After introduction of neuromuscular blockade (NMB) by neuromuscular blocking agents (NMBAs) in clinical anaesthesia in 1946 (1), Beecher and Todd (2) firstly reported in 1954 that the risk of death related to anaesthesia was six times higher in patients receiving NMBAs compared to those applied no muscle relaxants. Further studies demonstrated that postoperative residual curarisation (PORC), defined as a train-of-four ratio (TOFR) < 0.9, is one of the main causes of postoperative pulmonary complications (POPCs), hypoxia, upper airway obstruction and delayed recovery, which increase the risk of tracheal re-intubation, coma and long-term mortality (3-13).

Studies also refuted the common used clinical premise that, following a single intubating dose (2x ED95) of an intermediate acting, non-depolarising NMBA, adequate spontaneous recovery will occur after 90 min (14-16). At least 30% of patients had a TOFR < 0.9 and 10% a TOFR < 0.7 (14). Even small degrees of residual paralysis (TOFR 0.8-0.9) impair the ability to swallow and entail the risk of microaspiration (17).

Neither clinical muscle function tests (5-second head lift, sustained hand grip) nor simple peripheral nerve stimulators (tactile, visual evaluation) are able to detect PORC (18-22). Subjective estimation of TOF fading is unreliable, when TOFR exceeds 0.4 and a 50 Hz tetanic stimulation is also insensitive (20). So unsafe period of neuromuscular recovery (TOFR: 0.5-0.9) can’t be differentiated and residual paralysis can’t be excluded with this methods (17).

Despite of routine use of shorter acting NMBAs and acetylcholinesterase inhibitors (for instance, neostigmine), 20-40% of patients arrive in the PACU with symptoms of residual paralysis (18, 23, 24). Especially elderly patients (70-90 years) are at almost twice as big risk for PORC and POPCs as younger patients (57.7% vs. 30%) (25).

Possibly even in some cases, where neuromuscular block has already recovered completely, routinely applied neostigmine without neuromuscular monitoring in recommended doses (2.5 mg) may cause neuromuscular transmission failure by desensitation (26), depolarisation block (27) and open chanel block of the acetylcholine receptors (28). This may impair upper airway dilator volume, genioglossus muscle function and diaphragmatic functionality (29).

But also tracheal extubation after reversing with sugammadex, a modified γ-cyclodextrin, without using neuromuscular monitoring has a risk of residual paralysis as high as 9.4% (30-32).

However the incidence of residual paralysis and associated complications can be significantly reduced by using the combination of intermediate acting NMBAs, objective neuromuscular monitoring and pharmacological reversal.
of residual neuromuscular block by neostigmine and sugammadex (6, 8, 9, 11, 13, 33-35).

Despite all that objective neuromuscular monitoring and pharmacological reversing are rarely regularly utilized by many practitioners in the operation room worldwide (36, 37). Furthermore 80% to 90% respondents of an international survey stated that they had never seen residual paralysis in the PACU (36).

No method alone is appropriate to delete residual paralysis. A preventive strategy might be the introduction of a treatment bundle, for example an algorithm combining different key elements of PORC treatment to reduce the incidence of residual paralysis.

Furthermore anaesthesiological societies should develop standards and recommendations how to manage perioperative neuromuscular blockade (38, 39). Especially at the institutions objective neuromuscular measurement devices should be integrated in the operating room monitoring system. Continuous education of the clinicians in correct use of neuromuscular monitoring and the interpretation of the results is eminently important (40). Tools like dosing charts and algorithms might pull down obstacles.

First element of the bundle might be the avoidance of long-acting NMBA, like pancuronium. It was shown, that the use of intermediate- and short-acting NMBA lowers the incidence of POPCs in the PACU (41-43).

Second part of the bundle might be the mandatory, perioperative use of quantitative, objective NMB monitoring (acceleromyography, electromyography, kinemyography), whenever NMBA are used. It is recommended to apply this real time measurement in a calibrated mode intraoperatively to adjust depth of NMB for optimizing surgical conditions and to modulate the optimal dose for pharmacological reversal (38, 44). Calibrated acceleromyography is able to identify up to 97% of patients with residual paralysis (45). Most appropriate stimulation pattern is the TOF stimulation. Post tetanic count (PTC) should be used to monitor deeper (TOF count [TOFC]=0) neuromuscular blockade (44). The current recommendation for sufficient recovery of NMB is a TOFR ≥0.9 measured at the adductor pollicis muscle (44). Objective monitoring has been shown to reduce residual paralysis and POPCs (8, 40).

The third, probably the most important part of the bundle would be the appropriate pharmacological reversal of NMB. Recovery of NMB after neostigmine is dependent on several factors, including the depth of NMB, type of muscle relaxant and dosing of neostigmine (46). During inhalative anaesthesia recovery times are signifi-

Figure 1. Standard operating procedure of the University Medical Centre Regensburg: Reversing algorithm guided by quantitative neuromuscular monitoring (benzylisoquinolinium NMBA without option for sugammadex) (15, 17, 46, 48, 58, 61-64, 74, 77-79).
cantly prolonged in comparison to intravenous application using neostigmine (47). In contrast to neostigmine, sugammadex, just encapsulating aminosteroidal NMBA (rocuronium, vecuronium, pancuronium, pipercuronium), is equally effective in inhalative and intravenous anaesthesia (47). Sugammadex in appropriate dosing rapidly reverses profound (PTC=0, TOF count [TOFC] = 0) and deep (PTC ≥1, TOFC = 0) NMB (48, 49). Because of its ceiling effect at a dose of 0.07 mg kg⁻¹ higher doses of neostigmine do not result in a faster recovery of deep NMB (50, 51). During deep NMB effects of neostigmine have a very slow onset and time to full recovery is prolonged with a large interindividual variability (52). Geometric mean recovery time to a TOFR of 0.9 after neostigmine 0.07 mg kg⁻¹ at a PTC of 1-2 during sevoflurane anaesthesia was 49 min (range: 13-146 min) for rocuronium and 50 min (range: 46-313 min) for vecuronium (31, 52).

In contrast sugammadex 4 mg kg⁻¹ effectively reverses a rocuronium-induced deep NMB in 2.0 to 2.9 min (range: 0.9-20.4 min) (31, 52, 53). Whereas reversing of a vecuronium-induced deep NMB with sugammadex 4 mg kg⁻¹ has a slower progress (4.5 min) and a wider range (1.4-68.4 min) of recovery (31). Recreation period is less variable with sugammadex 94-95% of sugammadex recipients recover within 5 min, whereas just 20% of patients receiving neostigmine (53, 54).

So currently it is recommended to avoid acetylcholine inhibitors in reversal of profound and deep NMB. Neostigmine should only be applied in a dose ≤0.07 mg kg⁻¹ after evidence of spontaneous neuromuscular recovery, a TOFC of at least two (17, 49).

At the reappearance of T2 (moderate NMB) recovery of the neuromuscular function to a TOFR ≥0.9 was significantly faster with sugammadex 2 mg kg⁻¹ than with neostigmine 0.05-0.07 mg kg⁻¹. Geometric mean times of recovery were less variable with sugammadex (2.0 min; range: 1.0-8.3 min) than with neostigmine (12.9 min; range: 3.7-106 min). Just 11% of neostigmine recipients reached a TOFR of 0.9 within 5 min in contrast to 98% of sugammadex recipients (55-57). Surprisingly sugammadex reversing a vecuronium-induced moderate neuromuscular blockade had a wider range of neuromuscular recovery from 1.2 to 64.2 min (32). Cisatracurium antagonized with neostigmine 0.034 mg kg⁻¹ and sugammadex 0.22 mg kg⁻¹ would reverse every level of NMB rapidly and effectively (55, 67).

Despite of neostigmine doses as high as 0.07 mg kg⁻¹ it is not possible to reverse a TOFR from 0.2 to ≥0.9 within 10 min in 95% of patients. In contrast low-dose sugammadex 0.26 mg kg⁻¹ can do so (61). Antagonizing a TOFR of 0.4 with neostigmine 0.035 mg kg⁻¹ mean recovery time was 5 min (range: 3-7 min) during total intravenous anaesthesia (62). Schaller et al. (63) estimated that 0.034 mg kg⁻¹ of neostigmine and sugammadex 0.22 mg kg⁻¹ would reverse a TOFR of 0.5 within 5 min effectively and comparably (63). Using rocuronium or cisatracurium, 10 minutes after the application of neostigmine 0.04 mg kg⁻¹ at a TOFR of 0.5, 100% of patients had recovered to a TOFR of 1.0 (46).

Generally effectiveness of neostigmine and sugammadex should be observed with caution, because there are outlier patients in both groups, who exceed the mean recovery times (30, 31, 61, 64). So quantitative monitoring is essential throughout to examine the reversing success (TOFR ≥0.9) (44, 49, 65, 66).

The main advantage of sugammadex compared to anticholinesterase inhibitors is its fast recovery time and its unique ability to reverse every level of NMB rapidly and effectively (55, 67). This might be beneficial in situations, where deep neuromuscular blockade is required like in precision procedures, where unexpected movements might be deleterious (robot-guided procedures, neurosurgery, vocal cord and eye laser surgery) or in interventions where maximal muscle relaxation might improve operating conditions, like in laparoscopic surgery (68). Meta-analysis identified fewer composite adverse events in using sugammadex compared to neostigmine (risk ratio [RR]: 0.6), with a number needed to treat (NNT) of 8 in order to prevent adverse events as follows (55, 67): Bradycardia (RR: 0.16; NNT: 14), postoperative nausea and vomiting (RR: 0.52; NNT: 16), risk of overall signs of POPC (headlift-test, general muscle weakness, amnesia, oxygen desaturation, POPCs (RR: 0.40; NNT: 13) (55). Patients receiving sugammadex had 40% fewer adverse events compared to those who received neostigmine (55). Both were associated with serious adverse events in less than 1% of patients. Surprisingly there was no significant difference between sugammadex and neostigmine regarding serious adverse events (55). Atropine showed no differences in adverse events compared to glycopyrrolate (55). For a wonder the authors judged none of the studies as having low risk of bias (55). Furthermore Ledowski was able to show in a retrospective study a weak evidence for sugammadex lowering the incidence of respiratory events in elderly ASA 3/4 patients (69, 70).

Former large propensity score-matched studies concluded that neostigmine reversal did not improve oxygenation, was associated with increased atelectasis and high-dose neostigmine application increases the incidence of respiratory morbidity. Furthermore it was suggested that the association between NMBA and POPCs was dose-dependent (5, 12, 71, 72). These studies severely criticized, were limited by many factors like the accuracy of data collection, insufficient propensity scoring and the questionable efficacy of qualitative neuromuscular monitoring (69, 73).
However current studies identified that appropriate dosing of neostigmine for reversing of residual paralysis is able to eliminate effectively the incidence of respiratory complications and that the application of sugammadex 1.0 mg kg⁻¹ at a TOFR ≥0.9 does not improve patient’s motor function (9, 12, 35, 66). Murphy and colleagues revealed in a clinical setting that application of neostigmine 0.04 mg kg⁻¹ at a TOFR of ≥0.9 did not raise the incidence of postoperative muscle weakness, hypoxemia and airway obstruction (74).

In the context of the existing literature and the restriction of sugammadex to aminosteroidal muscle relaxants, neostigmine is currently indispensable, especially in reversing of shallow and minimal residual NMB of benzylisochinolinium NMBAs. Regarding the better safety profile of sugammadex, it might be advisable to avoid high-dose neostigmine (0.07 mg kg⁻¹), especially in aminosteroidal NMBAs.

But in the daily life where economic deliberations play an important role, trebling of the reversing costs from A$42 to A$127 when using sugammadex, might be unacceptable, especially regarding the questionable benefits for the time management (75). So a more pragmatic way of NMB management might be suitable (76):

- a goal-directed, neostigmine integrating, algorithm-guided reversal of NMB based on careful quantitative neuromuscular monitoring combining the three proposed bundles to reduce PORC-associated POPCs (Figure 1) (15, 17, 46, 48, 58, 61-64, 74, 77-79).

In the year 2018 residual paralysis and its consequences are still a relevant problem in clinical anaesthesia. Despite of the advantages of sugammadex, neostigmine has not lost its relevance in antagonizing NMB generated by benzylisochinolinium NMBAs. So a pragmatic way of NMB management might be an algorithm-guided reversal of intermediate-acting NMB with sugammadex and neostigmine using quantitative neuromuscular monitoring devices.

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FULESDI, ASZTALOS, TASSONYI VS. UNTERBUCHNER

**NEUROMUSCULAR BLOCK: STILL A DISCUSSION**

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