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Perspective

Is it always necessary to reverse the neuromuscular blockade at the end of surgery?

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Neuromuscular blocking agents (NMBAs) were introduced into clinical anesthesia in the 1940s[1], and have enabled anesthesiologists to safely anesthetize patients with significant cardiopulmonary diseases. By employing neuromuscular blockade patient movement could be abolished, without producing excessive cardiovascular depression. The risks of employing neuromuscular blocking drugs, however, are the potential for intra-operative awareness and the persistence of the neuromuscular block into the post-operative period, especially with non-depolarizing NMBAs[2–3].

Residual neuromuscular blockade

Residual paralysis following extubation of the trachea, unfortunately, is still common[4–8]. It should always be reversed to prevent diplopia, laryngeal weakness, atelectasis, CO_2 retention and respiratory acidosis. The diplopia contributes to post-operative nausea and vomiting (PONV), and the CO_2 retention and respiratory acidosis lead to delayed emergences at the end of surgery[9]. Residual neuromuscular block should always be considered in the differential diagnoses of prolonged emergences from anesthesia. The combination of laryngeal weakness and atelectasis produced by the residual block often requires re-intubation in the recovery room. If re-intubation occurs too late, it may even lead to a hypoxic cardiac arrest. Therefore, residual neuromuscular block should no longer be tolerated in the recovery room, even if it is not severe enough for the patient to require re-intubation. Residual block is associated with excess morbidity and is quite uncomfortable for the patients. The anesthesia care giver needs to explain the phenomenon to the patients to alleviate fear. If the phenomenon is not explained to the patients, they usually think that they have suffered a stroke under anesthesia. A residual neuromuscular block should therefore always be reversed.

Diagnosis of residual blockade with a nerve stimulator

Being able to reliably identify the presence of a residual block is an essential skill that must be mastered by any anesthesia care provider. Two twitches on train-of-four (TOF) monitoring were historically deemed sufficient to safely reverse a neuromuscular block with a standard dose of 35–50 μg/kg of neostigmine[10]. In recent studies, it was found that as many as four twitches may be required to eliminate residual blockade with a standard reversal dose of neostigmine[11]. Another study found that, with a TOF ratio of 0.2, even four twitches were insufficient to reverse the neuromuscular block with 70 μg/kg of neostigmine[12]. The TOF response depends on many variables, especially the nerve that is monitored. Monitoring of the facial nerve greatly underestimates the depth of neuromuscular blockade compared to that of the ulnar nerve. When assessing thumb adduction with ulnar nerve monitoring, we are definitely assessing neuromuscular conduction. The opponens

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pollicis muscle is innervated by the ulnar nerve and cannot be stimulated directly *via* electrodes located over the ulnar area of the anterior forearm. The assessment of the ulnar nerve is therefore preferred over that of the facial nerve, because electricity may excite the facial muscles directly and make them contract even though the neuromuscular junction has been blocked completely. This may lead an observer to erroneously conclude that neuromuscular blockade has not yet been established.

Assessing TOF ratio by visual or tactile evaluation is difficult. Even experienced neuromuscular researchers are unable to visually or manually detect fade at TOF ratios greater than 0.4[13]. With qualitative assessment of double burst stimulation (DBS), fade can be detected up to TOF ratios of 0.6[14]. Both of these are much lower than the level of 0.9 currently recommended for safe extubation. Quantitative TOF monitoring that utilizes the technologies of acceleromyography or electromyography is therefore necessary to be able to reliably identify persistent weakness with a TOF stimulus[15]. Studies have indeed shown less residual block after rocuronium when acceleromyography was used to monitor the depth of the neuromuscular block[16–17].

Clinical signs of residual block

A prominent clinical sign of residual neuromuscular block is a lag of the eye lids, when the patient attempts to open the eyes. The frontalis muscle is resistant to neuromuscular blockade, and wrinkling of the forehead can therefore often be observed together with the ptosis and lid lag when residual paralysis is present. The diaphragm is also resistant to the effects of NMBAs and patients with persistent block can usually breathe spontaneously through an endotracheal tube that splints the larynx opening. If the patient is extubated with a residual block, however, reintubation often becomes necessary because laryngeal weakness leads to upper airway obstruction. It is essential to be able to distinguish the signs of residual weakness from excessive administration of opioids. Opioid excess usually is associated with slow deep breathing and pinpoint pupils (miosis). It is the responsibility of the anesthesiologist to monitor the depth of the neuromuscular blockade and to ensure that it has been reversed completely, prior to waking the patient up and performing extubation.

Decision on administration of reversal agents

The risk of a persistent block is clearly much greater than any side effects of the reversal drugs. This is especially true since the advent of sugammadex because it lacks the cholinergic side effects of neostigmine, physostigmine and edrophonium. If there is any doubt about the completeness of the neuromuscular recovery, a reversal agent must be administered, because persistent weakness has clearly been shown to be associated with worse outcomes[18–19].

There are several reversal agents available to reverse the neuromuscular block. Sugammadex is a cyclodextrin that is a selective binding agent for rocuronium and also has some capacity to reverse other aminosteroid muscle relaxants like vecuronium and pancuronium. It acts by encapsulating the rocuronium molecule[20]. It can reverse even very deep levels of neuromuscular blockade by rocuronium, because unlike neostigmine and other anticholinergic reversal agents, it does not have a ceiling effect[21]. The reversal with sugammadex is more rapid and more reliable than with neostigmine[22–23], and there are no cholinergic side effects like nausea, vomiting, bowel cramps, bradycardia and bronchospasm. Sugammadex also does not potentiate the neuromuscular block like neostigmine, when it is given in large doses. A lower rate of residual block has been shown with sugammadex than with neostigmine reversal[24]. Given the better side effect profile of this drug, anesthesiologists should have a lower threshold to administer this reversal drug for neuromuscular blockade. It is now easy to completely reverse even very deep levels of residual block, as long as the muscle relaxant that was used was rocuronium. Pulmonary outcome scores were significantly improved in older patients with sugammadex, compared to those with neostigmine or with no reversal agents[25].

Neostigmine has a ceiling effect and the maximal dose that should be administered to reverse neuromuscular blockade is 50 μg/kg. Doses greater than this may make the patient weaker by precipitating a cholinergic crisis and potentiate the neuromuscular block[26–29]. This phenomenon limits the depth of neuromuscular blockade, which the patient can be reversed from with neostigmine. Large doses of neostigmine also produce excessive salivation, nausea and vomiting, bowel cramps, bradycardia and bronchospasm. Neostigmine should therefore always be given together with an anti-cholinergic drug like glycopyrrolate.

Other causes of prolonged neuromuscular blockade

Causes of prolonged neuromuscular blockade in-

clude atypical plasma cholinesterase enzyme following the administration of succinylcholine. Low blood levels of potassium, magnesium, and lithium, aminoglycoside antibiotics, subclinical myasthenia gravis or other neuromuscular diseases like botulism or Eaton-Lambert syndrome may cause prolonged paralysis with the use of non-depolarizing neuromuscular blockers.

In summary, a neuromuscular block should always be fully reversed if it is still present at the end of surgery. Withholding a reversal agent should only be considered, after spontaneous recovery from neuromuscular blockade has been demonstrated with a TOF ratio of 0.9 or greater which requires an acceleromyography or an electromyography monitoring. Given the situation that the high incidence of residual block occurs despite the use of standard neuromuscular monitors, it seems clear that reversal agents should be employed in all patients that received non-depolarizing NMBAs. Compared to the risk of an unrecognized persistent neuromuscular block in the recovery room, the side effects of sugammadex are minimal and it allows for complete reversal of neuromuscular blockade—even from very deep levels of blockade. It is the reversal agent of choice in situations where other drugs have potentiated rocuronium, or the patient has a subclinical and unrecognized neuromuscular condition, because the maximum dose of neostigmine is usually insufficient for reversing the block under these circumstances. With the availability of sugammadex, residual paralysis in the recovery room can therefore be eliminated and will become a phenomenon of the past.

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