

Residual Paralysis: Does it Influence Outcome After Ambulatory Surgery?

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Abstract Neuromuscular blocking agents are used to facilitate tracheal intubation in patients undergoing ambulatory surgery. The use of high-dose neuromuscular blocking agents to achieve muscle paralysis throughout the case carries an increased risk of residual post-operative neuromuscular blockade, which is associated with increased respiratory morbidity. Visually monitoring the train-of-four (TOF) fade is not sensitive enough to detect a TOF fade between 0.4 and 0.9. A ratio <0.9 indicates inadequate recovery. Quantitative neuromuscular transmission monitoring (e.g., acceleromyography) should be used to exclude residual neuromuscular blockade at the end of the case. Residual neuromuscular blockade needs to be reversed with neostigmine, but its use must be guided by TOF monitoring results since deep block cannot be reversed, and neostigmine administration after complete recovery of the TOF-ratio can induce muscle weakness. The development and use of new selectively binding reversal agents (sugammadex and calabation) warrants reevaluation of this area of clinical practice.

Keywords NMBA · Ambulatory surgery · Residual paralysis · PORC · Respiratory complications · Neostigmine · Sugammadex · Calabation

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Introduction

In the USA, it is estimated that over 60 % of surgical and non-surgical procedures are now performed as day-cases [1, 2], with approximately 40 % of these occurring in free-standing ambulatory surgery centers [3]. For anesthesiologists, the challenge of ambulatory surgery lies in balancing good anesthesia with a safe and rapid recovery to a level of minimal or no residual cognitive and psychomotor impairment [4].

Muscle relaxation is an important component of good anesthesia, and is achieved by the use of neuromuscular blocking agents (NMBA). These drugs are used by anesthesiologists to facilitate tracheal intubation [5•] and enhance surgical exposure [6]. The use of high-doses of NMBAs to achieve deep neuromuscular blockade has been shown to increase the risk of post-operative complications (Table 1) [7–19, 20•, 21, 22]. Residual paralysis is the term applied to the persistence of muscle weakness post-operatively following NMBA administration. Clinically significant muscle paralysis occurs at train-of-four ratios (TOFR) < 0.9 [23••, 24, 25, 26••]. Residual paralysis is common when NMBAs are administered, occurring in up to two-thirds of patients [27, 28], and is often undetected in the immediate post-operative period [20•, 29].

Residual paralysis delays the recovery of the patient and the efficiency of ambulatory care centers [30]. Crucially, it also compromises patient safety putting patients at increased risk of post-operative complications such as weakness, hypoxia and respiratory failure [31, 32] thus making it an important patient safety issue.

In ambulatory surgery, residual paralysis occurs less frequently, however the proportion of patients affected is still significant at 38 % [21]. The overall risk of perioperative morbidity and mortality in day-case surgeries is low [33] with one recent study quoting the risk to be as low as 0.1 % [2]. By

Table 1 Clinical trials on NMBA use for outpatient surgery and reported side effects

Authors	Title	Year	Number of patients	Surgery	NMBA and dose	Induction agents	Reversal	Side effect
Raeder et al. [7]	Outpatient laparoscopy in general anaesthesia with alfentanil and atracurium. A comparison with fentanyl and pancuronium	1986	62	Outpatient sterilization by laparoscopy	Atracurium (0.5 mg/kg) or pancuronium (0.07 mg/kg)	Fentanyl, alfentanyl	Used, but drug was not specified	Worst functionality after reversal of anaesthesia, in the afternoon after the procedure, and at home in the evening in patients with pancuronium.
Sengupta et al. [8]	Post-operative morbidity associated with the use of atracurium and vecuronium in day-case laparoscopy	1987	Not available	Day-case gynaecological laparoscopy	Atracurium or vecuronium	Not available	Not available	Greater number of patients in the vecuronium group were able to resume normal activity 24 h after laparoscopy; significantly higher incidence of abdominal pain in the vecuronium group.
Melnick et al. [9]	Decreasing post-succinylcholine myalgia in outpatients	1987	395	Healthy outpatients	Succinylcholine (1.5 mg/kg)	Lidocaine and D-tubocurarine as premedication	None	Succinylcholine without premedication is associated with a higher incidence of postoperative myalgia.
Sosis et al. [10]	Comparison of atracurium and D-tubocurarine for prevention of succinylcholine myalgia	1987	44	Outpatient females undergoing laparoscopy	Atracurium and D-tubocurarine	Thiopental	None	Fasciculations occurred in 79 % of patients given saline, in 46 % of those receiving atracurium, and in 12 % of those given D-tubocurarine. 85 % of atracurium patients were free of postoperative myalgia on postoperative day 1.
Zuurmond et al. [11]	Atracurium versus vecuronium: a comparison of recovery in outpatient arthroscopy	1988	40	Outpatient arthroscopy of the knee under general anaesthesia	Atracurium (0.5 mg/kg) and vecuronium (0.1 mg/kg)	Methohexitone, isoflurane, N ₂ O/O ₂	None	All but one patient (95 %) in the atracurium group required neostigmine versus nine patients in the vecuronium group (45 %).
Trépanier et al. [12]	Myalgia in outpatient surgery: comparison of atracurium and succinylcholine	1988	60	Outpatient surgery	Succinylcholine (1.5 mg/kg) and atracurium (350 mg/kg)	Isoflurane, fentanyl, and thiopentone	None	Myalgia was present in 76 % of the succinylcholine patients compared to 23 % in the atracurium group. 50 % of the patients in the succinylcholine group had myalgia necessitating bed rest or analgesics compared to 23 % in the atracurium group
Zahl et al. [13]	Muscle pain occurs after outpatient laparoscopy despite the substitution of vecuronium for succinylcholine	1989	28	Outpatient laparoscopy	Succinylcholine (1.5 mg/kg), vecuronium (50 mcg/kg)	N ₂ O, thiopental, and fentanyl.	Glycopyrrolate (7 mcg/kg) and edrophonium (0.5 mg/kg).	Rocuronium and succinylcholine are related with postoperative myalgia
Luyk et al. [14]	Comparative trial of succinylcholine vs low dose atracurium-lidocaine combination for intubation in short outpatient procedures	1990	40	Surgical removal of molar teeth	Atracurium (0.2 mg/kg), succinylcholine (1 mg/kg)	Halothane, lidocaine	Edrophonium (0.5 mg/kg) and atropine (0.6 mg)	Succinylcholine was related with significantly more myalgia. Spontaneous respiration was slower after low dose atracurium/lidocaine relative to succinylcholine
Poler et al. [15]	Mivacurium as an alternative to succinylcholine during outpatient laparoscopy	1992	60	Female healthy outpatients	Succinylcholine and mivacurium (0.15 mg/kg)	Thiopental sodium, alfentani	Neostigmine	Side effects with mivacurium included flushing and occasional wheezing
Laxenaire [16]	Drugs and other agents involved in anaphylactic shock occurring during anaesthesia. A French multicenter epidemiological inquiry	1993	1585	Outpatient clinics with allergy-anaesthesia unit	Not available	Not available	Not available	Succinylcholine was responsible for 43 % of the IgE-dependent reactions involving a muscle relaxant, vecuronium for 37 %, pancuronium for 13 %, alcuronium for 7.6 %, atracurium for 6.8 % and gallamine for 5.6 %

Table 1 continued

Authors	Title	Year	Number of patients	Surgery	NMBA and dose	Induction agents	Reversal	Side effect
Tang et al. [17]	Comparison of rocuronium and mivacurium to succinylcholine during outpatient laparoscopic surgery	1996	100	Healthy women undergoing outpatient laparoscopic surgery	Succinylcholine (1 mg/kg), rocuronium (0.6 mg/kg), or mivacurium (0.2 mg/kg)	Midazolam, fentanyl and thiopental	Edrophonium (0.5 mg/kg) and atropine (10 mcg/kg)	One patient with succinylcholine and six patients with mivacurium displayed erythema on the upper body. Postoperative myalgia was experienced by 16 % of the patients with succinylcholine compared to none with rocuronium and mivacurium
Whalley et al. [18]	Comparison of neuromuscular effects, efficacy and safety of rocuronium and atracurium in ambulatory anaesthesia	1998	41	Laparoscopic gynaecological surgery	Rocuronium (0.6 mg/kg) or atracurium (0.5 mg/kg)	Propofol, alfentanil, N ₂ O/O ₂	Used, but drug was not specified	One patient in the atracurium group experienced transient flushing of the head and neck. The most frequent adverse event was nausea and vomiting (two patients in the rocuronium group; three patients in the atracurium group)
Savaresev et al. [19]	The clinical neuromuscular pharmacology of mivacurium chloride (BW B 109 OU): a short-acting nondepolarizing ester neuromuscular blocking drug	1998	72	Healthy volunteers	Mivacurium 0.03–0.30 mg/kg in boluses, and continuous infusions from 35 to 324 min in length	N ₂ O, narcotic and thiopental	Neostigmine (0.06 mg/kg) and atropine (0.03 mg/kg)	Long onset time (even when doses ED95X3 are used) and prolonged duration of action when higher doses are administered. In patients with atypical plasma cholinesterase, NMB may be prolonged
Debaene et al. [20]	Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action	2003	526	Gynecologic and plastic surgery	Rocuronium (0.58 ± 0.08 mg/kg), atracurium (0.55 ± 0.08 mg/kg), and vecuronium (0.09 ± 0.02 mg/kg)	Not reported	None used	After vecuronium, atracurium or rocuronium single intubating dose ED95X2 and no reversal, residual paralysis was still present 2 h after administration in almost 50 % of patients
Cammu et al. [21]	Postoperative residual paralysis in outpatients versus inpatients	2006	640 (320 inpatients and 320 outpatients)	Outpatient surgery, not specified	Mivacurium (50 %) for outpatients and, rocuronium (44 %) and atracurium (36 %) for inpatients	Not reported	Used, but drug was not specified	Postoperative respiratory complications: 38 % in surgical outpatients and 47 % inpatients. Mivacurium was used frequently for outpatients
Pendeville et al. [22]	A comparison of intubation conditions and time-course of action with rocuronium and mivacurium for day case anaesthesia	2007	50	Outpatient surgery, not specified	Mivacurium (0.15 mg kg ⁻¹) or rocuronium (0.3 mg kg ⁻¹)	Propofol, sufentanil, N ₂ O	None used	Mivacurium has the risk of unexpected prolonged relaxation due to a possible defect in plasma cholinesterase

these observations the effect of residual paralysis on post-operative outcomes in day case surgery must be very minimal. Despite this, concerns over patient safety remain as more procedures are carried out on an ageing population in ambulatory care centers with fewer resources to rapidly identify and treat post-operative complications. This review will consider current evidence on neuromuscular management, strategies aimed at preventing residual paralysis, and the effects on post-operative outcomes. The development and use of new selectively binding reversal agents warrants reevaluation of this area of clinical practice.

Residual Paralysis and Outcomes

Respiratory Complications

Respiratory events are the most common complication of residual paralysis. They are also the most common reason for post-surgical unplanned admission to intensive care, and the mortality rate for these patients is high [34]. Respiratory events include airway obstruction, hypoxia, atelectasis, aspiration, pneumonia and negative pressure pulmonary edema. Respiratory events are a common complication of residual paralysis due to impairments in several important facets of normal respiratory physiology, as illustrated in Fig. 1.

Impairment in Hypoxic Ventilatory Response

At TOFR < 0.7 the hypoxic ventilatory response (HVR) is significantly impaired [35, 36]. This is thought to be due to NMBA effects on carotid body chemosensitivity, causing a reduction in nerve discharge in response to hypoxia [35, 37]. Volunteer studies have shown that this effect can be reproduced with both long and intermediate acting NMBAs [35, 36]. HVR was depressed by up to 306 % when train-of-four ratios were maintained at 0.7 by continuous infusion of either atracurium, pancuronium or vecuronium [36]. This innate response to hypoxia was only found to return to normal at TOFR > 0.9 [36, 37]. Partial paralysis thus interferes with ventilatory responses to hypoxia putting patients at risk of hypoxic injury. This impaired ventilation can lead to atelectasis, which in turn predisposes patients to post-operative pneumonias.

Impaired Respiratory Muscle Function

Airway patency is governed by complex interactions between neuromuscular function and inherent airway structural properties [38, 39]. Upper airway integrity is impaired by minimal levels of neuromuscular blockade due to the susceptibility of the upper airway muscles to the

effects of NMBAs [6, 40]. The lingering effects of NMBAs can thus have profound and potentially serious consequences on airway patency. Upper airway dilator muscles counter-act the negative intraluminal pressure generated by the respiratory pump muscles to maintain airway patency during inspiration [40, 41]. With residual paralysis however, the efficacy of these dilator muscles is markedly impaired, enough to significantly increase airway collapsibility [40, 41]. By measuring pharyngeal and pulmonary function, we observed that upper airway obstruction occurs commonly during inspiration, even at minimal levels of neuromuscular block [40]. Increased airway vulnerability was detected at TOFR 0.5–0.8 as assessed by pressure-flow analysis, MRI, flow-volume curves and pressure-flow analysis (upper airway closing pressure calculation). This vulnerability to airway obstruction during inspiration predisposes patients to postoperative respiratory failure [32].

Impaired Ability to Protect the Airway from Aspiration

Weakness of the airway muscles results in pharyngeal dysfunction, which impairs innate protective mechanisms during swallowing [23••, 24]. This puts patients at increased risk of aspiration [42••]. Using video fluoroscopy, Sundman et al. [23••] observed that pharyngeal dysfunction was evident in 28 % of volunteers with a TOFR 0.6, compared to only 6 % in the control recordings ($P < 0.05$). Pharyngeal dysfunction was found to occur due to impaired initiation of swallowing, impaired co-ordination of the pharyngeal muscles and a reduction in tone of the upper oesophageal sphincter [23••]. 80 % of swallows in those with pharyngeal dysfunction resulted in laryngeal penetration [23••]. Mirzakhani et al. [42••] observed that 70 % of critically ill patients with muscle weakness developed symptomatic aspirations. Moreover, muscle weakness was found to increase the risk of symptomatic aspiration almost 10-fold.

Critical Respiratory Events

Multiple studies have shown an association between partial paralysis and critical respiratory events (CRE). Berg et al. [31] observed that patients randomized to receive pancuronium were more likely to become hypoxic on emergence and require supplemental oxygen to maintain saturations >90 % than those randomized to atracurium (intermediate NMBA). Bissenger et al. [43] have demonstrated that TOF ratios <0.7 were associated with significantly higher incidences of hypoxemia (60 %) in comparison to TOF ratios of >0.7 (10 % $P < 0.05$). In a case-control study, Murphy et al. assessed whether residual paralysis contributed to CRE. The most common CRE's were severe hypoxemia (59.0 %) and upper

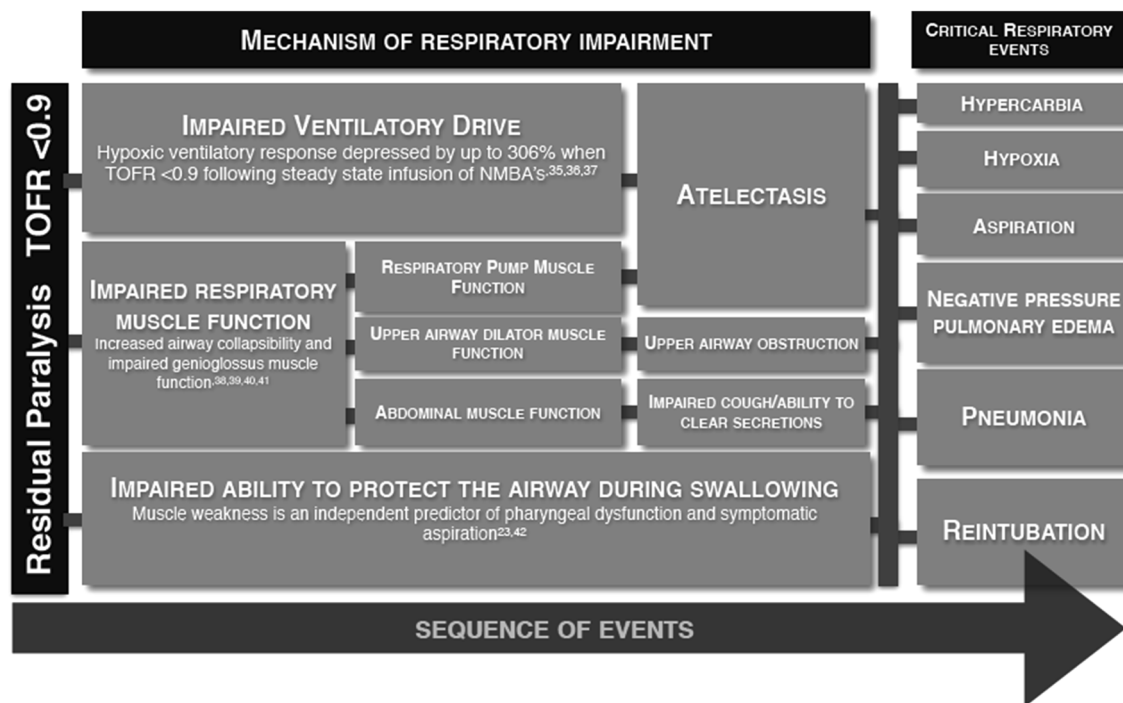


Fig. 1 Mechanisms of residual paralysis induced postoperative respiratory failure. A small level of residual paralysis that cannot be detected without quantitative monitoring of the train-of-four (TOF) response impairs several important facets of respiratory function. The main mechanisms of respiratory failure induced by minimal, residual neuromuscular blockade (TOF: 0.5–0.9) are impairments of hypoxic

ventilatory response, and respiratory muscle function. In addition, the coordination between breathing and swallowing is impaired, leading to the inability to protect the airway during swallowing. Consequently, paralysis increases the vulnerability to hypoxia, symptomatic aspiration, pulmonary edema, and reintubation

airway obstruction (34.4 %). 78.3 % of the CRE case group had a TOF ratio <0.7, whereas none of the patients in the control group has a TOFR <0.7 [32]. More recently, Grosse-Sundrup et al. demonstrated that intermediate NMBAs significantly increased risk of oxygen desaturation to both <80 and <90 % in the first 20 min after extubation. The risk of postoperative reintubation and unplanned intensive care admission was also significantly higher in patients who had received intermediate NMBAs intra-operatively. Patients undergoing shorter operations (<2 h) were found to be at increased risk of severe post-operative respiratory complications, a finding of particular significance to ambulatory surgery [44••].

Although minimal neuromuscular transmission failure (TOF-ratio: 0.5–0.8) is a significant contributing risk factor for post-operative respiratory complications, partial paralysis alone does not typically translate to morbidity in healthy patients undergoing minor surgical procedures, but a combination of multiple hits increase the risk of upper airway related respiratory complications in the perioperative period. Repeated airway interventions, upper airway surgery and excessive fluid administration can all result in tissue swelling

that may increase airflow resistance [39]. During anesthesia there is also a reduction in the functional residual capacity of the lung, which can increase airway collapsibility, especially in obese patients [45]. Other contributing factors to post-operative airway collapse include the supine position versus elevated back position, increased respiratory pump muscle activity (sepsis), postoperative pain relief with opioid drugs, concomitant use of other anesthetic agents such as benzodiazepines and co-morbidities such as obstructive sleep apnea and obesity [39, 46, 47]. This airway obstruction can go undetected until severe desaturation occurs because reliable and continuous monitoring with capnography and tidal volume measurements ceases following extubation [39].

Skeletal Muscle Weakness

Patients are at increased risk of falls due to skeletal muscle weakness as a result of residual neuromuscular blockade [48•]. Significant skeletal muscle weakness occurs even after recovery of the TOFR to unity. This is especially pertinent in ambulatory cases where patients are expected to mobilize shortly after surgery.

Residual Paralysis: Costs

Residual paralysis is costly to both patients and healthcare institutions. Discharge times were significantly longer in patients with a TOFR < 0.9 on arrival to PACU [30]. This was found to reduce PACU throughput, and incur additional costs as staff recover patients beyond allocated times [30]. Residual paralysis is associated with postoperative respiratory complications. The average cost of treating respiratory complications following surgery is \$62,704, versus \$5,015 for uncomplicated surgery [49, 50]. In the USA alone, it is estimated that postoperative pulmonary complications lead to an additional 92,000 ICU admissions and incur a cost of \$3.42 billion each year [49]. Strategies to prevent residual paralysis and its complications thus have great economic benefit.

Strategies to Prevent Residual Paralysis

Techniques to Avoid or Reduce NMBA Use

Regional Anesthesia

The balanced technique has long been used by anesthesiologists to achieve adequate anesthesia with lower doses of multiple agents, thereby limiting the risk of side effects from each agent. The motor block that accompanies local anesthesia can reduce or negate the need for NMBAs [51]. Combining regional anesthesia with NMBAs however has been shown to delay both the spontaneous and facilitated recovery from NMBA induced muscle paralysis [52]. This is only the case when NMBAs are given at unchanged doses, not taking into account the reduced doses required to achieve surgical relaxation when combined with regional anesthesia.

Laryngeal Mask Airway

Laryngeal mask airways (LMAs) do not require NMBAs for insertion. The use of LMAs allows for spontaneous breathing to be maintained during surgery. This can lead to shortened duration of surgery without affecting surgical procedures or views. Williams et al. compared use of LMA with maintained spontaneous breathing to the use of tracheal intubation with mechanical ventilation in laparoscopic gynecological day-case procedures. Although the initial intra-abdominal pressure in the LMA group was significantly higher, there was no significant difference in the volume of insufflated CO₂ or the time taken to reach a steady state pneumoperitoneum [53]. Surgical views were reported as similar for both groups and complications did not differ. Operation time was significantly shorter in the

LMA group [53]. For many elective surgical procedures in ambulatory anesthesia, LMAs can thus entirely negate the need for NMBAs without affecting the quality of surgical conditions.

NMBA Dose & Duration of Action

The choice of NMBA can influence post-operative outcomes. The longer the duration of action of NMBAs, the greater the risk of residual paralysis and its complications [54–56]. Intermediate acting NMBAs improve patient safety compared to the use of long-acting NMBAs, but residual paralysis is still present in up to two-thirds of patients given an intermediate NMBA intra-operatively [27, 28]. Benzylisoquinoline NMBAs such as cisatracurium have been demonstrated to have a more predictable duration of action than steroidal NMBAs such as rocuronium, particularly in elderly patients [28]. However, recent data suggests that risk of pulmonary complications increases in a dose-dependent manner, regardless of NMBA group [57], probably because anesthesiologists take these pharmacokinetics into account and may believe it safe to use benzylisoquinoline NMBAs later during cases.

Succinylcholine, a short acting depolarizing NMBA, has a rapid onset and short duration of action [58, 59] and higher doses carry little risk of prolonged paralysis, unless a patient carries a mutation for choline esterase. The use of short acting NMBAs such as succinylcholine and mivacurium may also translate to economical advantages in the context of ambulatory surgery [17, 60]. Succinylcholine can however have serious side effects and has considerably more contraindications than intermediate NMBAs, thus limiting its use [59]. Moreover, the metabolism of succinylcholine and mivacurium is cholinesterase-dependent and any quantitative or qualitative abnormality of this enzyme extends the duration of the neuromuscular blockade [61], which affects safety and represents a logistic challenge in ambulatory surgery centers.

Optimizing Surgical Conditions

Anesthesiologists aim to provide adequate muscle relaxation for tracheal intubation and surgery whilst also ensuring complete recovery of muscle strength at the end of the procedure. Complete recovery means that the patient can independently maintain a patent airway during wakefulness and sleep, breathe normally, prevent aspiration, clear secretions, cough, smile and talk [62••].

NMBAs facilitate tracheal intubation and reduce the incidence of airway tissue injury, leading to fewer upper airway symptoms post-operatively [5••, 63]. Neuromuscular transmission blockade also helps to improve surgical

exposure and performance by blocking reflexive movements to surgical stimuli intra-operatively [6].

Determining how much muscle relaxation is required for optimal surgical conditions can be difficult for several reasons. There is considerable inter-individual variability in patient response to NMBAs, making it difficult for anesthesiologists to predict peak effect and recovery times, which is reflected clinically by the high incidence of residual paralysis [6]. The effects of NMBAs are also muscle dependent. For example, the diaphragm is less sensitive to NMBAs than upper airway muscles [64]. After total block of adductor pollicis (AP) function as assessed by TOF ratio, the diaphragm might still be able to contract in a clinically meaningful fashion [64–67]. Almost twice the dose of NMBAs is required for diaphragmatic relaxation than for AP relaxation [64]. The duration of action and the recovery of the twitch height are also faster in the diaphragm than at the AP [65–67]. Even when evaluating muscle strength in a well-defined muscle such as the adductor pollicis muscle, at absence of TOF count, a strong tetanic stimulus can lead to a muscle contraction. Accordingly, it is impossible to ensure complete blockade of neuromuscular transmission of all muscles during the entire surgical procedure. Anesthesiologists need to apply a variable combination of anesthetics, opioids, local anesthetics and NMBA in order to provide optimal surgical conditions throughout the surgical procedure.

Submaximal Block

Complete and continuous neuromuscular block is rarely indicated in surgery, indeed some operations can be performed without any neuromuscular block at all, when the airway is secured with a supraglottic device. The requirement for choosing whether to use neuromuscular blockade or not, varies according to the type of surgical procedure. NMBAs are helpful to achieve optimal conditions for intubation and surgery. Adequate relaxation of the upper airway muscles is important for tracheal intubation, reducing the incidence of hoarseness and vocal cord sequelae; a common postoperative patient complaint and source of litigation against anesthesiologists [5•]. Incision and closure of open abdominal surgery may also require a degree of paralysis in order to prevent reflexive movements to surgical stimuli [6]. Upon exposure of the abdominal cavity however, very little block is required. Even with surgeon-controlled muscle relaxation, surgeons did not request complete neuromuscular block during open abdominal procedures [68] demonstrating that ideal surgical conditions can be accomplished in the absence of NMBAs.

Laparoscopic gynecological surgery for example can be performed safely and adequately without neuromuscular blockade [53]. In cardiac surgery, the lack of continuous neuromuscular blockade had no influence on intraoperative patient movement observed [69]. Moreover, patients who did not receive continuous NMBAs recovered more quickly post-operatively.

Maintenance of Muscle Paralysis

Administering NMBAs by boluses as opposed to a continuous infusion in order to maintain neuromuscular block significantly reduces the likelihood of residual paralysis [70]. Fawcett et al. [70] observed that 24 % of patients receiving NMBA as an infusion arrived at the PACU with residual paralysis and this persisted in 12 % of this patient group when reassessed 15 min later. Of the patients who were given boluses, 12 % had clinically significant muscle weakness on arrival to PACU and only 2 % had not fully recovered at 15 min. The authors of this paper believe that infusions of non-depolarizing NMBAs should not be applied in ambulatory anesthesia. Continuous deep paralysis (i.e. maintaining one twitch on the TOF response) is not necessary for most surgical procedures performed in the outpatient setting. By administering NMBAs when clinically necessary rather than on TOF response, and by also avoiding deep paralysis, the total dose of NMBAs used in surgery is likely to be reduced which may subsequently reduce the risk of postoperative residual paralysis. It might also be reasonable to consider using a low dose of the short acting NMBA succinylcholine at the end of the case, for example to facilitate closure of the peritoneum.

Neuromuscular Transmission Monitoring

Perioperative neuromuscular monitoring by train-of-four stimulation can help guide timing and dosage of NMBAs and their antagonists, helping to reduce the incidence of residual paralysis. Multiple studies have shown that qualitative assessment of TOFR by visual or tactile palpation is an unreliable and inaccurate method of identifying residual paralysis, as evaluators are often unable to detect fade when $\text{TOFR} > 0.3$ [4, 71–75, 76••] thus residual paralysis may go undetected when actual TOFR is between 0.4 and 0.9 [20•, 74]. For this reason detectable fade on TOF stimulation indicates that NMB reversal is required.

Quantitative measurements of TOFR, such as acceleromyography (ACM) are used to aid titration of NMBAs and their antagonists. ACM is more reliable at identifying residual paralysis [75]. Murphy et al. [76••, 77] has demonstrated in 2 randomized trials, that the use of ACM

significantly reduces the incidence of residual paralysis. In the first trial, residual paralysis was observed in the PACU in only 4.5 % of patients monitored with ACM, whereas 30 % of patients monitored with conventional TOF had residual neuromuscular blockade. More importantly, the incidence, severity and duration of hypoxemic events in the first 30 min in PACU were less in the ACM group [76••].

Surveys of clinical practice in the US and Europe have shown that neuromuscular monitoring is performed in approximately 50 % of surgeries only, perhaps explaining the high incidence of residual paralysis [78, 79]. Proposals to rectify this inadequacy in patient perioperative care include better education and the development of formal best practice guidelines encouraging the use of quantitative measurement [80].

Reversal

Residual blockade promotes postoperative complications increasing morbidity and mortality. Reversal agents are used to accelerate and facilitate neuromuscular recovery to avoid future complications. Currently available reversal agents are Neostigmine and Sugammadex.

Neostigmine

Reversal of shallow levels of paralysis following administration of a nondepolarizing NMBA can be achieved with an acetylcholinesterase inhibitor combined with an antimuscarinic agent [81, 82]. Neostigmine is commonly used in the United States to antagonize the effects of NMBAs and expedite restoration of muscle function post-operatively [83•].

Acetylcholinesterase inhibitors are ineffective at reversing deep neuromuscular blockade [84]. The pharmacological efficacy of acetylcholinesterase inhibitors is limited as their maximum effect is reached when the enzyme is 100 % inhibited, at which point administering further antagonist does not increase the concentrations of acetylcholine. This means that during deep neuromuscular blockade, when NMBA concentration is high, it is not possible to fully reverse paralysis with acetylcholinesterase inhibitors. In a prospective randomized trial, Kopman et al. attempted reversal of neuromuscular block 1 min after a continuous infusion of either cisatracurium or rocuronium, i.e. at the point of deep neuromuscular block. After 20 min, only 11 of 40 patients had recovered to a TOFR > 0.9 [74]. This finding was more recently reproduced by Della Rocca et al. [85] who also found that in some patients residual paralysis persisted more than 20 min after reversal with neostigmine following deep neuromuscular block. To avoid suboptimal reversal, neostigmine should only be

administered when there is a degree of spontaneous recovery, or following shallow block. Practically, this translates to a TOF level of 2 or 3 [83•].

In addition, if neostigmine is used for reversal in the OR, total twitch suppression should ideally be avoided, unless essential for the particular surgical procedure. The dose of neostigmine should be based upon the degree of blockade at the time of reversal. Failure to detect tactile or visual TOF fade does not mean that reversal can be spared. However, in these circumstances doses of neostigmine as low as 0.015 mg/kg are often sufficient [82, 83•].

The use of neostigmine/atropine or glycopyrrolate can have undesirable side effects such as arrhythmias, dry mouth [86], bronchospasm [87], and even asystole [88, 89]. As well as these side effects, neostigmine can also cause neuromuscular transmission failure when given to patients who have already recovered from muscle paralysis [90, 91•]. Furthermore, in the absence of neuromuscular block, neostigmine can impair upper airway dilator volume, genioglossus muscle function and diaphragmatic function, thus putting the patient at risk of respiratory complications [91•, 92•].

Sugammadex

Sugammadex is a γ -cyclodextrin that binds selectively to the NMBAs rocuronium and vecuronium [93]. It works by encapsulating and inactivating these NMBAs directly. When dosed appropriately, sugammadex rapidly reverses any level of neuromuscular block without the autonomic effects seen with neostigmine [85, 93]. These findings are particularly relevant in the context of ambulatory surgery where a rapid and full recovery from neuromuscular block is essential to a safe discharge.

Sugammadex has also been shown to improve recovery times and peri-operative safety in groups of patients who are classically at greater risk of residual paralysis and its complications. Rocuronium's duration of action can vary with organ dysfunction, age and when larger doses are used. This becomes less relevant when rapid and reliable reversal can be achieved with sugammadex [93]. Morbidly obese patients for example are at increased risk of residual paralysis and critical respiratory events in the post-operative period [94]. Morbidly obese patients receiving sugammadex however, recover to a TOFR 0.9 or greater 3.5 times faster than those given neostigmine [94]. The rapid recovery seen with sugammadex use even in co-morbid patients has the potential to open up safe access to ambulatory surgery to a larger group of patients. However, sugammadex does not eliminate residual neuromuscular blockade in a real world scenario and it is important to conclude that neuromuscular transmission monitoring needs to be applied to all patients who have received NMBAs.

Calabadiion

Currently available reversal agents have undesirable side effects. Calabadiion is an acyclic member of the cucurbit[n]uril family of molecular containers [95•] that, similar to Sugammadex, forms host–guest complexes with specific targets and thereby modifies the properties of drugs bound within its interior.

Calabadiion is derived from urea and its C-shaped structure promotes the ability to flex the glycoluril oligomer backbone, expand its cavity, and accommodate guests of a wide range of sizes. The structural features also enhance the solubility of Calabadiion, which caused by additional electrostatic interactions (p–p interactions and hydrophobic effect). Carbonyl portals promote the binding affinity of Calabadiion towards the positively charged ammonium ions of NMBAs. The distance between anionic SO₃-solubilizing groups of Calabadiions selectively complement the N–N separation within Rocuronium, Vecuronium and Pancuronium.

Calabadiion I, the first member of this family, was found to have effects on reversal of non-depolarizing NMB in rats [96•]. However, its binding affinity to NMBAs was lower than Sugammadex. Preclinical studies have shown that Calabadiion II promotes earlier recovery of muscle function as expressed by time to recovery of righting reflex and to TOF > 0.9, compared to Neostigmine, Sugammadex, Calabadiion I and placebo [97]. Calabadiion II is also more potent than Sugammadex, as it requires a lower number of molecules to promote faster recovery of neuromuscular function, compared to what would be needed of Sugammadex. Moreover, Calabadiions are broad-spectrum reversal agents, which also reverse NMBAs with a benzylisoquinoline-structure. This is important, as the market volume of benzylisoquinoline NMBAs is significant: around 20 % of all NMBA. Calabadiion II does not affect subsequent Succinylcholine-induced NMB, promoting a safe relaxation in cases where re-intubation would be needed after reversal [97]. Calabadiions are well tolerated and do not affect heart rate, mean arterial blood pressure, pH, carbon dioxide pressure, and oxygen tension. Due to its structure and lack of a sugar moiety, it has been speculated that Calabadiion II may have a lower allergenic profile compared to Sugammadex. Unlike Sugammadex, Calabadiion II does not appear to affect PTT and activated factor X. All these reasons place Calabadiion as a promising agent for reversal of NMBAs.

Conclusion

Although the risk of perioperative morbidity and mortality in ambulatory surgery is low [33], residual paralysis occurs

frequently following NMBA use, even in day-case surgeries [21]. The most common and serious consequences of residual paralysis are postoperative respiratory complications. Freestanding ambulatory surgery centers may not be adequately equipped or staffed to manage these complications. Outcomes can be improved by employing techniques to minimize the risk of residual paralysis such as neuromuscular transmission monitoring and judicious use of low-dose neuromuscular blocking drugs. Neuromuscular blocking agent effects should be reversed. Neostigmine reversal improves muscle strength in patients with residual neuromuscular blockade, but carries risks related to incomplete reversal and unspecific effects of the reversal agent. New reversal agents that are so far not approved by the FDA such as calabadiion and sugammadex may allow for a better control of surgical conditions whilst also improving patient safety.

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Compliance with Ethics Guidelines

Conflict of Interest Hassan Farhan, Ingrid Moreno-Duarte and Duncan McLean declare that they have no conflict of interest. Matthias Eikermann has received financial support through a grant from Merck, and has submitted a patent application for Calabadiion to reverse NMBA and anesthesia.

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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