

# **New Concepts in Neuromuscular Blockade: Emphasis on Postoperative Residual Paralysis**

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## **Introduction**

With reduced revenue and increased costs, there is an increased emphasis on improving efficiency and productivity of ambulatory surgery centers [1]. Thus, there is an increased emphasis on expeditious recovery and shorter hospital stay after ambulatory surgery, which has led to an increasing trend towards using minimal concentrations of hypnotic-sedatives (i.e., propofol and inhaled anesthetics) for the maintenance of anesthesia [2]. This may lead to use of higher doses of muscle relaxants to ensure patient immobility [3], probably due to a perception that unlike hypnotic-sedatives, muscle relaxants can be reversed and thus do not have any deleterious effects on the recovery process. However, over-reliance on muscle relaxants can contribute to postoperative residual weakness, which may be present despite the signs of clinical recovery from neuromuscular blockade [4-6]. Because residual paralysis can increase postoperative morbidity, there is increasing emphasis on its prevention [4-6].

## **Incidence of Residual Paralysis in the PACU**

Traditionally, a train-of-four (TOF) ratio of  $\geq 0.7$  has been considered to reflect adequate recovery of neuromuscular function because it is associated with ability to maintain a 5-s head lift and return of adequate ventilatory function [4, 5]. However, several subsequent studies suggest that a TOF ratio of  $>0.9$  is necessary to ensure return of adequate voluntary muscle strength and the ability to ambulate, both of which are of critical importance in outpatients [4-7]. Thus, recent evidence suggests that the threshold for recovery of neuromuscular function must be a TOF ratio of  $>0.9$  [4, 5]. Several studies have demonstrated that many patients return to the postanesthesia care unit (PACU) with residual paralysis defined as a TOF ratio of  $<0.9$  [4-9].

Cammu et al [8] reported that the incidence of residual paralysis (as determined by TOF ratio of  $<0.9$ ) was 38% in outpatients and 47% in inpatients. The lower incidence of residual paralysis in outpatients was thought to be due to the use of shorter-acting muscle relaxants (i.e., mivacurium). In this study, neuromuscular monitoring was used in only 11-12%, while reversal drugs were administered in 25-26%, and clinical criteria were recorded in 45-49%. This emphasizes the need to monitor neuromuscular function and reverse neuromuscular blockade.

## **Consequences of Residual Paralysis**

Incomplete neuromuscular recovery is most likely to affect sensitive muscle groups (e.g., upper airways, pharynx, and proximal esophageal sphincters). Even minimal degrees of neuromuscular blockade (TOF ratio  $\leq 0.9$ ) can result in functional impairment of the muscles of the pharynx and esophagus leading to lack of coordination causing misdirected swallowing and frequent episodes of aspiration [6, 10]. Normal pharyngeal function was restored when the TOF ratio was greater than 0.9 [11]. In addition, residual muscle paralysis impairs hypoxic ventilatory response probably due to effects of muscle relaxants on the carotid body [12]. In a recent study, Murphy et

al [9] found a high incidence of critical respiratory events in the PACU patients with TOF ratio <0.9. Kopman et al. [7] reported that even minor degrees of residual paralysis (TOF ratio = 0.9) can cause diplopia, decreased grip strength, inability to maintain incisor teeth apposition, inability to sit up without assistance, severe facial weakness, including inability to maintain an airtight seal around a drinking straw with the lips, and overall weakness. These symptoms were present despite the signs of clinical recovery from neuromuscular blockade. Of note, most of the studies evaluating the effects of residual paralysis were performed in healthy volunteers. The detrimental effects of residual paralysis may be even worse with the additional postoperative residual effects of sedative-hypnotics and opioids used during general anesthesia [4-6]. Furthermore, residual paralysis may be significantly detrimental in the morbidly obese and those with obstructive sleep apnea.

### **Prevention of Residual Paralysis**

Obviously, avoidance of muscle relaxants would prevent residual paralysis. Unlike tracheal tube placement, use of the laryngeal mask airway avoids the need for muscle relaxants [13]. Because propofol and opioids depress laryngeal and pharyngeal reflexes, tracheal intubation may be accomplished without muscle relaxants; however, the intubating conditions are not always satisfactory [14]. Nevertheless, use of propofol allows adequate intubating conditions with lower doses of nondepolarizing muscle relaxant. Furthermore, inhaled anesthetics also have some muscle relaxant properties [15].

Interestingly, the choice of relaxant may be more decisive in avoidance of residual paralysis than manual evaluation of the response to TOF nerve stimulation [16]. If muscle relaxants are deemed necessary, use of shorter-acting or intermediate-acting relaxants should reduce the incidence and severity of residual paralysis, although their use has become a standard-of-care in an outpatient setting. Incomplete recovery of neuromuscular function is most likely to occur in patients with slow spontaneous recovery rate (e.g., obese, elderly, hypothermic, and organ dysfunction).

Importantly, the need for the routine use of muscle relaxants to provide adequate surgical conditions remains controversial. An isoflurane-fentanyl anesthetic technique alone has been shown to produce good-to-excellent surgical conditions in approximately two-thirds of the patients undergoing lower abdominal procedure without the use of muscle relaxants [17]. Thus, it is recommended to use the smallest dose of muscle relaxant that will provide optimal surgical conditions [6], rather than to maintain a certain TOF count (e.g., one twitch of the TOF response).

### **Assessment for Return of Neuromuscular Function**

At the end of the procedure, clinical assessment for return of neuromuscular function includes ability to sustain head-lift for at least 5 s and clench teeth. However, these clinical indicators are not sensitive or specific and therefore, minimal neuromuscular blockade cannot be reliably detected on clinical examination.

Peripheral nerve stimulation has been adopted widely because it facilitates quantification of the neuromuscular response to muscle relaxants without the need for comparison with control response. Generally, absence of tactile estimation of fade after TOF stimulation, double-burst, and 100-Hz, 5-s tetanic stimulation is considered adequate recovery. However, absence of fade does not correlate with the TOF ratio. It is very difficult, if not impossible, to visually or manually evaluate a TOF ratio with sufficient certainty to exclude residual blockade. Once the TOF ratio exceeds 0.4 most clinicians are unable to detect that any fade exists. Therefore, tactile assessment of TOF ratio is not reliable [18, 19]. Not surprisingly, a recent meta-analysis found that

intraoperative evaluation of TOF response using a conventional nerve stimulator did not influence the frequency of postoperative residual paralysis [16].

Recently, quantitative methods of evaluation of neuromuscular function (i.e., TOF ratio) using acceleromyography have been reported to reduce the incidence and the severity of postoperative residual paralysis [19, 20].

### **Use of Reversal Drugs to Reduce Residual Paralysis**

Because clinical judgment can easily err, general opinion favors administration of an anticholinesterase inhibitor at the end of anesthesia [21]. However, many practitioners avoid the use of reversal drugs because of their potential side effects (e.g., increased the incidence of postoperative nausea and vomiting [PONV]). Recent, systematic reviews of the published studies report that the incidence of PONV and the need for antiemetics does not increase with the use of neostigmine [22, 23]. Because of the potential for detrimental effects of residual paralysis [4-6], particularly in an outpatient setting, it is necessary that reversal drugs be used without hesitation. Using appropriate dose of reversal drugs matched for the degree of blockade should avoid the side effects of reversal drugs.

Once it is decided to reverse the neuromuscular blockade, it is important to determine the appropriate dose of neostigmine; however, this remains controversial. Although the time required to reach a given response is reduced if a large neostigmine dose is administered, this does not mean that a large dose is always indicated. In fact, when spontaneous recovery is almost complete, large doses might, at best be unnecessary. In addition, it must be noted that doses of neostigmine larger than necessary can exacerbate the muscle paralysis [24]. Unwarranted administration of neostigmine (i.e., administration after recovery of the TOF ratio  $>0.9$ ) increased upper airway collapsibility, presumably by impairing upper airway dilator muscle activity [25]. Access of neostigmine can also lead to muscle weakness [26].

It is clear that the rapidity of recovery of neuromuscular function is dependent on the intensity of the neuromuscular blockade at the time of reversal. Therefore, some suggest that neostigmine should be administered according to the intensity of blockade at the time of reversal. For example, if the patient has all 4 twitches with a fade then a lower dose (i.e., 30-40  $\mu\text{g}/\text{kg}$  neostigmine) may be adequate, and a maximum dose of 70  $\mu\text{g}/\text{kg}$  may be administered in patients with a dense block [21]. A recent preliminary study designed to determine neostigmine dose at varying levels of residual paralysis randomized patients to receive varying doses of neostigmine (0.01, 0.02, or 0.03 mg/kg or saline) at different levels of residual paralysis (TOF ratio of 0.4 or TOF of 0.6) [27]. The investigators found that reduced doses of neostigmine may be sufficient to antagonize low levels of residual paralysis (i.e., 0.023 mg/kg neostigmine at TOF ratio of 0.4 versus at 0.013 mg/kg neostigmine at TOF ratio of 0.6) [27].

If residual paralysis is encountered in the immediate postoperative period and other causes for delayed return of neuromuscular function (e.g., residual inhaled anesthetics, antibiotics, hypothermia, acid-base or electrolyte abnormalities, and underlying neuromuscular dysfunction) are ruled out, neostigmine may be repeated assuming that the total dosage does not exceed 70  $\mu\text{g}/\text{kg}$ . Administration of a second dose of neostigmine 70  $\mu\text{g}/\text{kg}$  does not hasten the recovery of neuromuscular function [28].

Sugammadex (Org 25969), a synthetic cyclodextrin derivative, is a selective relaxant-binding agent designed to reverse a rocuronium-induced neuromuscular block through chemical encapsulation [29]. The binding of sugammadex and rocuronium results in a rapid decrease in plasma concentration of rocuronium, and subsequently decreased concentration at the motor endplate.

With decrease in the availability of rocuronium to block acetylcholine receptors in the neuromuscular junction, muscle activity should reappear. Thus, sugammadex can cause a rapid and complete reversal of rocuronium-induced neuromuscular block. Although sugammadex is supposed to be specific for rocuronium, a recent study reported that it was also effective in reversing vecuronium-induced neuromuscular blockade at reappearance of the second muscle twitch [30]; however, it was not effective in reversing atracurium or mivacurium-induced neuromuscular blockade [29].

### Summary

Over-reliance on muscle relaxants to prevent patient movement can contribute to postoperative residual paralysis. Patients often arrive in the PACU with residual paralysis that may be related to inappropriate use of muscle relaxants and reversal drugs. Even a minor degree of residual blockade (usually not appreciated clinically) can increase postoperative morbidity including inadequate ventilation, hypoxia, the need for reintubation, and delayed discharge from the operating room and the PACU. Residual paralysis may be even more critical in the high-risk patients (e.g., obese, sleep apnea, and elderly) that are increasingly undergoing surgical procedures on an outpatient basis. Therefore, avoidance or minimization of muscle relaxants may facilitate recovery. If muscle relaxants are deemed necessary, selection of a drug with a short duration of action and a reliable offset of neuromuscular blockade is of prime importance. The use of objective neuromuscular monitoring (e.g., acceleromyography) providing TOF ratio should reduce the incidence and severity of postoperative residual paralysis. Because clinically unrecognized residual paralysis is common, use of neostigmine (in appropriate doses) should be utilized without hesitation.

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