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Profound Neuromuscular Blockade: Advantages and Challenges for Patients, Anesthesiologists, and Surgeons

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Abstract

Rarely has the introduction of an anesthetic agent or adjunct been as anticipated or needed as that of sugammadex. Residual paralysis after neuromuscular blockade (NMB) occurs frequently and is associated with a range of adverse effects ranging from patient discomfort to respiratory complications and death. Residual neuromuscular block is due to a number of factors that include overdosing of neuromuscular blocking agents (NMBAs), inadequate monitoring of the effect of NMBAs, and the limitations of anticholinesterses to antagonize neuromuscular block (relatively slow onset of effect and inability to antagonize deep levels of NMB. Sugammadex, a selective relaxant binding agent, will, when dosed appropriately, rapidly and completely reverse the effects of vecuronium and rocuronium, steroidal NMBAs, from any depth of NMB. While this approach has the potential to increase safety in the perioperative use of NMBAs, it also allows clinicians to revise dosing paradigms to improve surgical conditions and, importantly, patient outcome.

Keywords Neuromuscular blocking agents · Sugammadex · Post-tetanic potentiation · Train-of-four · Postoperative residual neuromuscular block · Neuromuscular function · Anticholinesterase · Quantitative monitoring

Introduction

Discovery and clinical implementation of new practices is frequently accompanied by fits and starts as the impact of the new practice is fully realized. Neuromuscular blocking agents are not exempted from this concept. One year after the introduction of d-tubocurarine, its use was described in 131 surgical patients [1]. Ten years later, Beecher and Todd described a sixfold increase in mortality with the use of neuromuscular blocking agents (NMBAs) [2]. Since this time, despite having been described as enhancing the development of modern surgical practices [3], NMBAs continue to contribute to postoperative morbidity and mortality [4••, 5••, 6].

Morbidity associated with the use of nondepolarizing NMBAs is associated with failed airway management after inducing neuromuscular blockade, awareness during anesthesia, hemodynamic effects due to histamine release, the autonomic effects of the older NMBAs, allergic reactions, and residual weakness after tracheal extubation (with the associated complications). The likelihood of many of these adverse effects can be lessened by either not overdosing, or decreasing the dose of NMBA administered, except when specifically indicated. Typically, large doses of nondepolarizing NMBAs (2× ED_{95} or the dose that on average will cause 95% depression of a single "twitch" following nerve stimulation) have been recommended for endotracheal intubation. Use of larger doses shortens onset time to maximal effect and increases the likelihood that conditions for intubation will be optimal [7–10]. While administration of these larger doses of NMBAs will shorten onset of effect, they also prolong the duration of action the NMBAs and increase the time period before administered of an anticholinesterse to reverse their effect. Historically NMBAs have been redosed intraoperatively to maintain 1–3 responses to train-of-four (TOF) stimulation. With this degree of neuromuscular blockade, patients can physically respond with subtle movements (such as furrowing their eyebrows) if they are inadequately anesthetized and residual neuromuscular block is more likely to be completely antagonized at the conclusion of surgery (although anticholinesterase reversal should ideally be

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administered at a TOF count of 3–4). The introduction of sugammadex into clinical practice has lessened concerns of residual neuromuscular block and may allow clinicians to "push the envelope" as to dosing of NMBAs. Exploration of the need for increased depths of NMB, required monitoring when maintaining profound neuromuscular block, and some of the risks associated with maintaining profound neuromuscular block will be explored in this chapter.

Role of Neuromuscular Blockade in Surgery

The use of NMBAs is evolving as surgical practice changes. The majority of adult patients receiving a general anesthetic with an endotracheal tube receive a NMBA. NMBAs facilitate intubation, inhibit reflex movement to stimulation in procedures where immobility is essential, and assist in the management of some patients in the intensive care unit. However, for many patients, maintenance of neuromuscular blockade (NMB) is not required for intubation or surgery. While it is neither a standard nor recommended technique in adults, NMBAs are frequently not part of the induction/intubation sequence in children. Endotracheal intubation in adults without NMBAs can be being facilitated with different combinations of sedative hypnotics and opioids [11–13] and provide good to excellent intubating conditions. Use of total intravenous anesthetics without NMB is routine in neurosurgical procedures where intraoperative electromyography or monitoring of motor evoked potentials is planned. The routine need to maintain NMB in ambulatory surgery patients has been questioned for several reasons including that the incidence of residual paralysis in this patient population (38%) is higher [14], residual NMB is associated with delayed patient discharge and increased cost [15] and, emergence after a total intravenous anesthetic is rapid and not associated with an increased risk of nausea or vomiting [16].

Appropriate dosing of NMBAs as part of a general anesthetic enables care of increasingly ill patients for more complex surgical procedures. Traditionally, when used to maintain intraoperative neuromuscular blockade, NMBAs should be dosed to maintain 1–3 responses to TOF stimulation. The depth of NMB that is maintained depends on the surgery being performed and the anesthetics being administered, with less NMB required during a volatile anesthetic. Volatile anesthetics potentiate NMBAs and may cause fade in the TOF ratio when administered in high concentrations [17]. The presence of volatile anesthetics also slows neostigmine-facilitated recovery of neuromuscular function [18–20]. While NMBAs provide muscle relaxation when administered during a general anesthetic, they are only a single component of an anesthetic and do not provide unconsciousness, analgesia or amnesia. A recent retrospective study of electronic health records [21••] described an incidence of just under 1% of inadequate NMB—defined as patient movement, coughing, bucking, or the surgeon's request for a deeper level of NMB. This may have been the result of an inadequate depth of anesthesia rather than a reflection on the quality of NMB. Diaphragmatic movement is not abolished unless a patient is profoundly paralyzed with a post-tetanic count (PTC) of 3 or less, which is deeper than the traditionally recommended TOFC of 1–3. Recommendations for maintenance of depth of NMB at 1–3 responses to TOF stimulation have been made so that pharmacologic antagonism with an anticholinesterase is possible at the conclusion of a surgical procedure [22, 23]. Now, however, sugammadex—when dosed appropriately with neuromuscular monitoring—allows rapid and complete recovery of neuromuscular function from any depth of neuromuscular block if a patient has received either vecuronium or rocuronium.

When maintaining greater depths of NMB, the risk of awareness may be increased since profoundly paralyzed patients are unable to initiate any movement and patient movement with lesser degrees of NMB likely reflects an inadequate depth of anesthesia [21••]. Importantly, the bispectral index, which may be used as an indicator of awareness during general anesthesia, declines during neuromuscular blockade in the absence of any anesthetic [24]. Awareness during a general anesthetic is uncommon yet may have serious postoperative consequences; it is estimated that between 20,000 and 40,000 patients in the USA experience awareness each year [25]. Recollections of intraoperative events while paralyzed may be vivid and cause fear and a feeling of helpless causing long-term sequelae.

The physiologic and pharmacologic impact of nondepolarizing NMBAs is far greater than simply competitive blockade at the post-junctional nicotinic acetylcholine receptor (nAchR). While some NMBAs will cause histamine release, vagolysis or ganglionic blockade, there are AchR throughout the body—accounting for some of the other untoward effects of these compounds, such as suppression of the respiratory drive to breathe and discoordination of muscles required for swallowing and airway protection. Additionally NMBAs interact with pre-synaptic neuronal [26] acetylcholine receptors at the neuromuscular junction to decrease the release of acetylcholine from the motor neuron and exacerbate muscle weakness. All of these factors contribute to inadequate recovery of NM function which delays discharge from the post-anesthesia care unit [15] and decreases a patient's sense of well-being and satisfaction with their care [27].

The risk of residual NMB has been reported to be as high as 60%. When intermediate-acting NMBAs were initially introduced into clinical practice, the incidence of residual paralysis, defined at that time as a TOFR < 0.7, decreased from approximately 40% with long-acting NMBAs to 5% with the intermediate-acting NMBAs, atracurium, and vecuronium [28, 29]. However, as these agents became more commonly used and the familiarity with their perceived recovery profile grew, the frequency of residual NMB associated with their administration increased [30]. Since the definition of adequate recovery of neuromuscular function is now a TOFR ≥ 0.9, residual paralysis with theses NMBAs is reported to occur far more frequently than when they were first introduced into practice.

Although the routine use of quantitative monitors of neuromuscular function decreases the incidence of residual neuromuscular block [31••, 32], quantitative monitors, or any monitor of depth of neuromuscular block, are not commonly used [33]. Clinical tests of neuromuscular function are inadequate to detect residual neuromuscular block [34] and qualitative "twitch" monitors do not allow clinicians to detect fade unless TOF ratios are less than 0.4 and fade with double-burst stimulation is > 40% [35]. While sugammadex should be able to eliminate residual neuromuscular block in patients who have received either vecuronium or rocuronium, its dosing is dependent on the response to neuromuscular stimulation. Studies of routine clinical practice and residual paralysis since the introduction of sugammadex demonstrate that while the occurrence of residual NMB is decreased, it has not been eliminated [36••, 37, 38]. The possibility of eliminating post-operative residual NMB with appropristely dosed sugammadex, however, creates the opportunity to reassess historical dosing recommendations for nondepolarizing NMBAs.

Trends in Surgery and Neuromuscular Blockade

Since the introduction of sugammadex into practice, there have been recommendations to increase the depth of NMB maintained during microlaryngeal, robotic, and laparoscopic surgery. Immobility of the vocal cords is required during microlaryngeal surgery. In patients receiving a remifentanil/propofol anesthetic profound NMB (post-tetanic count of 1–2) was associate with an easier laryngoscopy and exposure of the vocal cords, decreased movement of the vocal cords, better surgical conditions, less coughing during surgery, and less patient movement during surgery when compared to patients receiving the same anesthetic and a lesser degree of NMB (TOFC 1–2) [39]. Depth of anesthesia was monitored with a bispectral index and one surgeon, blinded to the treatment group, assessed surgical conditions. NMB was maintained with rocuronium and reversed with either sugammadex in the profound NMB group or neostigmine in the TOFC 1–2 group. The muscles of the larynx, relative to the adductor pollicis [40], are resistant to nondepolarizing NMBAs. Therefore, less movement of the vocal cords would be expected during profound NMB, as was found in the study. What was notable, though, was that in spite of this difference, the surgeries in both groups required approximately the same amount of time and complications described as nausea, vomiting, and sore throat were not different between the study groups. Patients in the TOFC 1–2 group reported more severe mouth dryness—likely because of the glycopyrrolate administered to the patients with a lesser degree of NMB.

Work has also been conducted to study the potential advantages of profound NMB for laparoscopic gynecologic or urologic surgery. There are a number of physiologic changes that occur with the increased intra-abdominal pressure required for laparoscopic surgery. Cardiac effects include decreased venous return and left ventricular end-diastolic volume, increased right atrial and pulmonary artery occlusion pressures, increased systemic and pulmonary vascular resistance and arterial pressure. The cause of these effects are multifactorial and include carbon dioxide absorption which may result in hypercapnia and acidosis-induced decreases in myocardial contractility, stimulation of the sympathetic nervous system causing release of catecholamines, and vasopressin resulting in increased SVR and MAP. In addition, compression of venous capacitance vessels results in a decrease in preload and compression of arterial vasculature which increases afterload. The resulting decrease in cardiac index is proportional to intra-abdominal pressure, SVR, and left ventricular contractility, and returns toward baseline 30 min after establishing the pneumoperitoneum. Similarly, changes in respiratory effects are multifactorial. Abdominal insufflation decreases pulmonary compliance, increases peak airway pressure and decreases functional residual capacity. Carbon dioxide absorption can result in respiratory acidosis. While renal function is negatively impacted with decreased glomerular filtration rate, renal plasma flow, and urine output because of increased intra-abdominal pressure, the effects of pneumoperitoneum on splanchnic function are a balance of vascular compression and vasodilation. Finally, carbon dioxide pneumoperitoneum results in postoperative incisional, intra-abdominal, and referred shoulder pain—likely because of acidification of the pneumoperitoneum by formation of carbonic acid from carbon dioxide.

Given the physiologic changes that occur with pneumoperitoneum, decreasing the amount of intra-abdominal pressure required for surgery would seem a natural goal and a number of studies [41–46] have demonstrated that deep NMB allows for either lower intra-abdominal pressures during laparoscopic surgery or greater intra-abdominal volume during laparoscopic procedures where deep NMB was maintained. The impact of these findings on clinical practice, though, is difficult to determine. In these studies, either the anesthetic administered was not described, patients did not receive any volatile anesthetics or, the treatment group was compared to patients receiving no NMBAs. For example, one study [46] compared surgical conditions during a desflurane anesthetic (6–7%) in which only a single dose of rocuronium was administered with surgical conditions during an anesthetic in which deep NMB (described by the authors as a TOFC < 2), was maintained. The patients in whom NMB had been maintained throughout surgery, or reintroduced for inadequate surgical conditions, had improved operating conditions. However, what the authors described as deep NMB is typical of more moderate NMB. Whether or not these results would still apply when compared to patients who had been maintained with a profound (TOFC = 0) depth of NMB is not known.

Other studies are more circumspect in terms of the actual impact of the changes (decreased intra-abdominal pressure and greater intra-abdominal space) on surgical conditions and patient outcome [47–50]. In these studies, the volume change was found to be small, was not observed in all patients with deep NMB or, there was no improvement in surgical conditions. As described in a recent review [51], peak inspiratory and intra-abdominal pressures during laparoscopic surgery are not impacted by depth of NMB with atracurium. Consistent with this, there is no difference in surgical conditions whether or not NMB is maintained in patients receiving total intravenous anesthesia with ventilation controlled through a laryngeal mask airway for laparoscopic gynecologic surgery [52].

If there is not a clear difference between a profound depth of NMB in patients undergoing laparoscopic procedures and a moderate depth of NMB in surgical conditions, there are other potential advantages such as a decrease in gas embolization, greater hemodynamic stability, improved renal function, and decreased postoperative pain. Although theoretically, the use of a lower inflation pressure could provide some of these beneficial effects, current evidence does not support the use of lower intra-abdominal pressures for these reasons. Oliguria occurs with low pressures [53] and hemodynamic changes are not lessened when lower pressures are used [54]. Similarly, patient satisfaction is not impacted by the use of lower pressures and pain is effectively managed by multimodal therapy that includes acetazolamide, which inhibits carbonic anhydrase to decrease the formation of carbonic acid from carbon dioxide [55] and not reduced by low pressure pneumoperitoneum [56••].

The disadvantages and risks of postoperative paralysis, which have been previously reviewed [57–60], cannot be overstated and may negate any potential advantage of routinely maintaining profound NMB. Recently, the negative impact of incomplete recovery of neuromuscular function on reintubations and unplanned ICU admissions was described [61]. Residual NMB occurs frequently [62, 63] and even the addition of sugammadex to the clinical armamentarium has not completely eliminated the risk of its occurrence [36••, 38, 64]. It is possible to have incomplete recovery of neuromuscular function even after the administration of sugammadex. Published studies have examined the return of muscle strength from a specific depth of neuromuscular block. When depth of neuromuscular block is not monitored and large doses of NMBAs are administered to eliminate the possibility of patient movement, the appropriate dose of sugammadex necessary to allow full recovery of muscle strength is uncertain. Inadequate recovery of neuromuscular function is associated with an increased rate of readmission within 30 days—especially in ambulatory surgery [65••]. The results are consistent with those in an earlier retrospective study documenting increased morbidity and mortality in patients who had received larger doses of NMBAs [6, 66].

Whenever a NMBA is administered, depth of paralysis should be monitored. Dosing recommendations for administration of additional NMBA and reversal agents are based on the response to TOF stimulation [67, 68]. In spite of the need to determine the depth of NMB to appropriately dose NMBAs and their reversal agents, monitoring is not routine and even when monitors of NMB are available, they are not commonly used [33]. However, just as vasopressors would not be administered without knowing what the blood pressure is, NMBAs should not be administered unless depth of paralysis is monitored. Although the usefulness of available quantitative monitors is limited in clinical practice (response is dependent on position of the extremity being monitored and acceleromyography can overestimate recovery) [69], their use will guide dosing of NMBAs and reversal agents and decrease the incidence of residual neuromuscular block.

Conclusion

While neuromuscular blocking agents have contributed to the development of modern surgical practices, their impact on patient outcome is incompletely understood. Understanding of their effects on patient function and recovery has improved since the time these compounds were first introduced into clinical practice [1, 2], their use though, is still associated with increases in patient morbidity and mortality. What is adequate recovery of neuromuscular function? Until several years ago, it was considered to be recovery to a TOFR ≥ 0.7. Even with this degree of recovery, though, patients are at increased risk for respiratory complications, prolonged PACU stays and greater dissatisfaction with their course of recovery after surgery. These findings contributed to a revision of the definition of adequate recovery of neuromuscular function after administration of a nondepolarizing NMBA to a TOFR ≥ 0.9. However, even this degree of recovery may not be complete. Kopman demonstrated that in volunteers a TOFR > 0.9 was associated with visual disturbances and other indications of inadequate recovery of muscle strength [34] and Eikermann has demonstrated that stressing neuromuscular function, even after complete recovery of the TOFR, brings out previously unrecognized weakness [70]. Administration of sugammadex does not eliminate the motor dysfunction present at a TOFR ≥ 0.9 [71••].

Until a definition of complete recovery is determined and monitoring of depth of NMB is consistent, dosing of NMBAs to maintain profound levels of neuromuscular blockade—except for brief periods and accepted indications such as endotracheal intubation—is difficult to recommend. Justification of a change in practice, such as maintaining profound levels of NMB intraoperatively, that potentially put patients at risk, will require that large, multicenter studies are done to define effective dosing paradigms and that better quantitative monitors are both available and a routine part of clinical practice.

Compliance with Ethical Standards

Conflict of Interest Cynthia A. Lien has received compensation from Merck for service as a consultant.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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