugammadex | | | |
| Number of responses | | | | 4 | 3 | 2 | 1 | 0 |
| TOF ratio | | 1 | 0.9 | | | 0 | |

**Table 2. Clinical consequences of residual neuromuscular blockade.**

| TOF ratio | Number of responses | Percentage of occupied acetylcholine receptors, % | Clinical implication |
|---|---|---|---|
| 1–0.9 | 4 | <70 | safe extubation |
| 0.8–0.7 | 4 | <70 | double vision, poor vision, weakness |
| 0.6 | 4 | >70 | swallowing and articulation disorders |
| 0.5 | 4 | >70 | lifting the head is possible |
| 0.2 | 4 | 70–75 | spontaneous breathing, antagonism by neostigmine is possible |
| 0 | 3 | 85 | laryngeal muscle relaxation |
| 0 | 2 | 85 | intubation, deep neuromuscular block |
| 0 | 1 | 85–90 | intubation, deep neuromuscular block |
| 0 | 0 | 90–100 | intubation, deep neuromuscular block |

### 4.2. Sensitivity of different muscle groups to neuromuscular conduction blockers blocking agents

After intravenous administration of a non-depolarizing muscle relaxant, small muscle groups such as extraoculamuscles, finger muscles, then muscles within the face, throat, limbs, abdomen and spine are the first affected, lastly, the diaphragm and intercostal muscles are affected. The normal muscle function returns in reverse order.[23] This is because the diaphragm is the least sensitive to non-depolarizing muscle relaxants, as Buzello noted as early as 1929, treating tetanus with curare.[24] Compared to the adductor pollicis muscle, almost twice the doses of the non-depolarizing muscle relaxant were needed to paralyze the diaphragm. Although the diaphragm requires 60 s less than the pollicis adductor muscle for muscle relaxation to occur. Muscle relaxation of the diaphragm was 30% shorter than muscle relaxation of the adductor pollicis muscle. The cause of this is considered to be rich vascularization of the diaphragm. This causes that even at a low TOF ratio of 0.2 measured after stimulation of the ulnar nerve, respiratory movements of the patient can be observed, which are often felt by the surgeon as tightening of the abdominal muscles, which can complicate surgical conditions.

### 4.3. Physiological and clinical consequences of residual blockade

Since 1975, a TOF ratio of 0.7 has been considered the standard as a sufficient criterion for the safe extubation of the patient's trachea. This was mainly related to the back of the systolic function of the diaphragm at these values. In contrast, when the TOF ratio was less than 0.6, muscle weakness was often observed in patients, which presented as drooping eyelids and tracheal deviation.[25] Subsequently, in 1988, a TOF ratio of 0.8 was required for extubation.[26] Currently, at a TOF ratio of 0.9 muscle strength returns which allows for safe extubation of patient's trachea.[27,28] Clinical signs of residual muscle block TOF ratio ranging 0.5–0.9 measured on the intrinsic muscles of the thumb are shown in Table 3.

#### 4.3.1. Respiratory muscles

Patients recovering from anesthesia can reach the normal respiratory volume when the TOF ratio is 0.3 can be misleading for the anesthesiologist which may lead to early extubation of the patient's trachea during which the laryngeal muscles and swallowing apparatus are still relaxed. Often

**Table 3. Clinically relevant effects of a partial neuromuscular blockade based on the TOF-ratio 0.5–0.9 at the thumb.**

| TOF ratio at the thumb | 0.5 | 0.8 | 0.9 |
|---|---|---|---|
| Tidal volume | Normal | Normal | Normal |
| Act of swallowing | Severely impaired | Impaired | Normal |
| Integrity of the upper airway | Severely impaired | Impaired | Normal |
| Hypoxic respiratory response | Usually impaired | Often normal | Normal |

after surgery, the patient is ventilated in assisted pressure mode and therefore the patient can breathe spontaneously on their own. A strong cough reflex is important to cough up residual lung secretion which is possible only when the TOF ratio is 0.8.

#### 4.3.2. Regulation of the respiratory center

In 1996, it was proven that peripheral chemoreceptors in the cervical glomeruli are blocked by non-depolarizing muscle relaxants. Chemoreceptors are more sensitive to neuromuscular conduction-blocking drugs than peripheral muscles or the diaphragm. The blockage of the reflex causes an increase the minute volume and respiratory volume at hypoxia. An increase in ventilation caused by hypoxia can occur only the TOF ratio is at least 0.9.[29] Even minimal neuromuscular conduction block can cause respiratory depression. Opioid overdose or insidious anesthetics can strengthen the residual block and pose a threat to the health and life of the patient.

#### 4.3.3. Muscles of the throat and larynx

The muscles of the pharynx and larynx are much more sensitive to non-depolarizing muscle relaxants than the respiratory muscles. At a TOF ratio of 0.6–0.7, we can expect impaired function of the laryngeal muscles, especially the genioglossus muscle, continues to occur and the tension of the upper esophageal sphincter is reduced, which poses a risk of regurgitation and aspiration of gastric contents to the respiratory tract.[30,31] Swallowing disorders may persist when the TOF reaches 0.9. Even during complete resolution of the neuromuscular block, measurements recorded on the adductor pollicis muscle may show that the swallowing reflex is still impaired.

### 4.4. Clinical tests used in the evaluation of the return of neuromuscular function

For decades, the degree of the neuromuscular block has been assessed on the basis of clinical tests. Unfortunately, this is still the case today, even though this approach is unreliable and can cause life-threatening conditions. Moreover, there are recommendations for standards of neuromuscular monitoring during anesthesia stating that 'a peripheral nerve stimulation must be used whenever muscle relaxants are given. In Poland, according to the Regulation of the Minister of Health of December 2016 on the organizational standards of healthcare in the field of anesthesiology and intensive care,' there should be a device for monitoring neuromuscular transmission designated for each patient station.

Clinical manifestation of persistent residual neuromuscular block can be presented by but not limited to; uncoordinated respiratory movements, incomplete eye opening and uncontrolled movements of the limbs. There are several different clinical tests that can be used to assess the degree of muscle relaxation of a patient. However, carrying out these tests requires patient cooperation, which after general anesthesia can be difficult. Sticking out the tongue, raising the hand, opening the eyes and normal respiratory volume are considered unreliable tests. In contrast, raising the head, upper limb or lower limb for at least 5 s and the tongue depressor test are more reliable tests but are also insufficient in determining (the most adequate conditions for) safe extubation of the patient's trachea. Lifting the head or limb over 5 s was long considered a definitive test indicating the return of neuromuscular conduction. Also, extending the testing time from 5 s to 10 s did not improve the quality of this test. After testing TOF stimulation and similar monitoring methods, it was concluded that at TOF ratio of 0.5 the presence of residual muscle relaxation cannot be excluded. The tongue depressor test is the most sensitive test for clinical evaluation of residual muscle relaxation. The patient is asked to bite on a spatula, which the anesthesiologist tries to slowly remove. If the spatula is maintained between the clamped teeth, the test is considered positive, this test is possible from a TOF ratio of 0.8. One of the biggest drawbacks of this test is the inability to perform it in patients who are intubated and/or sleeping. In addition, when performing this procedure, there is a high risk of tooth damage and gastroesophageal reflex. Therefore, in clinical practice, the tongue depressor test is very rarely carried out.[32]

### 4.5. Causes of incorrect interpretation of neuromuscular transmission states and pharmacology leading to PORC

The duration of action of a non-depolarizing muscle relaxant is characterized in clinical practice by a high individual variability and can vary significantly among people. The main causes of this phenomenon is dependent on: age, gender and concomitant diseases such as renal and hepatic insufficiency. Other factors such as inhalation anesthetics (except nitrous oxide), certain groups of antibiotics, antiarrhythmic drugs, diuretics, magnesium, hypocalcemia, respiratory acidosis and metabolic disorders can lead to the greater degree and/or prolongation of the duration of action of non-depolarizing muscle relaxant agents.[33] Especially in the elderly, the duration of action of non-depolarizing relaxants varies greatly. Hypothermia is also important in this regard (reduced body temperature of the patient less than 36°C), which significantly increases the neuromuscular block[34]. When using modern anesthetics such as desfluran or an ultrashort-acting opioid (remifentanil), patients wake up faster after surgery – which is desirable, however, patients are more likely to experience discomfort associated with the trace effects of the administration of non-depolarizing muscle relaxants.

Another very important issue which often occurs is the misinterpretation of the clinical duration of neuromuscular blockade agents DUR 25 (duration 25). The time measured from the moment of drug administration to drug resolution with a TOF ratio of 0.25 is the moment when surgical block resolves. The average time is about 40 minutes for rocuronium or cisatracurium. The duration of action of non-depolarizing muscle relaxants that is written in textbooks is often misinterpreted and understood as the time between administration of the agent and the recovery time to the TOF ratio of 0.9. However, between the clinical duration of action

and the recovery time to a TOF ratio over 0.9 often requires several tens of minutes even after the administration of non-depolarizing muscle relaxants from the intermediate-acting group such as rocuronium or cisatracurium.[32]

Besides all of the issues discussed above what is also important is the incorrect use of acetylcholinesterase inhibitors. Neostigmine is often administered too soon, when the first and second twitch responses of a peripheral nerve stimulator are not present, especially in treatments with short operation times. It should be noted that neostigmine requires a minimum of 5 minutes in order to reverse the effects of the neuromuscular blockade. The peak concentration of neostigmine occurs after about 7 to 10 minutes from time of drug administration. In addition, potential side effects of neostigmine include bronchospasm, bradycardia, hyperperistalsis, hypersalivation and increased mucus production from the lower respiratory tract so it is needed to use it together with atropine in order to prevent or reduce these side effects[32]. Acetylcholinesterase inhibitors as opposed to sugammadex can only be administered when neuromuscular conduction returns spontaneously at a TOF ratio of at least 0.2 or when the patient begins to breathe on their own. Too early administration of acetylcholinesterase inhibitors not only does not reverse the neuromuscular block, but paradoxically can prolong it.[35] Therefore, reversal of the neuromuscular block requires that a patient be monitored. It is also necessary to remember that in order to effectively reverse the neuromuscular block with neostigmine, it is necessary to achieve at least three responses in TOF stimulation. Current scientific studies show that neostigmine should only be administered when TOF is equal to 0.4 at a dose of 20–40 mcg/kg (TOF ratio 1.0 is achieved within 11 minutes). By contrast, a dose of more than 60 mcg/kg misses the target due to the ceiling effect and results in a significant increase in muscarinic side effects.[36] In daily anesthesia practice, the reversal of the neuromuscular block is observed with acetylcholinesterase inhibitors in gastrointestinal procedures. This is not advisable as there may be a 10-fold increase in pressure in the abdomen, thereby increasing peristalsis and reducing mesenteric blood supply, which may present a risk of early leakage of anastomosis.[37] Sugammadex is unrivalled compared to acetylcholinesterase inhibitors as it reverses the neuromuscular block quickly, completely and at any depth of muscle relaxation without exhibiting cholinergic effects[38]. However, the still persistently high price of the drug can be an argument against the routine use of sugammadex in anesthesiological practice. Neostigmine, which is a much cheaper drug, despite its side effects, is still widely clinically used.[39]

It should not be forgotten that both the throat muscles and the muscles of the larynx are very sensitive to non-depolarizing muscle relaxants, and this means that even a small sagging residual impairs their function. The diaphragm is the least sensitive to non-depolarizing muscle relaxants, so approximately 80% of acetylcholine receptors (TOF ratio 0.25) may be occupied during spontaneous breathing. Extubation of the patient on the basis of efficient breathing volume often happens in anaesthesiological practice and exposes the patient to complications.

Another error encountered in clinical practice is the administration after a depolarizing drug (succinylcholine) of a high dose of a non-depolarizing drug, which means that the neuromuscular block is prolonged. From the authors' experience, in such a situation, one third dose of a non-depolarizing drug required in order to intubate the patient is very often sufficient. Succinylcholine has a different mechanism of action than non-depolarizing drugs, which causes an increased sensitization of acetylcholine receptors.[40] It should be kept in mind that the depolarizing drug is given only after we are sure that the muscle relaxation caused by succinylcholine begins to subside, as it may happen that the patient has a genetic deficiency of plasma cholinesterase (1 : 3000). In this situation, this very short-acting depolarizing drug causes the neuromuscular blockade to last for even up to several hours.[41]

In obese patients, the dosage of the non-depolarizing muscle relaxants, such as rocuronium, vecuronium or cisatracurium should be based on the ideal body weight. For rocuronium and vecuronium, the effective dose in women is lower than in men due to relatively lower muscle mass.[42]

## 5. CONCLUSIONS

The primary strategy to avoid residual neuromuscular block is not by means of clinical evaluation, but consistent monitoring of neuromuscular conduction and extubating the patient when the TOF ratio over 0.9. Monitoring neuromuscular conduction provides a similar to optimal moment of intubation and extubation, determines more precisely the dose and metabolism of the drug, indicates to the anesthesiologist the best time if necessary to reverse neuromuscular blockade.

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## References

1 Arbous MS, Meursing AE, van Kleef JW, et al. Impact of anesthesia management characteristics on severe morbidity and mortality. *Anesthesiology*. 2005;102(2):257–268. https://doi.org/ 10.1097/00000542-200502000-00005.

2 Frank SM, Fleisher LA, Olson KF, et al. Multivariate determinants of early postoperative oxygen consumption in elderly patients. Effects of shivering, body temperature and gender. *Anesthesiology*. 1995;83(2):241–249. https://doi.org/ 10.1097/00000542-199508000-00002.

3 Sauer M, Stahn A, Soltesz S, Noeldge-Schomburg G, Mencke T. The influence of residual neuromuscular block on the incidence of critical respiratory events. A randomised, prospective, placebo-controlled trial. *Eur J Anaesthesiol*. 2011;28(12):842–848. https://doi.org/10.1097/EJA.0b013e328345cd11.

4 Murphy GS, Szoko JW, Marymont JH, Greeberg SB, Avram MJ, Vender JS. Residual neuromuscular blockade and critical respiratory events in the postanesthesia care unit. *Anesth Analg.* 2008;107(1):130–137. https://doi.org/10.1213/ane.0b013e31816d1268.

5 Plaud B, Debaene B, Donati F, Marty J. Residual paralysis after emergence from anesthesia. *Anesthesiology.* 2010;121(4):1013–1022. https://doi.org/10.1097/ALN.0b013e3181cded07.

6 Baillard C, Clec'h, Catineau J, et al. Postoperative residual neuromuscular block: a survey of management. *Br J Anaesth.* 2005;95(5);622–626. https://doi.org/10.1093/bja/aei240.

7 Veiga Ruiz G, Garcia Cayuela J, Orozco Montes J, Parreno Caparros M, Garcia Rojo B, Aguajo Albasini JL. Monitoring intraoperative neuromuscular blockade and blood pressure with one device (TOFCuff): A comparative study with mechanomyography and invasive blood pressure. *Rev Esp Anastesiol Reanim.* 2017;64(10):560– 567. https://doi.org/10.1016/j.redar.2017.03.013.

8 Markle A, Horn K, Weiter J, Dullenkopf A. An observational study comparing the performance of TOF-Cuff with TOF-Scan monitoring during anaesthetic induction in clinical routine. *Anaesthesiol Intensive Ther.* 2020;52(3):181–186. https://doi.org/10.5114/ait.2020.98124.

9 Viby-Mogensen J, Jørgensen BC, Ording H. Residual curarization in the recovery room. *Anesthesiology.* 1979;50(6): 539–541. https://doi.org/10.1097/00000542-197906000-000.

10 Cooper AL, Leigh JM, Tring IC. Admissions to the intensive care unit after complications of anaesthetic techniques over 10 The first 5. *Anaesthesia.* 1989;44(12);953–958. https://doi.org/10.1111/j.1365-2044.1989.tb09194.x.

11 Berg H, Roed J, Viby-Mogensen J, et al. Residual neuromuscular block is a risk factor for postoperative pulmonary complications. A prospective randomized, and blinded study of postoperative pulmonary complications after atracurium, veruronium and pancuronium. *Acta Anaesthesiol Scand.* 1997;41(9):1095–1103. https://doi.org/10.1111j.1399 6576.1997.tb048851.x.

12 Stewart PA, Liang SS, Li OS, et al. The Impact of Residual Neuromuscular Blockade, Oversedation and Hypothermia on Adverse Respiratory Events in a Postanesthetic Care Unit: A prospective Study of Prevalence, Predictors, and Outcomes. *Anesth Analg.* 2016;123(4):859–868. https://doi.org/10.1213/ANE.0000000000001513.

13 Murphy GS, Szokol JW, Franklin M, Marymont JH, Avaram MJ, Vender JS. Postanesthesia care unit recovery times and neuromuscular blocking drugs: a prospective study of orthopedic surgical patients randomized to receive pancuronium or rocuronium. *Anesth Analg.* 2004;98(1):193–200. https://doi.org/10.1213/ 01.ANE.0000095040.3648.

14 Baurain MJ, Hoton F, D'Hollander AA, Cantraine R. Is recovery of neuromuscular transmission complete after the use of neostigmine to antagonize block produced by rocuronium, vecuronium, atracurium and pancuronium? *Br J Anaesth.* 1996;77(4):496–499. https://doi.org/101093/bja/77.4.496.

15 Maybauer DM, Geldner G, Blobner M, et al. Incidence and duration of residual paralysis at the end of surgery after multiple administrations of cisatracurium and rocuronium. *Anaesthesia.* 2007;62(1):12–17. https://doi.org/10.1111/j.1365-2044.2006.04862.x.

16 Anderson BN, Madsen JV, Schurizek BA, Juhl B. Residual curarisation: a comparative study of atracurium pancuronium. *Acta Anaesthesiol. Scand.* 1988;32(2):79–81. https://doi.org/10.1111/j.1399-6576.1988.tb02692.x.

17 Hayes AH, Mirakhur RK, Breslin DS, Reid DS, McCourt KC. Postoperative residual block after intermediate-acting neuromuscular blocking drugs. *Anaesthesia.* 2001;56(4): 312–318. https://doi.org/10.1046/j.1365-2044.2001.01921.x.

18 Debaene B, Plaud B, Dilly MP, Deonati F. Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action. *Anesthesiology* 2003;98(5):1042–1048. https://doi.org/10.1097/00000542-200305000-00004.

19 Schreiber JU, Mucha E, Fuchs-Buder T. Residual paralysis following a single dose of atracurium: results from a quality assurance trial. *Eur J Anaesthesiol.* 2010;27(11): 993–994. https://doi.10.1097/EJA.0b013e32833addf9.

20 Mclean DJ, Diaz-Gil D, Farhan HN, Ladha KS, Kurth T, Eikermann M. Dose-dependent association between intermediate-acting neuromuscular-blocking agents and postoperative respiratory complications. *Anesthesiology.* 2015;122(6): 1201–1213. https://doi.org/10.1097/ALN.0000000000000674.

21 Fuchs-Buder T. Neuromuscular Monitoring in Clinic and Research Springer. Verlag, Heidelberg, 2008. https://doi.org/10.1007/978-3-540-78570-5.

22 Patton WD, Waud DR. The margin of safety of neuromuscular transmission. *J Physiology.* 1967;191(1):59–90. https://doi.org/10.1113/jphzsiol.1967.sp008337.

23 Donati F, Bejan D. Not all muscles are the same. *Br J Anaesth.* 1992;68:235–236. https://doi.org/10.1093/bja/68.3.235.

24 Buzello A. The tetanus in humans [in German]. *New German Surgery.* 1929;199–200.

25 Ali HH, Wilson RS, Savarese JJ, Kitz RJ. The effect of tobocurarine on indirectly elicited train-of-four muscle response and respiratory measurements in humans. *Br J Anaesth.* 1975;47(5):570–574. https://doi.org/10.1093/bja/47.5.570.

26 Bevan DR, Smith CE, Donati F. Neuromuscular blockade after surgery: comparison of clinical assessment and evoked twitch responses. *Anesthesiology.* 1988;69(3A):A475. https://doi.org/10.1097/00000542-19880910- 00475.

27 Eriksson LI, Sundman E, Olsson R, et al. Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans: simultaneous videomanometry and mechanomyography of awake human volunteers. *Anesthesiology.* 1997;87(5):1035–1043. https://doi.org/10.1097/00000542-199711000-00005.

28 Kopman AF, Yee PS, Neumann GG. Relationship of the train-of-four fade ratio to clinical signs and symptoms of residual paralysis in awake volunteers. *Anesthesiology.* 1997;86(4):765–771. https://doi.org/10.1097/00000542-199704000-00005.

[29] Eriksson LI. Reduced hypoxic chemosensitivity in partially paralysed man. A new property of muscle relaxants? *Acta Anaesthesiol Scand*. 1996;40(5):520–523. https://doi.org/10.1111/j.1399-6576.1996.tb04482.x.

[30] Herbstreit F, Peters J, Eikermann M. Impaired upper airway integrity by residual neuromuscular blockade: increased airway collapsibility and blunted genioglossus muscle activity in response to negative pharyngeal pressure. *Anesthesiology*. 2009;110(6):1253–1260. https://doi.org/10.1097/ALN.0b013e31819faa71.

[31] Sundman E, Witt H, Olsson R, Ekberg O, Kuylenstierna R, Erikson LI. The incidence and mechanisms of pharyngeal and upper esophageal dysfunction in partially paralyzed humans pharyngeal videoradiography and simultaneous manometry after atracurium. *Anesthesiology*. 2000;92(4):977–984. https://doi.org/10.1097/00000542-200004000-00014.

[32] Döcker D, Walther A. Muscle relaxants and neuromuscular monitoring-Introduction for a safe clinical application [in German]. *Intensivmed Notfallmed Schmerzthe*. 2012;47(5):296–305. https://doi.org/ 10.1055/s-0032-1313567.

[33] Milde AS, Motsch J. Drug interactions and the anesthesiologist [in German]. *Anaesthesist*. 2003;52(9):839–859. https://doi.org/10.1007/s00101-003-0563-2.

[34] Heir T, Caldwell JE. Impact of hypothermia on the response to neuromuscular blocking drugs. *Anaesthesiology*. 2006;104(5):1070–1080. https://doi.org/10.1097/00000542-200605000-00025.

[35] Fuchs-Buder T, Meistelmann C, Alla F, Grandjean A, Wuthrich Z, Donati F. Antagonism of low degrees of atracurium-induced neuromuscular blockade: dose-effekt relationship for neostigmine. *Anesthesiology*. 2010;112(1): 34–40. https://doi.org/10.1097/ALN.0b013e3181c53863.

[36] Fuchs-Buder T. Neostigmine: Timing and dosing in 2016. *Anaesth Crit Care Pain Med*. 2016; 35 (4): 245–247. https://doi.org/10.1016/j.accpm.2016.06.004.

[37] Buzello W, Krieg N, Brobmann GF. Neostigmine and dehiscence of intestinal nastomoses. *Anasth Intensivther Notfallmed*. 1982;17(2):81–85.

[38] Glinka L, Braczkowska M, Karakina A. Comparison of mivacuronium and rocuronium in the microsurgery of the larynx. *Pol Ann Med*. 2021;28(2):168–173. https://doi.org/1029089/2020.2000167.

[39] Hawkins J, Khanna S, Argalious M. Sugammadex for reversal of neuromuscular blockade: Uses and limitations. *Current Pharmaceutical Design*. 2019;25(19):2140–2148. https://doi.org/10.2174/1381612825666190704101145.

[40] Cammu G. Interactions of neuromuscular blocking drugs. *Acta Anaestesiol Belg*. 2001;52(4):357–363.

[41] Miller R. Will succinylcholine ever disappear? *Anesth Analg*. 2004;98(6):1674–1675. https://doi.org/10.1213/01.ANE.0000126935.87196.4C.

[42] Gaszyński T, Możański M: Recommendations of perioperative care and general anaesthesia (including low and free opioid anaesthesia) for the obese. *Anest Ratow*. 2016;10:67–77 [in Polish].