Indicators of Recovery of Neuromuscular Function: Time for Change?

In this issue of Anesthesiology, Kopman et al. present a very interesting and intriguing study that brings new and relevant information to clinical anesthesia. The results (and the controversies that the study will undoubtedly provoke) are very timely, as they address an old anesthetic problem (residual neuromuscular weakness) in the context of evolving clinical practice (ambulatory anesthesia). The authors revisit the historical criterion that has been used as an indicator of adequate neuromuscular function after the use of nondepolarizing agents: recovery of the train-of-four (TOF) ratio to >0.70.

More than 20 years ago, investigators correlated the TOF ratio with clinical indicators of adequate recovery of neuromuscular function. \(^2,3\) Tests of respiratory function (vital capacity, inspiratory force, peak expiratory flow rate) and voluntary muscle function (tongue protrusion, head-lift, hand grasp, and sustained eye opening) were reported to have returned to clinically acceptable values once the TOF ratio was >0.70. Anesthetic practice, however, has undergone dramatic changes since then, with an increasingly larger proportion of surgical procedures being performed on an outpatient basis. It has been stated that 60% of all elective surgical procedures were performed in ambulatory centers in 1993, \(^4\) and the trend toward an increasing number of outpatient surgeries is likely to continue. Pressure to decrease the cost of delivering health care services has also led to an increasing number of debilitated, elderly surgical patients presenting to ambulatory centers. For these reasons, it is important to reassess the current standards of defining adequate neuromuscular recovery.

The unique aspect of the study by Kopman et al. is that they were able to correlate the volunteers' subjective findings of partial neuromuscular weakness with the clinical counterpart of neuromuscular recovery, a TOF ratio of 0.70. In their study, the authors enrolled 10 healthy, unpremedicated, and unanesthetized volunteers who underwent baseline testing of neuromuscular function, followed by administration of a single 5-µg/kg bolus of mivacurium plus a continuous infusion at 2 µg·kg\(^{-1}\)·min\(^{-1}\). Neuromuscular function was tested using TOF stimulation and was recorded electromyographically. When the target TOF ratio of 0.65-0.70 was achieved, the mivacurium infusion was titrated to maintain a stable TOF ratio of 0.70. All volunteers then repeated the tests of neuromuscular function, and the mivacurium infusion was titrated to allow recovery to a TOF ratio of 0.85-0.90. Neuromuscular function tests again were repeated, and the mivacurium infusion was discontinued to allow full recovery. All volunteers were observed until they believed they were back to “normal.” The results are as surprising as they are significant: all volunteers reported considerable visual disturbances even when the TOF ratio had recovered to 0.90. Head- and leg-lift usually were present at a TOF ratio of ≥0.60, whereas at a TOF ratio of <0.75, all volunteers felt uncomfortable, some reporting persistence of diplopia “for periods in excess of 1 hour after termination of the mivacurium infusion.” From a monitoring standpoint, all clinical tests of neuromuscular function, the most sensitive (when compared with the TOF ratio) was the ability of the volunteers to resist the removal of a wooden tongue blade from their clenched teeth.

The authors’ conclusion that “any definition of ‘satisfactory’ recovery of neuromuscular function” should probably be reevaluated in the context of current medical practice is appropriate for several reasons: 1) age and health status differ between patients and volunteers; 2) practice and relaxant use patterns differ between ambulatory centers; 3) monitoring of neuromuscular function is not performed routinely in all ambulatory centers; 4) the monitoring methods used in the study are applicable to a variety of clinical settings; and 5) economic pressures are to decrease drug spending.

First, surgical patients are likely to be older and sicker than the volunteers participating in this study. The volunteers were healthy, ASA physical status 1, within 15% of ideal body weight, and aged 23-33 years. The residual effects of nondepolarizing muscle relaxants are likely to be much more significant in today’s generally older and sicker ambulatory surgical patients. Although one may argue that sedated, postoperative surgical patients are less likely to be concerned by visual distur-
bances and facial weakness than unpremedicated healthy volunteers, it is also true that purely from a safety standpoint, postoperative patients may be at greater risk for significant morbidity; in patients recovering from anesthesia, residual neuromuscular weakness may be compounded by residual anesthetic effects.

Second, mivacurium is not the only neuromuscular blocking agent used in ambulatory surgical centers. Intermediate acting drugs, such as vecuronium, atracurium, rocuronium, and cisatracurium, actually dominate the market. Because significant residual weakness may persist for up to 1 hour after discontinuation of a short-acting drug (with a recovery index of 7–8 minutes), such weakness, even if not more severe in degree, may certainly persist longer after intermediate duration relaxants. This difference can be explained by the fact that there is a great margin of safety in neuromuscular transmission: up to 70% of the junctional receptors could be inactivated without any overt change in the elicited neuromuscular response. Thus, a TOF of 1.0 elicited at peripheral muscles (such as the adductor pollicis) represents a receptor occupancy of up to 70% (conversely, it implies that at least 30% of the receptors are functional). Because of the lack of sensitivity of current monitoring techniques, degrees of receptor occupancy less than 70% cannot be measured clinically. Thus, it is impossible to determine accurately at what point subjective symptoms (such as diplopia) associated with receptor occupancy less than 70% subsided. This degree of receptor occupancy, however, would be similar for most nondepolarizing relaxants. Because the 5–95% recovery time of the intermediate duration agents (25–30 minutes) is approximately twice that of mivacurium (14 minutes), it therefore would be reasonable to expect that the duration until recovery to equivalent degrees of receptor occupancy (at which point visual symptoms subside) would be longer for intermediate duration agents than for mivacurium.

Third, neuromuscular function is not monitored routinely, either intra- or postoperatively. The incidence of residual paralysis in postanesthesia care unit (PACU) remains alarmingly high after long-acting agents (36–45%)

5,6 intermediate-acting agents (4–9%),

5,6 and even short-acting agents such as mivacurium (4%), despite pharmacologic reversal.7 Although the use of nerve stimulators has been shown to significantly decrease the incidence of postoperative residual weakness, this complication still occurs.8,9 Therefore, the problem of the lack of neuromuscular monitoring standards is likely to be compounded; even when nerve stimulators are used clinically and the assessment of neuromuscular function is performed by objective means, postoperative residual weakness will likely continue to occur in the PACU.

Fourth, the results by Kopman et al. cannot be criticized on methodologic grounds. They intentionally did not attempt to reach supramaximal levels of stimulation in their unpremedicated volunteers. Subjective discomfort in awake patients and volunteers has been shown to be significantly greater at supramaximal TOF stimulation than at currents less than 40–50 mA.10,11 At the same time, the TOF ratio remains consistent over a range of stimulating currents (and pulse durations) as long as all four responses are elicited and the stimulus delivered exceeds the initial threshold for stimulation by at least 10 mA.5,12,13

Fifth, despite the recent decline in drug price inflation (from 6.9% in 1991 to 2.1% in 1995),14 and the report that “anesthesiologists have little control over PACU economics via choice of anesthetic drugs,”15 pressures to further reduce health care costs by using older (and less expensive) relaxants will most likely continue. In view of the important finding by Kopman et al., it may well be that what was at one time considered an acceptable indicator of recovery from neuromuscular blocking drugs is no longer acceptable. And perhaps we also should remember that “if the cost (of new drugs) is justifiable either in terms of patient outcome or in a greatly improved quality of care, then they will be accepted and embraced into practice. The purpose of pharmacoeconomics is not to identify the cheapest drug but to evaluate the total cost of treatment.”16

In conclusion, the study by Kopman et al. is very important because it addresses concerns related to the use of muscle relaxants, concerns that are articulated by clinicians and researchers. It emphasizes the fact that despite the tremendous advances in anesthesia monitoring techniques and equipment, currently we lack the ability to correlate subjective symptoms to degrees of receptor occupancy less than 70% and the ability do so consistently to degrees of receptor occupancy greater than 70%. Second, the study underscores the great variability of patients to the effects of muscle relaxants and the lack of a reliable clinical test for residual neuromuscular block. As importantly, it introduces the concept that under the conditions of the study protocol using mivacurium, the most reliable (although still fallible) clinical test is that of the masseter muscle strength (tongue depressor test) and not one of the previously considered “gold standards,” such as head-lift or leg-
lift. Third, in view of the great variability of muscle relaxant effects, monitoring using objective means becomes even more important from a patient safety standpoint. And finally, the study is salient because it will likely generate controversy and stimulate follow-up investigations that will most likely validate the current findings in future surgical patients undergoing anesthesia.

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References


