

NEWER NEUROMUSCULAR BLOCKING DRUGS - WHETHER TO REVERSE OR NOT?

Nandita Mehta¹, Shikha Sharma^{2,*}

¹Professor & Head, ²Assistant Professor, Department of Anaesthesiology, Acharya Shri Chander College of Medical Sciences and Hospital, Jammu, J&K.

***Corresponding Author:**

Email: shikha_2527@yahoo.co.in

An editorial by Churchill-Davidson in 1965 expressed the clinical problem succinctly: 'To reverse, or not to reverse': that is the question! Since the introduction of d-tubocurarine into clinical anaesthesia this question has received opposing answers'. Now, more than six decades later this issue has yet to be resolved.

The introduction of neuromuscular blocking drugs (NMBD) into anaesthetic practice 75 years ago revolutionized anesthetic management and currently more than 400 million people receive these agents annually. Neuromuscular blocking drugs (NMBDs) are widely used to facilitate endotracheal intubation during anaesthesia induction and provide muscle relaxation during surgery. This led to the development of major cardiac surgery, paediatric surgery, and neurosurgery, as well as the specialty of critical care. In the presence of muscle relaxants, anaesthesia could be lightened and postoperative recovery was faster. This allowed patients to protect their airway more rapidly on recovery, thereby preventing pulmonary aspiration of stomach contents.

Developments in pharmacological management of neuromuscular management have occurred over the last 60 years, which has improved their safety when being used. Residual neuromuscular block (NMB) in PACU is well recognized phenomenon that may increase postoperative morbidity.

WHAT IS RESIDUAL NEUROMUSCULAR BLOCK?

Residual NMB is defined as the presence of signs or symptoms of muscle weakness in the postoperative period after the intraoperative administration of an NMBD. The historical study of Beecher and Todd. "A study of the deaths associated with anaesthesia and surgery" based on a study of 599,548 anaesthesias in ten institutions from 1948–1952, observed that the use of neuromuscular blocking drugs (NMBDs) was associated with a 6-fold increased risk of death in the peri operative period¹.

In a retrospective analysis of nearly 200,000 anaesthetics in France, Tiret et al found that half of the 65 deaths associated with anaesthesia were due to

post anaesthesia respiratory depression². Lunn et al in 1983, demonstrated in a study based on anonymous reporting of deaths within six days of anaesthesia, that 11 of 32 deaths due entirely to anaesthesia were caused, at least in part, by post-operative respiratory failure, and the presence of neuromuscular blockade was considered to be contributory in six of these deaths³.

TRAIN OF FOUR (TOF)

The gold standard for assessing the onset and reversal of NMBDs is the TOF. It was introduced in 1970 for monitoring the degree or reversal of neuromuscular block. Fade of force of muscle contraction in response to repetitive nerve stimulation provides the basis for evaluation; the degree of fade is proportional to the intensity of the neuromuscular block. Most clinicians and researchers define residual block using a pre-established TOF ratio "threshold" value. A TOF ratio of <0.7 measured using either compound electromyography (EMG) or mechanomyography (MMG) has been considered to represent inadequate neuromuscular recovery. At TOF ratio < 0.6 signs of muscle weakness are obvious like ptosis and tracheal tug. At a TOF ratio of >0.7, there are no clinical signs of muscle weakness as assessed by sustained eye opening, hand grasp, and tongue protrusion and able to maintain a 5-second head lift⁴. More recent volunteer studies have demonstrated that pharyngeal dysfunction and an increased risk for aspiration occurs in patients with TOF ratios < 0.9^{5,6}. Impaired inspiratory flow and partial upper airway obstruction have been observed frequently at TOF ratios of 0.8 and subtle levels of neuromuscular blockade may produce distressing symptoms in awake patients, which may persist even at TOF ratios >0.9^{7,8}.

Patients with adequate neuromuscular recovery should have the ability to breathe normally, maintain a patent upper airway, preserve protective airway reflexes, swallow, cough, smile, and talk. These physiologic end points are achieved in most patients at a TOF ratio of 0.9. Therefore, a precise definition of residual block requires the measurement of TOF ratios using objective neuromuscular monitoring devices (TOF ratio >0.9 -1.0) but also a

careful clinical assessment of each patient for adverse effects potentially attributable to the use of NMBDs.

INCIDENCE

Earlier the critical pulmonary events was higher at TOF <0.7 and was considered as good recovery. The frequency of residual NMB in present-day clinical practice ranges from 4% to 50% depending on: the duration of action of the NMBA used; whether or not a reversal agent is given; the type of neuromuscular monitoring used; and the diagnostic tests used for assessing residual NMB. Using NMBDs as continuous infusions rather than in bolus doses also increases the incidence of the block⁹. The magnitude of the TOF ratio at the time of reversal is positively correlated with the time elapsed since the last dose of relaxant, and the incidence of residual NMB is greater in patients in whom the duration of the surgery was shorter than anticipated.

Baillard et al examined the incidence of residual neuromuscular block in 568 consecutive surgical patients who received vecuronium but no reversal. On arrival to the recovery room, TOF ratios < 0.7 measured with AMG were observed in 42% of subjects¹⁰. Murphy and colleagues collected data on critical respiratory events (CREs) in 7459 patients after surgery and 61 (0.8%) developed hypoxaemia and upper airway obstruction with eight patients needing re-intubation. Of these 61 patients, 42 had signs or symptoms of residual block. The mean TOF ratio was 0.62 in the CRE group vs 0.98 in the control group¹¹. In 1997, Berg and colleagues reported a significant incidence of postoperative pulmonary complications, if the TOF ratio was < 0.7 in the recovery room. In this study, the incidence of a TOF ratio <0.7 was higher after the long-acting NMBA, pancuronium (26%), compared with those who had received the intermediate-acting relaxants, atracurium and vecuronium (5.3%)¹².

REVERSAL AGENTS

Owing to the limitations of anticholinesterases and the complications of residual neuromuscular block, there has been a quest for an ideal reversal agent. Most of the compounds have been developed with a view to either more effectively suppressing AChE or to indirectly increasing the concentration of Ach. There are two classes:

1. Anticholinesterases: neostigmine, pyridostigmine, and edrophonium
2. Newer reversal agents: sugammadex, cysteine

WHY NOT TO REVERSE?

Many clinicians accept the premise that, following a single 'intubating dose' of a non-depolarising NMB of intermediate duration, adequate spontaneous recovery will occur at 90 min after drug

administration. Hence, antagonism is unnecessary. While this may frequently be the case, it will not be true in a large number of individuals. Caldwell administered a single 0.1 mg/kg bolus of vecuronium to a group of healthy patients under isoflurane-nitrous oxide anaesthesia and observed the rate of return of the TOF ratio. Two hours later, four of 20 subjects had TOF ratios < 0.75. In two of these individuals the TOF ratio was < 0.50. At the 3 hr mark three of 10 individuals still had TOF ratios in the range 0.6–0.7¹³. Debaene et al. reported similar results. In their study 238 patients were given a single intubating dose of vecuronium, rocuronium or atracurium. At the 2 hr mark 10% of individuals still had TOF ratios < 0.70 and 30% had not yet recovered to a value of 0.90¹⁴.

Neostigmine administration may induce a variety of muscarinic side-effects like nausea and vomiting, bradycardia and prolongation of the QT interval of the electrocardiograph (ECG), bronchoconstriction, stimulation of salivary glands, miosis, and increased intestinal tone. Severe bradycardia may occur after neostigmine injection and asystole has been reported following neostigmine reversal even when it has been given at the same time as an anticholinergic drug. Some authors have speculated that tension on intestinal anastomoses can be critically increased by neostigmine reversal, as neostigmine may increase intraluminal pressure and propulsive activity in the small bowel colon and rectum by up to 200%.

Another drawback to routine neostigmine reversal is that neostigmine, in clinically recommended doses, can actually cause neuromuscular transmission failure when given to patients who have already recovered from neuromuscular block. Cholinesterase inhibitors may cause neuromuscular transmission failure by desensitisation of acetylcholine receptors, depolarisation block of neuromuscular transmission, or open channel block. Thus, ideally cholinesterase inhibitors should only be given if needed. Unfortunately, in the absence of objective neuromuscular monitoring it may be difficult to ascertain if residual block still exists. Thus patients completely recovered from the effects of neuromuscular blocking agents may occasionally be given unwarranted reversal. However, it should be noted that at TOF ratios as high as 0.50, neostigmine 0.04 mg/kg will still improve neuromuscular function rather than degrade it.

THE CASE FOR ROUTINE REVERSAL

Full restoration of a patient's muscle strength is essential to ensure a safe postoperative recovery. Residual neuromuscular block is perhaps most accurately defined as the presence of signs or symptoms of muscle weakness in the postoperative

period after the intra operative administration of an NMBD. Lingering effects of neuromuscular blocking agents, however, may cause partial paralysis, a condition in which symptoms of muscle weakness prevail in the postoperative period. This may impair breathing, upper airway patency, protective airway reflexes, swallowing, and coughing, thereby putting patients at risk for serious complications in the vulnerable postoperative period. Unanticipated postoperative intubation is associated with increased mortality and increasing healthcare costs.

The long acting neuromuscular blocking agent pancuronium has been associated with a higher risk of postoperative respiratory failure. Consequently, long acting compounds have almost quantitatively disappeared from the market, being replaced by modern intermediate acting non-depolarizing neuromuscular blocking agents, but it is unclear if the use of these drugs represents a risk factor for adverse peri-operative respiratory outcomes. Intermediate acting neuromuscular blockers were introduced into clinical practice almost 30 years ago with the objective of producing a more predictable, noncumulative, and easily reversible block. These desirable pharmacological features were associated with a false sense of security by a significant number of anesthesiologists who felt that antagonism of residual neuromuscular block could be safely eliminated especially with the use of atracurium, which is spontaneously metabolized by Hofmann elimination. Many recent studies confirmed the fact that the widespread use of intermediate acting neuromuscular blockers reduced but did not eliminate post operative residual curarization (PORC)¹⁵. When neuromuscular blocking drugs with intermediate duration of action became available, some anesthesiologists thought they could dispense altogether with anticholinesterase agents to reverse neuromuscular blockade at the end of a procedure. In fact, in some countries and some hospitals, the use of anti-cholinesterase agents is not common. However, omitting the anticholinesterase agent gives rise to a high incidence of residual paralysis.

DECISION

The question whether to reverse or not to reverse neuromuscular block at the end of surgery seems irrational. In addition to careful clinical assessment, anesthetists commonly use two strategies to control the effects of non-depolarizing neuromuscular blocking agents and restore patients' optimal muscle strength. Firstly, the monitoring of neuromuscular transmission during surgery to assess the degree of a patient's neuromuscular block and secondly, reversal of neuromuscular blockade with acetylcholinesterase inhibitors to antagonise potentially lingering effects of non-depolarizing neuromuscular blocking agents at the end of surgery.

Pharmacologists, anesthesiologists, and biomedical engineers have done strenuous relentless efforts with impressive outcomes to optimize neuromuscular blockers, antagonists, and monitoring equipments. The armamentarium of neuromuscular blockers now includes several intermediate acting neuromuscular blockers with improved metabolic pathway and minor hemodynamic effects.

CONCLUSION

Residual paralysis undoubtedly contributes to a large proportion of postoperative respiratory complications such as hypoxia, hypoventilation, airway obstruction, atelectasis, and even death. Undetected neuromuscular block following the administration of non-depolarising NMBs of intermediate duration is still a common occurrence in today's PACUs. Even mild residual paralysis has been shown to increase the incidence of adverse respiratory events. Several Conclusions follow from the above which are:

1. Informed decisions regarding neostigmine dosage and timing are not possible unless neuromuscular function is monitored during anaesthesia. Recovery of TOF upto 0.9 is a gold standard. While objective monitoring is ideal, used with intelligence conventional peripheral nerve stimulators suffice in most situations.
2. In the absence of objective evidence that neuromuscular recovery is complete (TOF ratio \geq 0.90) a reversal strategy must be planned from the initial administration of a neuromuscular blocking agent, which should have an intermediate duration of action and be given in a dose that is appropriate for the planned duration of the surgical procedure. However, not all patients require neostigmine in doses of 0.04–0.05 mg/kg. Doses as small as 0.015 mg/kg will often be adequate.
3. The advent of the g-cyclodextrin, sugammadex, which will reliably reverse even profound block produced by aminosteroid NMBDs will be advantageous especially in a 'cannot intubate, cannot ventilate' scenario. It is too soon to know the extent of any side-effects produced by this drug. At present, its limitations seem to be confined to its cost, availability only in Europe and its inability to reverse non-aminosteroidal agents.

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