Residual Neuromuscular Block: Rediscovering the Obvious

“Anesthesia... is not of itself the therapeutic act which makes possible the correction of deformity, the restoration to health, or the staying of death. It merely makes possible the acts which can accomplish these things.” (Beecher & Todd, 1954)

Beecher and Todd introduced their seminal article with “… evidence will be given that where the muscle relaxants are involved, an appreciable increase in the anesthesia death rate is presented.”1 The evidence on which this assertion was made was their finding that the mortality rate ascribed to anesthesia when muscle relaxants were used (1:370 anesthetics) was six times greater than the mortality rate when muscle relaxants were avoided (1:2100 anesthetics). Furthermore, 63% of the “curare” deaths (deaths that involved the use of a muscle relaxant) were caused by respiratory failure.

Although the safety of general anesthesia has improved markedly over the past half century, morbidity continues to be reported, even in areas in which significant progress has been made, such as the pharmacology of neuromuscular blockers. In this issue of Anesthesia & Analgesia, Murphy et al.2 report the incidence of critical respiratory events that occurred in patients after surgery within the first 15 min of admission to the postanesthesia care unit (PACU). Data were collected over 1 yr for a large number of patients (n = 7459) who received general anesthesia. Of these patients, 42 cases (patients with signs and symptoms of postoperative residual neuromuscular blockade) were matched with 42 controls (patients without residual paralysis) for statistical analysis. The incidence of prospectively defined critical respiratory events observed in the Murphy et al. study during the first 15 min in the PACU is significant (0.8%), considering the total number of general anesthetics performed annually in the United States. The Joint Commission noted that 21 million patients underwent general anesthetics in 2004.3 If we assume that two-thirds of these patients received nondepolarizing neuromuscular blockers for general anesthesia, then by extrapolation, approximately 112,000 patients annually are at risk of adverse events associated with discharge from the PACU with residual neuromuscular blockade.

The findings reported by Murphy et al. are significant on several levels. Outcome studies that investigate the clinical implications of residual neuromuscular blockade (train-of-four [TOF] ratios of <0.9 or <0.7) are lacking. Several studies have demonstrated that residual neuromuscular blockade after long-acting neuromuscular blockers is a risk factor for postoperative pulmonary complications.4,5 Nevertheless, as Kopman6 pointed out in an editorial, “There are no outcome data to substantiate the position that patients who arrive in the postanesthesia care unit with TOF ratios of 0.50 experience more adverse events than did those who have recovered to values >0.80–0.90.” Murphy et al.,2 in reporting short-term outcome data after the use of neuromuscular blocking drugs, noted that of the 7459 patients who received general anesthetics, 8 required reintubation, 3 of them emergently. This finding is important in that these cases of obvious

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Accepted for publication March 7, 2008.

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DOI: 10.1213/ane.0b013e3181753266
residual neuromuscular blockade occurred, despite intraoperative use of a conventional (simple) peripheral nerve stimulator and the use of neostigmine for antagonism of residual neuromuscular blockade in 100% of the patients. The authors give no insight into how clinical decisions about reversal were made in these eight patients. Two of the patients who required reintubation in the PACU had chronic renal insufficiency, probably suggesting an increased risk for prolonged neuromuscular block in patients with impaired renal function.

Conventional nerve stimulator units require the clinician to evaluate the evoked response by subjective means (i.e., visually or tactiley). A 5-s head lift and lack of subjective evidence of fade were documented in all patients in the Murphy et al. study. Head lift, however, is an insensitive indicator of the adequacy of neuromuscular recovery.7 Kopman et al.8 noted that patients could sustain a 5-s head lift at a TOF ratio of 0.60. Similarly, subjective evaluation of the evoked muscular response to TOF and tetanic stimulation are notoriously inaccurate as estimates of fade or postoperative residual neuromuscular blockade.9,10

Despite the aforementioned limitations, we believe that with appropriate knowledge of clinical neuromuscular pharmacology, nondepolarizing neuromuscular blockers can be administered safely. Appropriate intraoperative use of a conventional nerve stimulator may decrease (but not eliminate) the incidence of postoperative residual neuromuscular blockade.11 If neostigmine administration is timed at a TOF count of 4, then clinically significant postoperative residual neuromuscular blockade should be a rare event. However, since neuromuscular blockers are often given without the concomitant use of a quantitative neuromuscular function monitor, pharmacologic reversal should be routine.

Patients in Murphy et al.’s study2 underwent intraoperative monitoring that included testing of both ulnar and facial nerve sites. In one study, recovery of the four twitches of the TOF in the face occurred 17.0 min (sd ± 6.2) before a similar degree of recovery was noted at the thumb.12 This means that, during recovery, monitoring of evoked responses at peripheral sites (such as the adductor pollicis muscle at the thumb) introduces an extra “margin of safety:” recovery of airway muscles, including the diaphragm, (i.e., axial musculature) happens before recovery of peripheral muscles. Conversely, the time course of recovery at facial muscles (orbicularis oculi and corrugator supercilii) occurs at the same time as respiratory muscles, such that the “margin of safety” no longer exists. We do not know how the use of intraoperative monitoring of facial nerve sites influenced the incidence of postoperative residual neuromuscular blockade reported by Murphy et al.

The obvious question then is, “Is there any evidence that the use of a quantitative neuromuscular function monitor that displays TOF ratios in real time is associated with a reduction in the incidence of postoperative residual neuromuscular blockade?” A recent meta-analysis could not demonstrate that the intraoperative use of a nerve stimulator (conventional or quantitative) was associated with a reduced incidence of residual neuromuscular blockade.13 This finding should not be interpreted as indicating that there is no clinical advantage to using intraoperative neuromuscular function monitors, but rather that the widely cited studies are often poorly designed and inadequate in detecting any advantages that might be conferred by quantitative monitoring. Although quantitative neuromuscular function monitoring is frequently recommended, many anesthetics are given without such monitoring. This places even greater emphasis on using simple monitoring and routine pharmacologic reversal as vehicles for avoiding residual neuromuscular blockade. Do we need additional studies to prove that neuromuscular monitoring improves clinical outcomes? With regard to monitoring, prospective studies are needed to determine whether the intraoperative use of objective measurements of reversal (mechanomyographic or acceleromyographic TOF or double-burst stimulation) will decrease the incidence of critical respiratory events in the PACU.

Murphy et al.2 address several limitations of their study. Although a prospective observational trial may identify associations between residual paralysis and critical respiratory events, causality cannot be proven. Likewise, the investigators measuring the TOF ratios were not blinded to the patients’ obvious respiratory distress. Other limitations include the introduction of a delay between the patients’ admission to the PACU and the time of TOF fade measurement. It is therefore likely that the TOF on initial PACU admission was even lower than reported. For example, Murphy et al. noted that acceptable neuromuscular recovery (defined as a TOF ratio >0.90) was present in 90.5% of subjects in the control group, whereas the same authors reported a lower incidence (68%) in a similar clinical setting.14 Furthermore, in a study of patients undergoing orthopedic surgical procedures, Murphy et al.15 reported a 20.5% incidence of severe hypoxemia (SpO2 <90%) in patients in the PACU who had received rocuronium intraoperatively. This incidence is significantly less (P < 0.001, 2 test) than the 52.4% reported in the “cases” group of their current study. Could these differences be attributed to lack of blinding? Could bias have been introduced by the initial identification of patients with critical respiratory events (cases) by nurses in the study group, while investigators identified those in the control group? Furthermore, neither the cases nor the controls were prospectively matched for acuity of disease, and no a priori calculation of the number of patients necessary for statistical significance was considered. In defining critical respiratory events, some of the criteria were
subjective (e.g., “inability to breathe deeply when requested to by the PACU nurse”) and may have influenced the diagnosis. The choice of monitoring equipment may also have introduced variability. Acceleromyography has been shown to be only minimally sensitive to low levels of residual paralysis, and a minimum TOF ratio of 1.0 is needed to exclude residual weakness.16 Interestingly, Murphy et al. have chosen a “higher current” in an attempt “to increase the accuracy of TOF measurements.” Although experts debate the issue of the importance of supramaximal current for TOF monitoring,17 there is no indication of the precision of TOF measurements, as information on how often the measurements differed by more than 10% is lacking.

Despite these minor criticisms that are, for the most part, limitations of any observational design, the study by Murphy et al. reiterates that postoperative residual neuromuscular blockade continues to occur in the PACU. Critical respiratory events occurred despite: (1) intraoperative monitoring to guide the degree of neuromuscular relaxation; (2) intraoperative monitoring to document adequacy of reversal; (3) administration of neostigmine for reversal of neuromuscular block; and (4) delivery of clinical care by knowledgeable clinicians with significant experience in quantitative neuromuscular monitoring techniques. In the current environment of evidence-based medicine, production pressure, diagnosis-based reimbursement, and financial austerity, Murphy et al. have done our patients a huge service by underscoring the continuing morbidity associated with the use of muscle relaxants in the absence of objective means of assessment of neuromuscular recovery.

In summary, the data inexcusably associate low TOF ratios (TOF = 0.61 ± 0.25) with the occurrence of severe hypoxemia (SpO2 <90%). This report is seminal for several reasons: (1) it demonstrates that postoperative residual paralysis is associated with critical respiratory events; (2) it confirms that the “classical” threshold for recovery (TOF = 0.70) is insufficient to guarantee absence of critical respiratory events postoperatively; (3) it underscores the need for appropriate intraoperative assessment; (4) it confirms that reversal of competitive neuromuscular block by cholinesterase inhibitors has limitations; and (5) it dispels the myth that subjective intraoperative determination of adequacy of recovery (suggested by lack of visually or tactiley determined fade or clinical signs such as tidal volume) is sufficient to make clinical decisions about tracheal extubation and spontaneous respiration.

Future progress in achieving rapid return of neuromuscular function will probably result from some form of “chemical reversal” of residual block.18–21 Binding of free drug molecules in plasma such as the encapsulation of rocuronium and vecuronium by gammagadex or rapid degradation by amino acids of new relaxants still under development (gantacurium) should have a significant impact on the incidence of postoperative residual neuromuscular blockade.20,21 What Beecher and Todd remarked half a century ago might indeed have been prophetic: “These data suggest strongly that great caution in the use of the muscle relaxants should be exercised, that the agents available at present be considered as on trial, and that they be employed only when there are clear advantages to be gained by their use, that they not be employed for trivial purposes or as a corrective for generally inadequate anesthesia.”

REFERENCES


