Abstract: Oro-tracheal intubation and selected surgical conditions are facilitated by a deep neuromuscular block (NMB), but patient’s security can be jeopardized by its residual effects at the time of tracheal extubation. Although neostigmine remains the reference reversal agent in many situations, the limitations of its efficacy must be well understood (ceiling effect, delay of action, side effects). It is best administered after re-emergence of the 3rd or 4th train-of-four (TOF) response. Sugammadex causes more predictable and more rapid recoveries from much deeper rocuronium-induced NMB. Therefore, maintaining deep NMB during surgery is no longer incompatible with rapid recovery and safe extubation. In Belgium, the use of sugammadex and its reimbursement depend on specific conditions. The excellent clinical tolerance of sugammadex benefits to patients at risk of developing complications related to residual NMB or to the undesirable effects of neostigmine. In all cases, neuromuscular transmission monitoring is the key to adequate NMB management.

Key words: Neuromuscular block; residual neuromuscular block; rocuronium; neostigmine; sugammadex; neuromuscular transmission monitoring.

In Belgium, sugammadex has been available for clinical practice since March 1st, 2009. The patients, who pay for the drug, benefit from specific reimbursement conditions by the 'Institut national d’assurance maladie-invalidité / Rijksinstituut voor Ziekte en Invaliditeitsverzekering - INAMI/RIZIV' (National Health and Disability Insurance Institute), which became effective on July 1st, 2010. This new drug has several clinical benefits, either for the patient or for the clinician, and practitioners did not wait for the establishment of the INAMI/RIZIV reimbursement program before using the drug. Unfortunately, sugammadex has a relatively high cost, which remains a barrier to its routine clinical use in Belgium. The progressive recovery of functional nicotinic receptors is related to the decision of most clinicians as to use of the new drug instead of neostigmine, the historically classic reversal agent.

Currently, only a limited number of anesthesiologists have changed their practice of neuromuscular block (NMB) management and reversal. Most of them have changed their protocols for a limited number of procedures. As a result, the use of specific relaxants and their antagonists varies among hospitals, and even between anesthesiologists within the same team.

Considering the wide variability in daily clinical practices, the authors of this review aimed at listing the reasons for inducing and reversing neuromuscular blockades (NMBs) in 2013. We here propose an algorithm for proper NMB management and reversal, based on the technical and pharmacological options available in Belgium. We also suggest specific modifications to the current state of clinical practice. In particular, we propose a specific role for sugammadex as a reversal agent within the context of Belgian anesthesia practice.

Definitions and scope

The authors will describe the management modalities for non-depolarizing NMBs. The depolarizing block induced by succinylcholine is generally short in length and cannot be reversed by the pharmacologic agents discussed here. After the induction of NMB, spontaneous recovery is defined as the progressive recovery of neuromuscular transmission and muscular contractile strength. The progressive return to normal function of the nicotinic receptors is related to the
plasma clearance of neuromuscular blocking agents (NMBAs), a phenomenon that is linked to their redistribution, metabolism, and/or physiologic breakdown (1).

Pharmacological reversal is the use of pharmacological agents that are able to accelerate NMB recovery. Several mechanisms of actions of these drugs exist, with varying levels of specificity for NMBAs. Drugs used for pharmacological reversal include neostigmine, edrophonium, sugammadex, and cysteine, among others. We will focus on the sole two agents that are currently available in Belgium: neostigmine and sugammadex.

Clinical tests were established to estimate the possible residual effects of NMB, including the head lift and tongue depressor tests. Using nerve stimulators, subjective visual or tactile evaluation appreciated the muscular responses fading during the train-of-four (TOF), double burst stimulation (DBS) or tetanic stimulations. Both methods have limitations (2).

Objective neuromuscular transmission (NMT) monitoring allows, to a certain degree, the objective measurement of the depth of NMB and the level of subsequent recovery. Mechanomyography is the standard method, but acceleromyography (3) (and, to a lesser extend, kinemyography) are the most commonly used techniques in clinical practice in Belgium. NMT monitoring allows for the collection of information to differentiate between different levels of NMB (4-6).

The post-tetanic count (PTC) consists of an automatic sequence starting with 1 Hz stimulations for 15 seconds to ensure the absence of muscular response. If a muscular response is present, the sequence is stopped. If there is no muscular response, a 50 Hz supra-maximal tetanic stimulus is applied for 5 seconds. Three seconds later, the 1 Hz single twitch is applied again for 20 seconds. The number of potentiated muscular responses is counted or recorded to determine the PTC.

The train-of-four (TOF) stimulation consists of four single twitches (T1-T4) delivered at 2 Hz for 2 seconds. The TOF count is the number of induced muscular responses (0-4). Similar to PTC, TOF can be determined by objective (e.g., acceleromyography) or subjective means (manual or visual evaluation). The TOF ratio is the ratio of the amplitude of the 4th response (T4) over the amplitude of the first one (T1) (T4/T1). The TOF ratio allows for objective quantification of NMB recovery on a scale ranging from 0.01 (after obtaining four clear twitches) to 1. The results can also be displayed as percentages (1 to 100%).

Different NMB levels are defined according to responses obtained during NMT monitoring. The levels are defined as follows:

- Intense NMB: no response to PTC.
- Deep NMB: from the reappearance of 1 PTC up to, but not including, a TOF count of 1.
- Moderate NMB: from the reappearance of the first TOF response up to the fourth TOF response.
- Recovery in progress: from the detection of four clear TOF responses and the calculation of the TOF ratio, up to a TOF ratio of 0.9.
- Extubation safety level: a TOF ratio of 0.9.

Problems related to the use of neuromuscular blocking agents

Inter-individual variability and unpredictable duration of action

The pharmacokinetic properties of the available NMBAs provide the clinician with interesting differences with regard to the onset and duration of action. A wide range of inter-individual variability in duration of action of each of the non-depolarizing NMBAs exists (7). Many physical and pharmacological factors interfere with the duration of NMB, potentiating the basic inter-individual variability, including magnesium sulphate, halogenous vapors, and aminoglycoside antibiotics. (8). Therefore, the spontaneous evolution of a NMB can last much longer than expected and can be completely unpredictable, potentially introducing significant delays in the operating room (OR) turn over. The time and money lost while waiting for spontaneous recovery or sufficient recovery to allow the administration of neostigmine (as well as its duration of action) can be unacceptable, particularly if the NMB was deep (9). Postoperative ventilation in post-anesthesia care units or intensive care units is rarely applied in Belgium. Therefore, except for rare cases, the Belgian anesthesiologist must remain in the OR, waiting for his patient to recover. The pressures of revenue and of OR turnover are omnipresent, but should not take priority over the quality and safety of anesthesia.

Postoperative residual muscle relaxation

Every NMBA administration during general anesthesia carries the risk of residual effects after surgery. Based on numerous studies using mechanomyography, postoperative residual curarization
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(PORC) is defined as a TOF ratio < 0.9. Its incidence in post-anesthesia care units is estimated to be approximately 40% (2-64%) (10). Such residual effects (even at levels of recovery as high as a TOF ratio of 0.7-0.8) have clinical consequences and complications that can prolong hospitalization. The most frequent complications include patient anxiety, dyspnea, hypoxia, atelectasis, and pneumonia. Those complications are related to decreased sensitivity of chemoreceptors to hypoxia, upper airway collapse, dysphagia, and reduced protection against aspiration (2, 10, 11). For these reasons, guidelines should be observed to rule out PORC. Current recommendations prone the use of short- or intermediate-acting NMBAs, routine reversal of NMBs, and monitoring neuromuscular transmission whenever relaxants are used, especially before and after NMB reversal (12-14). By decreasing the incidence of PORC, patient safety is improved, as demonstrated by the reduction in postoperative respiratory complications (15, 16).

Neuromuscular Transmission Monitoring in Clinical Practice

The use of NMT monitoring is necessary for determining the threshold for reversal agent administration, and determining its appropriate dosage. NMT monitoring also confirms the efficacy of reversal by asserting recovery of TOF ratio to values over 0.9. After electrical stimulation of a motor nerve, the ulnar nerve at the wrist in most cases, a manual subjective evaluation can detect the presence of muscular contractions (typically of the adductor pollicis). It is possible to use PTC or TOF count to guide the administration of reversal agents (see below). Visual or manual evaluation of the contraction intensity after DBS or TOF stimulation does not allow for an effective quantification of the relative force of the successive muscular responses, and, consequently, lacks accuracy. This method cannot exclude PORC (2, 17). The use of objective measures to confirm NMB recovery at a minimum 0.9 TOF ratio before extubating the trachea is currently recommended (13). The routine administration of reversal agents such as neostigmine in the absence of any quantitative monitoring during the interval between the end of surgery and tracheal extubation does not ensure complete recovery (18). Measurements obtained by recording techniques (i.e., the application of custom sensors) using the principles of acceleromyography (TOF-Watch, Organon, Oss, The Netherlands), kinemyography or electromyography (NeuroMuscular Transmission Module, GE Healthcare, Finland) have demonstrated their efficacy, with some specific precautions (12, 19).

First, it is worth remembering that different muscle groups have different sensitivities to NMBAs (20). The adductor pollicis is one of the last muscles to recover from NMB. In contrast, the diaphragm, some abdominal wall muscles, and the vocal cord adductors are more resistant to NMBAs, and might still contract or have a high tone while TOF count is 0 at the thumb adductor muscle. The depth of blockade at the thumb does not reflect the exact level of blockade at the other muscle groups, but a PTC between 1 and 5 allows proper monitoring of deep NMB at the thumb. This technique is sensitive enough to ensure adequate diaphragm paralysis for most clinical purposes (4, 21).

Second, during surgery, the hand is not always accessible for NMT monitoring. Because of external disturbances or constraints imposed by surgical conditions, the results obtained with the measurement techniques may considerably vary, and lead clinicians to choose to disregard them (22). Some authors have looked for other NMT monitoring sites (including the diaphragm and larynx) (23). TOF count at the corrugator superciliii has proved to be interesting for the purposes of monitoring deep NMB. The patient’s head is more commonly accessible to the anesthesiologist during surgery. In clinical practice, objective NMT monitoring (with acceleromyography) is difficult on such small muscles. The post-tetanic count at the adductor pollicis seems to be a better indicator of early diaphragmatic recovery than the TOF count at the corrugator superciliii (23, 24). Consequently, the hand (ulnar nerve stimulation and objective assessment of adductor pollicis muscular responses) remains the best place to monitor deep NMB and full recovery. This is the reason why the following algorithm is based on that standard. When using acceleromyography or kinemyography, the hand must be positioned in a way to avoid any external disturbances and to ensure freedom of movement for the thumb (25).

Pharmacological Reversal

Neostigmine

Neostigmine antagonizes a non-depolarizing NMB by increasing the availability of acetylcholine (Ach) in the synaptic cleft, tipping the competitive
balance in favor of the neurotransmitter. It primarily inactivates the acetylcholinesterases at the muscle endplate. The time needed for reversal depends on antagonist dose and depth of blockade at the time of neostigmine administration, halogenated vapor concentration, acid-base status and electrolyte imbalances, and muscle relaxant clearance (including all factors that could prolong the block). Classically, neostigmine can be administered to antagonize moderate blocks, that is those with a minimum TOF count of 2 (26, 27).

When routinely administered at the end of anesthesia, neostigmine has proved to improve postoperative mortality (28). Beyond this favorable overall trend, the efficacy of NMB reversal with neostigmine is limited by several specific problems.

First, neostigmine has a ‘ceiling effect’, most often observed when trying to reverse too deep NMB. Above the maximal recommended dose of 70 µg/kg (or 5 mg), there is no additional effect. Further recovery evolves at the underlying speed of spontaneous recovery, and mainly depends on NMBA clearance itself (29, 30). Neostigmine at higher doses or given after NMB spontaneous recovery could markedly impair the upper airway volume, genioglossus muscle function, diaphragmatic function, and breathing (31). These arguments do not plead for systematic reversal. Neostigmine should only be given if needed, according to NMT monitoring (32).

Second, a major under-estimated problem in clinical practice is the delay needed for NMB reversal by neostigmine. The average reversal time is approximately 12 minutes, as reported in one recent study (33). However, a large inter-individual variability exists. Ten % of patients might need more than 60 minutes to reach a TOF ratio of 0.9 (33). The problem is that most modern anesthesiologists will not wait for that extra time before performing tracheal extubation. In several cases, recovery is prolonged by physiological and/or pharmacological interferences that are commonly present in the OR. In particular, magnesium sulphate importantly prolongs spontaneous recovery and neostigmine reversal (34), as do halogenated vapors (35). This prolonged recovery time is more frequent in obese (body mass index (BMI) > 30) patients, who have an average reversal time of 26 minutes (36). The reversal times for morbidly obese patients (BMI > 40) are most likely longer, but this must still be demonstrated.

For these reasons, even a routine administration of neostigmine is frequently followed by incomplete reversal of a residual block at the time of tracheal extubation (18). Giving neostigmine without using NMT monitoring is no longer an option, as it does not guarantee complete reversal (37). According to the recommendations of experts, anesthesiologists must at least wait for the reappearance of the third TOF response before administering a standard 35-50 µg/kg dose of neostigmine, in order to increase efficacy and safety (38, 39). They must wait and monitor NMT until a minimal TOF ratio of 0.9 before allowing patient emergence and tracheal extubation (15).

Minimal residual NMB (a median TOF ratio of 0.7 (range 0.46-0.9), corresponding to the absence of fading to visually or manually estimated DBS or TOF) is still associated with hypoxemia in the post-anesthesia care unit. A low neostigmine dose (20 µg/kg) is effective at antagonizing rocuronium-induced minimal NMB within 10 minutes (40).

Insofar as neostigmine is an acetylcholinesterase inhibitor, it induces Ach stimulation on muscarinic receptors in smooth muscles, heart and various glands, as well as on autonomic ganglia nicotinic receptors. This leads to side effects, whose incidence remains controversial. Side effects may encompass postoperative nausea and/or vomiting (PONV), bradycardia, prolonged QT interval (which may precipitate life-threatening arrhythmias), unpredictable bronchoconstriction (especially in susceptible patients), ptyalism, and increased intraluminal pressure and propulsive activity in the bowels (41). To prevent some of these side effects, parasympatholytic drugs are used (atropine or glycopyrrolate). These compounds also have side effects (tachycardia, urinary retention, accommodation disorders, and dry mouth). Classically, neostigmine associated with atropine or glycopyrrolate should be avoided (relative contraindications) in patients with a tendency to PONV, chronic obstructive pulmonary disease (COPD), cardiac failure and/or arrhythmias, bowel obstruction, prostatic hypertrophy, and glaucoma. An allergy to neostigmine is a rare but absolute contraindication.

Sugammadex

In March 2009, a new drug was introduced into clinical practice in Belgium. With an innovative mechanism of action, sugammadex (Bridion, MSD, Belgium) is the only selective relaxant-binding agent (42-44). The modified gamma-cyclodextrin encapsulates the steroidal NMBA rocuronium and vecuronium in plasma and tissues. The concentration of the free steroidal NMBA is rapidly re-
ducted. The remaining steroidal NMBA molecules continue to detach from the nicotinic receptors and become further inactivated as long as free sugammadex remains available. The nicotinic receptors become available to Ach again, and the NMB fades rapidly. The steroidal NMBA-sugammadex complexes remain bound until excretion by the kidneys. Because of the molecular selectivity for steroidal NMBA, sugammadex has no effect on the benzylisoquinolines (atracurium, cisatracurium, and mivacurium). As vecuronium is currently rarely used in Belgium, the authors focused on rocuronium.

Different doses of sugammadex have been determined to guarantee effective reversal according to depth of NMB, which depend on steroidal NMBA plasma concentration (45). Similarly to neostigmine, the administration of sugammadex in the absence of NMT monitoring is not an option. The three recommended doses recommended are 16 mg/kg for immediate reversal after NMB initiation, 4 mg/kg to reverse deep NMB, and 2 mg/kg to reverse moderate NMB.

Since 2010, and because of high cost for the patient (the introductory factory price was 78 euros/200 mg), INAMI/RIZIV has imposed specific conditions for reimbursement. This reimbursement occurs in the context of hospitalization (100%), as well as outpatient surgery (75% of reimbursement, 85% if disabled). Sugammadex 16 mg/kg is reimbursed when used for the immediate reversal of intense NMB, as an emergency rescue if the anesthesiologist is not able to intubate the patient. This situation is extremely rare, as mask ventilation is often still possible, allowing more time to choose a different airway approach. Patients are reimbursed for sugammadex for routine NMB reversal at a dose of 4 mg/kg for a deep NMB. The anesthesiologist is required to explain why a deep NMB was needed up to the end of surgery and to certify that the level of blockade did reach the minimum threshold (PTC 1-2) at the time of administration. Sugammadex 2 mg/kg is reimbursed to reverse a moderate block (minimum TOF count of 2) when contraindications to neostigmine exist (postoperative bowel, biliary or urinary tract obstruction). Listed contraindications are rarely present at the time of reversal, limiting the availability of reimbursement for that dose.

When given at the abovementioned levels of blockade at the proper dose, sugammadex induces, in most patients, an effective NMB reversal within a few minutes. It is not only faster and more predictable than neostigmine, but also able to reverse all depths of blockades (33, 45).

Current clinical trials confirm that the administration of sugammadex is safe regardless of patient age, and does not require dose modification in pediatric, elderly, or obese patients (45). Doses based on an adapted ideal body weight formulation were demonstrated to be effective in morbidly obese patients (46). Unlike neostigmine, the effect of sugammadex does not depend on the type of anesthesia (propofol or sevoflurane) (33, 47). Currently available data confirm the high tolerance profile of this drug, including in patients with organ system insufficiency (renal, respiratory, or cardiac), in children, and in the elderly (45). However, sugammadex is not recommended in the presence of severe renal function impairment (creatinine clearance < 30 ml/min) and in cases of severe hepatic impairment accompanied by coagulopathy. A transient and limited prolongation of activated partial thromboplastin time (aPTT) and prothrombin time (PT) could occur when sugammadex is combined with vitamin K antagonists, unfractionated heparin, low molecular weight heparinoids, rivaroxaban or dabigatran. No clinically relevant increased incidence of bleeding events has been reported after sugammadex. Slight cough and movements can occur when anesthesia becomes too light at the time of sugammadex administration. Some patients complain of altered taste sensation. Few hypersensitivity reactions have justified complementary studies (48). Sugammadex seems to have no interaction with any drug used in anesthesia. To date, the only clinically relevant interaction concerns the possible capture of hormonal contraceptives. This effect is equivalent to a 12 hours delay of contraceptive intake. There are no undesired effects related to cholinergic stimulation, hence alleviating the need for concomitant antidote administration.

**Algorithm for clinical use** (see Table 1)

At the end of surgery, the following algorithm is proposed to guide NMB reversal according to PTC, TOF count, or TOF ratio. The administered NMBA, the patient’s characteristics, and the time allowable to wait for safe extubation are additional variables of interest to guide choice and dosing of the reversal agent.

When the objective mechanomyographic TOF measurement demonstrates a T4/T1 ratio higher than 0.9, no reversal is needed (2, 13). However, when using acceleromyography for NMT monitoring, a TOF ratio higher than or equal to 1.0 is recommended (2, 49). It is worth checking the monitoring device as to assert of an optimal functioning, and
Management of neuromuscular block reversal according to neuromuscular transmission monitoring. According to objective or subjective neuromuscular transmission monitoring (NMT) at the adductor pollicis muscle, and to corresponding level of blockade, choice and doses of reversal agents are recommended and commented. See the algorithm for clinical use section for more details.

**Table 1**

Management of neuromuscular block reversal according to neuromuscular transmission monitoring. According to objective or subjective neuromuscular transmission monitoring (NMT) at the adductor pollicis muscle, and to corresponding level of blockade, choice and doses of reversal agents are recommended and commented. See the algorithm for clinical use section for more details.

<table>
<thead>
<tr>
<th>Block level</th>
<th>NMT monitoring (Adductor pollicis)</th>
<th>Reversal agent</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Objective - Quantitative</td>
<td>Subjective - Qualitative</td>
<td></td>
</tr>
<tr>
<td>Full recovery</td>
<td></td>
<td></td>
<td>There is no monitoring able to confirm full recovery</td>
</tr>
<tr>
<td>Safe extubation</td>
<td>TOF ratio &gt; 0.9 (MMG) (≥ 1.0 with AMG?)</td>
<td>No fade to tetanus 100 Hz</td>
<td>Not needed. Up to 70% of nicotinic receptors are still occupied by NMBA! The patient is at risk of NMB recurrence.</td>
</tr>
<tr>
<td>Recovery in process</td>
<td>TOF ratio 0.5 - 0.9</td>
<td>No TOF or DBS fade</td>
<td>Neostigmine low dose 0.02 mg/kg</td>
</tr>
<tr>
<td>Moderate NMB</td>
<td>TOF count 3-4</td>
<td>DBS or TOF count 4 with fade</td>
<td>Neostigmine standard dose 0.05 mg/kg</td>
</tr>
<tr>
<td></td>
<td>TOF count 1-2</td>
<td></td>
<td>Sugammadex 2 mg/kg</td>
</tr>
<tr>
<td>Deep NMB</td>
<td>PTC 1-5-20</td>
<td></td>
<td>Sugammadex 4 mg/kg</td>
</tr>
<tr>
<td>Intense NMB</td>
<td>PTC 0</td>
<td></td>
<td>Sugammadex 16 mg/kg</td>
</tr>
</tbody>
</table>

Confirming the obtained value through the recording of multiple consecutive concordant measurements. No clinical test (including the head lift and tongue depressor test) can assert of a totally safe recovery level for tracheal extubation (2, 12).

The absence of fatigue from tetanic 100-Hz stimulation for 5 seconds is likely the only subjective test that can reasonably allow the exclusion of PORC (50, 51). The presence of fade is not correlated to a particular level of NMB, limiting the usefulness of this test to guide the proper administration of reversal agents.

It is important remembering that no monitoring can confirm the absence of NMBA on nicotinergic receptors. Objective NMT monitoring allows measuring the depth of NMB and the level of its recovery between PTC 1 and a TOF ratio of 1.0. When considering the large possible range of nicotinic receptor occupation rates by NMBA, NMT monitoring covers only a narrow window of it. At a TOF ratio recovery level of 0.9, up to 70% of postsynaptic receptors remain occupied by the NMBA (52, 53). This fact explains the danger of NMB recurrence following repeated administration of small doses of NMBA or other NMB promoting agents, such as magnesium (54).

At a TOF ratio between 0.5 and 0.9, low-dose neostigmine (0.02 mg/kg) (with adapted anticholinergic dose) is the first choice if no contraindication exists (40). While objective NMT monitoring is ideal, cautiously used conventional peripheral nerve stimulators can help guiding reversal. When no DBS or TOF fade can be manually detected, the above-mentioned low dose is most likely efficient enough. When fade is detected, the full dose must be administered. Manual appraisal of NMB has been proven unreliable for confirming complete recovery from NMB and to rule out PORC (32).

At a TOF count of 3-4, neostigmine’s standard dose of 0.05 mg/kg associated with 10 µg/kg glycopyrrolate or 10 µg/kg atropine is indicated. This level is the maximum depth of blockade that can be promptly antagonized by neostigmine. One must remember that recovery from this level of blockade may take much longer than the 10-15 minutes typically expected. Such a prolonged reversal time before being able to wake patients might sometimes be unaffordable in the context of OR turnover. In
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This case, an option could be the administration of 2 mg/kg sugammadex to accelerate the transition from moderate to full NMB recovery. This usage is currently not reimbursed in Belgium, except in specific circumstances such as the presence of strict contraindications to neostigmine (allergy or postoperative bowel, biliary or urinary track obstruction).

At a TOF count of 1-2, and only if rocuronium was used, 2 mg/kg sugammadex should be administered to reverse the moderate NMB. Patients can only be reimbursed for sugammadex in the presence of the abovementioned contraindications to neostigmine. In morbidly obese patients, sugammadex is dosed according to the adapted ideal body weight or lean body mass (46). From this depth of NMB, reversal is no longer possible with neostigmine. If a benzylisoquinoline NMBAs has been administered, one must wait until recovery to next level of blockade.

When TOF count is 0 and PTC 1, 2, or more, 4 mg/kg sugammadex can be administered, only to reverse a rocuronium-induced block. Reimbursement is allowed if deep NMB was medically justified until the end of surgery and if the NMT monitoring is recorded as evidence in the patient record. Otherwise, one must wait for a 3 or 4 TOF count before neostigmine can be given.

In cases of no response to PTC, the NMB is intense and too deep for routine reversal. The anesthesiologists must wait for the reappearance of a 1 or 2 PTC. This depth of NMB has poor interest in clinical practice to further improve surgical conditions. This situation appears after the induction of NMB with a high dose of rocuronium (rapid sequence induction). In this indication, the 16 mg/kg dose of sugammadex is effective to rapidly reverse the intense blockade, but patients are only reimbursed for it in the rare scenario of impossible ventilation and/or intubation. Note that airway patency is multifactorial and that the availability of sugammadex does not obviate the need for emergency airway management alternatives (55).

**Future perspectives**

As the first agent offering the ability to reverse deep NMB, sugammadex imposes to modify anesthesia daily practice. This drug has the potential to improve patient safety and surgical conditions, not at the cost of prolonged delays at the end of surgery to achieve the conditions needed for administering neostigmine safely.

The principal indications for deep NMB are oro-tracheal intubation and selected surgery. In the Belgian context of reimbursement conditions for sugammadex, INAMI/RIZIV requires the clinician to justify the maintenance of deep NMB through the entire procedure before allowing usage of the appropriate 4 mg/kg dose. It is important to know, as comprehensively as possible, the indications and advantages of deep NMB, as well as those of sugammadex, particularly for patient safety.

The interest of deep neuromuscular block

To secure the airway, oro-tracheal intubation is traditionally performed after muscle relaxation. The usual dose of 1.5-2 ED_{95} (95% Efficient Dose) induces a ‘shallow block’, i.e. a short period of deep enough blockade to facilitate intubation. Compared to other techniques, excellent intubating conditions are more easily obtained with NMB and are less frequently associated with postoperative hoarseness or vocal cord injuries (56). If NMT monitoring is not used to guide the onset intubation manoeuvres at the time of TOF responses disappearance, the anesthesiologist can start intubating too early, that is when NMB is not deep enough to provide optimal intubation conditions. Intubating conditions could be more frequently optimal if the latency of NMB onset was individually monitored, rather than systematically intubating all patients 3 minutes after NMBAs administration as is the case in the majority of inductions during routine clinical practice (56). Other anesthesia techniques have shown comparatively satisfactory results. The combination of high hypnotic and opioid doses, although less efficient, has been proposed as an alternative for intubation with NMBAs (57). The negative aspects of this combination are the associated hemodynamic changes, especially in elderly patients (58). These techniques spare NMBAs with the goal of reducing their respective complications. Anaphylaxis is very rare, and PORC can be eliminated by good clinical practice. In the absence of an alternative to oro-tracheal intubation (such as a laryngeal mask airway), the induction of deep NMB, confirmed by monitoring, remains the ideal solution for short delay tracheal intubation in terms of patient and anesthesiologist comfort.

Two groups of surgical procedures are indications for deep NMB. The first one includes those precision procedures where unexpected movements can be deleterious. Examples are vocal cord and eye surgery with lasers, neurosurgery, neuro-radiology embolization, robot-guided ablation, or other surgery in critical areas. A second group of indications includes procedures where there is a need to
relax muscles to their maximal length. Examples can be found in orthopedic fracture repositioning or dislocation reduction, laparotomy, laparoscopy, and mucosectomy. In some surgical contexts, deep blockade is sometimes justified for a long period of time. Deep NMB induced by the initial dose of NMBA (2 ED₉₅) can be maintained using a continuous infusion or repeated boluses. Using NMT monitoring is mandatory to guide repeated administration of NMBA. Needed depth of blockade depends on surgery type and aim of blockade. Maximal relaxation and the absence of any muscular reaction is ensured by intense blockade (PTC = 0), but, in most cases, deep blockade (PTC 1-5 or even higher, with TOF count = 0) is usually enough to improve surgical conditions (22).

The realignment of fractures or dislocations might require short moments of deep NMB during the realignment phase if deep. Most shoulder dislocations can be reduced with a traction maneuver after local intra-articular anesthesia. If reduction is delayed, deep NMB can reveal mandatory (59, 60).

The benefit of maintaining deep blockade to improve surgical operating conditions has been investigated. Requirements appear to depend on surgical approach (laparotomy or laparoscopy, upper abdomen or pelvis). King et al. questioned the surgeon on the quality of surgical exposure during retropubic prostatectomy by laparotomy and demonstrated better surgical conditions when patients were relaxed. Optimal surgical conditions can be found in the absence of NMB, but unacceptable conditions are far more frequent in non-paralyzed patients (61). Surgical guidelines for laparoscopy recommend low insufflation pressure (8 rather than 12-15 mmHg) to reduce postoperative complications, including pain, pulmonary complications, and length of hospital stay (62, 63). Although Chassard et al. investigated the intra-abdominal volume insufflated in pigs with or without NMB and did not find any significant difference (64), surgeons have demonstrated that NMB is necessary to prevent hyper-pressure during laparoscopy, and to improve surgical conditions (65). Measuring the effect of deep NMB, Mulier et al. found a reduction in abdominal pressure but no change in compliance, resulting in a 1-L net workspace increase at the same inflation pressure in most patients (66).

Deep NMB blocks are associated with prolonged recovery times. This recovery time between the end of a deep blockade and patient waking varies according to the type of procedure (laparotomy or laparoscopy). NMB may not return to a level compatible with the utilization of neostigmine (TOF count 3-4), whose effect can be slow. This obviously prolongs anesthesia for the patient, and is responsible for time loss in the context of the expensive hourly cost of an OR (9).

New short-acting anesthetic agents allow very deep anesthesia (with total intravenous anesthesia, inhalation anesthesia, or locoregional anesthesia) and effectively prevent sudden patient movements by blocking any active contraction. They could be an alternative to deep NMB, while allowing recovery within a reasonable delay. Active muscle contractions can be prevented by these techniques, but they have most likely no effect on resting muscle length, in contrast to deep NMB. Deep anesthesia with hypnotics and opioids might be less desirable than deep NMB, given the recent concerns related to cumulative deep hypnotic time and outcome (67).

The recent introduction of sugammadex now permits faster reversal, and more predictable and complete recovery from deep NMB than neostigmine (33). The anesthesiologist, the surgeon, and the patient can now benefit from the advantages of deep NMB (improved intubating and surgical conditions) without facing the difficulties and latencies of its recovery. Further studies must investigate the clinical and economic effect of the new association of deep NMB with sugammadex reversal, which could become a standard of care in some circumstances.

Specific benefits of sugammadex

For some patients more than others, PORC is a major problem, with potentially dramatic consequences. For others, neostigmine can induce adverse side effects (41). Through its specific mode of action and excellent clinical tolerance, sugammadex could become the ideal reversal agent in selected situations:

- Pulmonary diseases with significant respiratory insufficiency, including chronic obstructive pulmonary disease (COPD) and asthma. In that case, neostigmine increases the risk of bronchospasm. The excellent quality of sugammadex-induced NMB reversal could decrease the incidence of pulmonary complications in those patients (68).
- Patients with cardiac failure and arrhythmias could also benefit from the use of sugammadex. It does not cause QT prolongation and bradycardia or tachycardia as opposed to neostigmine and glycopyrrolate or atropine (69, 70). The cardiovascular stability after the administration of
sugammadex is remarkable, noticeably in cardiac surgery (71, 72).

- Although the use of sugammadex is discouraged in the setting of severe renal insufficiency, several studies have demonstrated a rapid and complete recovery from deep blockade following its administration in renal failure patients (73).
- In patients with neuromuscular diseases (74, 75), and particularly in patients with myasthenia gravis, sugammadex provides rapid and reliable recovery from NMB. This is much appreciable in the context of this autoimmune disease of the neuromuscular junction (76).
- The metabolic changes that are brought about by age increase the risk of PORC after 75 years of age. Sugammadex restores neuromuscular function in elderly patients, in an adequate and well-tolerated fashion (7, 77).
- Neostigmine-induced bradycardia is particularly relevant in pediatric patients. In that case, sugammadex is an adequate, rapid, and reliable alternative (78).
- In obese patients, recovery after sugammadex is more rapid and effective than with neostigmine. In that population, onset delay of neostigmine is prolonged and quite unpredictable (79).
- Full recovery of pharyngeal dilator strength is critical for sleep apnea syndrome patients that are at high risk of upper airway obstruction.
- PONV is a common postoperative complication, which could be favored by the administration of neostigmine (80); however, this finding remains controversial (81). Contrarily, sugammadex is well tolerated in that respect.
- Because of the stimulation it causes, neostigmine is contraindicated in the setting of mechanical obstruction of the bowel, biliary tract, and urinary tract. It can provoke rupture of fragile intestinal sutures.
- Allergy to neostigmine, although very rare, is an absolute contraindication to its administration.
- Warnings regarding the use of neostigmine and atropine or glycopyrrolate are sometimes given for Parkinson disease, diabetic, and epileptic patients, as well as for patients with thyrotoxicosis, Addison disease, prostatic hypertrophy, or glaucoma.

**Improved INAMI/RIZIV reimbursement conditions and new sugammadex doses**

By endorsing the financial cost of sugammadex when used at the end of deep NMB and when justified by the medical record, the INAMI/RIZIV reimbursement conditions currently favor the improvement of surgical conditions while ensuring patient safety. Some confusion exists, however, in the interpretation of these conditions by clinicians, leading sometimes to more profound NMB than necessary. This conditional reimbursement (requiring the recording of proof of the level of NMB at the time of reversal) appears to have promoted a more frequent use of NMT monitoring in clinical practice. An increasing number of Belgian hospitals are now equipped with objective NMT monitors. Insofar as frequency of use of these devices used to be low, this change represents undeniable progress (82).

The authors believe that reimbursement conditions would benefit from being redefined, taking account of the current surgical needs, which have changed since the introduction of sugammadex into clinical practice. Additional benefits come from NMT monitoring for the optimal management of surgical interventions and patient safety. Unrestricted reimbursement for the reversal of moderate NMB with sugammadex would benefit to many patients by reducing the incidence of PORC and limiting neostigmine-related adverse effects. Contrarily, reimbursement of the 16 mg/kg dose could be limited to the “cannot ventilate” rather than the “cannot intubate” condition. Indeed, when mask ventilation remains possible, emergency reversal is not crucial.

With the goal of lowering sugammadex-related cost for both patient and INAMI/RIZIV, new lines of investigation should be considered. In particular, optimal dosage of sugammadex for intermediate levels of NMB recovery could be sought at. If neostigmine is used in an attempt to reverse a moderate NMB, but complete reversal is not reached within an appropriate amount of time, the anesthesiologist should add a dose of sugammadex to force reversal, and, hence, reduce delay. However, this is not recommended at present, as no study has investigated this approach and required dosage yet. The Belgian reimbursement protocol should evolve according to current and future research.

**Conclusion**

The introduction of sugammadex into clinical practice provides the opportunity to modify the management of NMB. This must be driven by the improvement of patient safety, and should benefit to the surgeon and the anesthesiologist. The maintenance of a deep NMB is no longer incompatible
with rapid recovery and awakening in optimal conditions.

Although neostigmine remains the reference reversal agent in most moderate NMB (TOF count 3-4) situations, the limitations of its efficacy must be understood. Sugammadex causes a more predictable and more rapid recovery from rocuronium-induced deeper NMB. Its favorable profile aids in the development of new surgical strategies, and influences the choice of NMBA. Additionally, sugammadex excellent clinical tolerance is beneficial to numerous categories of patients who are at risk of developing residual NMB-related complications or are sensitive to the undesirable side effects of neostigmine.

In all cases, NMT monitoring is the key to adequate NMB management. Objective measurements allow for excellent intubation and surgical conditions, definition of thresholds and doses for the administration of reversal agents, and exclusion of PORC prior to tracheal extubation. For these reasons, objective measurements reduce postoperative complications.

The current Belgian reimbursement conditions of sugammadex permit maintenance of deep NMB for the performance of certain types of surgery with rapid recovery and awakening in optimal conditions. The authors wanted to thank the experts from all around Belgium who accepted to read and comment the manuscript: Pr L. Barvais, Pr JF. Brichant, Dr G. Cammu, Pr M. Dekock, Pr M. Van de Velde, Pr M. Vercauteren, and Pr P. Wauters.

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