*In recent years, we gained a new insight about "neuromuscular blockade"(NMB). We can consider that this is one of the "classical" concepts of our branch: its theory is very well-known; the scientific background has been exclusively studied decades ago. New developments have led to the fact that NMB has become again be a subject of debates and new studies.*

*In recent years, there has been only one molecule which has been introduced as a new-comer to our daily practice: Sugammadex. Sugammadex has changed a lot of things:*

*On one hand, we have now the feeling that we can use the neuromuscular blocking agents ("NMBA's") in a wider, safer margin. Yes, we are not so afraid of "rest-curarisation" or "re-curarisation", as we were before. We can allow a "deep" blockade, if necessary. And even during a deep block, we can safely (safely?) antagonise the effects of NMBA. Is this information really so true?*

*On the other hand, we have suddenly "realised" that in the past, we had probably more patients than we suggest who were suffering of the continuing effects of NMBA's. We see studies showing that actually we always need a TOF > 0.9, and "older" methods of reversal are often insufficient to achieve this goal. Again, we have suddenly "realised" that we actually needed a deep block more often than we performed. Is this information really so true, too?*

*These questions (and more) have to be discussed, even in 2018, decades after the "scientific clarification" of neuromuscular blockade.*

**Editor**
**Nüzhet Mert ŞENTÜRK**

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**Cite this article as:** Unterbuchner C. Neuromuscular Block and Blocking Agents in 2018. Turk J Anaesthesiol Reanim 2018; 46: 75-80.

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Turk J Anaesthesiol Reanim 2018; 46: 75-80
DOI: 10.5152/TJAR.2018.200318

Available online at www.jtaics.org

# Neuromuscular Block and Blocking Agents in 2018

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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 applicated 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 $ED_{95}$) of an intermediate acting, non-depolarising NMBA, adequate spontanous 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 fuction 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 acetycholinesterase 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 applicated 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). Furhermore 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 develope standards and recomendations 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 NMBAs are used. It is recommended to apply this real time measurement in a calibrated mode intraoperatively to adjust depth of NMB for optimising 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-

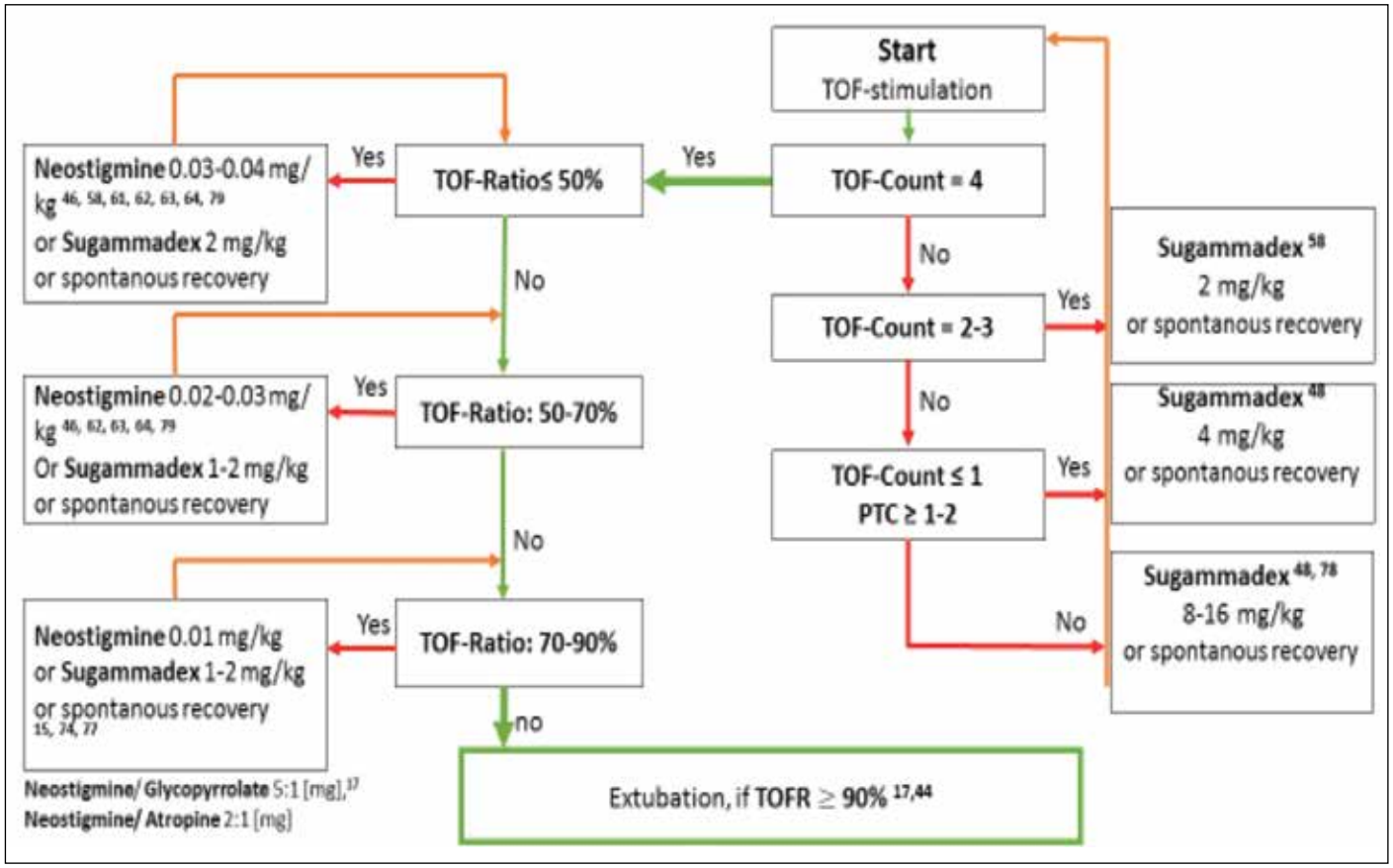


Figure 1. Standard operating procedure of the University Medical Centre Regensburg: Reversing algorithm guided by quantitative neuromuscular monitoring (benzylisoquinolinium NMBAs without option for sugammadex) (15, 17, 46, 48, 58, 61-64, 74, 77-79).

cantly prolonged in comparison to intravenous application using neostigmine (47). In contrast to neostigmine, sugammadex, just encapsulating aminosteroidal NMBA (rocuronium, vecuronium, pancuronium, pipecuronium), 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 recieving neostigmine (53, 54).

So currently it is recommended to avoid acetylcholineinhibitors in reversal of profound and deep NMB. Neostigmine should only be applicated in a dose ≤0.07 mg $kg^{-1}$ after evidence of spontanous neuromuscular recovery, a TOFC of at least two (17, 49).

At the reappearence 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 0.05 mg $kg^{-1}$ has comparable geometric mean recovery times (9.0 min; range: 4.2-28.2 min) to rocuronium (58).

In reversal of NMB with acetylcholinesterase inhibitors the only variables that can be modiefied are the degree of spontanous recovery and the interval between application of the inhibitor and the recreation of the TOFR ≥0.9 (47). So it is recommended to administer neostigmine until at least T4 to TOF stimulation appears. At this level reliability and speed of reversal with acetylcholine inhibitors markedly increases (47, 49, 59, 60). Shallow (TOFC=4; TOFR=0.1-0.4) and minimal (TOFC=4; TOFR >0.4 but <0.9) NMB should be reversed within 10 min after the application of the reversal agent because of safety issues (47).

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 sugammdex 0.26 mg $kg^{-1}$ can do so (61). Antagonizing a TOFR of 0.4 with neostigmine 0.03 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 effectivness 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 unexspected 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 laparscopic 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 PORC (head-lift-test, general muscle weakness, amblyopia, oxygen desaturation, POPCs) (RR: 0.40; NNT: 13) (55). Patients recieving sugammadex had 40% fewer adverse events compared to those who recieved 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 NMBAs 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 eleminate 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 NMBA.

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, neostigmime has not lost its relevance in atagonizing NMB generated by benzylisochinolinium NMBAs. So a pragmatic way of NMB managment might be an algorithm-guided reversal of intermediate-acting NMBA with sugammadex and neostigmine using quantitative neuromuscular monitoring devices.

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