"To Reverse or Not To Reverse?"

The Answer Is Clear!

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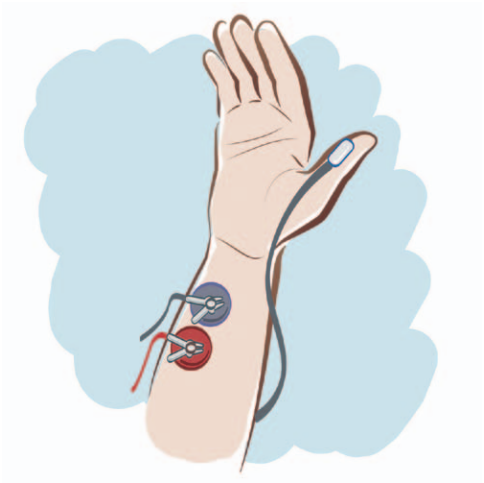
BY the late 1980s, it was well recognized that undetected postoperative residual neuromuscular block (PRNB) was a common occurrence in most postanesthesia care units (PACUs).[1–4] However, an editorial in 1989 noted that there was little, if any, objective evidence to validate the hypothesis that PRNB was associated with long-term or even transient adverse respiratory outcomes.[5] In the two and a half decades since the editorial by Miller[5] was published, outcome data regarding this important patient safety issue have slowly accumulated, but the relevant database remains quite sparse. In this issue of Anesthesiology, Bulka *et al.*[6] provide an important addition to the small list of studies that attempt to examine the long-term consequences of PRNB. They report two main findings: (1) the use of neuromuscular blocking agents (NMBAs) was associated with a higher absolute rate of postoperative pneumonia (POP) when compared to matched cases where patients did not receive relaxants and (2) failure to reverse NMBAs at the end of surgery was associated with a 2.25-fold increase in the incidence of POP. Why should these findings be less than surprising?



"The hazards of postoperative residual neuromuscular block are well-documented; reversal of neuromuscular blocking agents should be routine."

Bulka *et al.*[6] noted that the incidence rate ratio (1.79) for POP was significantly higher in patients who received NMBAs. This observation is consistent with the findings from several large database investigations, which have described an association between intraoperative NMBA use and major morbidity and mortality. More than 60 yr ago, Beecher and Todd[7] reported that the risk of death related to anesthesia was six times higher in patients receiving NMBAs compared to those administered no muscle relaxants. An analysis of data collected over a 10-yr period (1967 to 1976) involving 240,483 anesthetics revealed that "respiratory inadequacy after myoneural blockade" was the second most common cause of death after surgery.[8] Similarly, a study from Great Britain reported that postoperative respiratory failure secondary to dosing of NMBAs was a primary cause of mortality.[9] In a large prospective study, the use of the long-acting NMBA pancuronium entailed a higher risk of postoperative pulmonary complications.[10] More recent studies reported that patients administered NMBAs had a higher risk of postoperative desaturations and need for reintubation[11] and that those given high doses of NMBAs had an increased risk of postoperative respiratory complications.[12] The increased incidence of morbidity and mortality reported in patients administered NMBAs is likely secondary to PRNB. Incomplete neuromuscular recovery during a vulnerable postoperative period (between tracheal extubation and achieving a train-of-four [TOF] ratio of less than 0.9 in the PACU) may impair upper airway patency, protective airway reflexes, breathing, swallowing, and coughing, resulting in an increased risk of significant respiratory events (like POP) and death.

Data demonstrating an association between failure to reverse neuromuscular blockade and adverse postoperative outcomes are less certain. A large case–control database investigation revealed that the primary anesthetic management characteristic associated with a reduction in mortality and coma was reversal of the effects of NMBAs.[13] In a

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retrospective data analysis, pulmonary complication outcome scores were significantly improved in older patients with comorbidities reversed with sugammadex, compared to those reversed with neostigmine or not given reversal agents.[14] In contrast to these investigations, large-scale studies from the Massachusetts General Hospital suggested an association between neostigmine use and an increased risk of hypoxemia, atelectasis, and postoperative reintubation.[11,15] An important limitation of all of these investigations (as well as the study by Bulka *et al.*[6]) is that the presence or absence of PRNB was not measured in the PACU with quantitative monitoring; therefore, it is uncertain whether postoperative muscle weakness was the cause of the reported adverse events.

There is ample evidence that failure to antagonize nondepolarizing block may result in a very high incidence of PRNB. Baillard *et al.*[16] reported that 42% of patients who received vecuronium but no anticholinesterase had TOF ratios less than 0.7 on arrival to the PACU. A multicenter trial revealed that 95 of 175 patients (57%) administered cisatracuriums with no reversal agent had TOF ratios less than 0.9 in the PACU.[17] A recent observational study examined the incidence of PRNB when muscle relaxation was not antagonized and intraoperative monitoring of neuromuscular function was not performed.[18] On admission to the PACU, only 11% of elderly patients and 23% of younger patients had achieved an acceptable level of neuromuscular recovery ratio (TOF ratio less than 0.9)!

The authors of this editorial believe that appropriate doses of reversal agents (either neostigmine or sugammadex) should *always* be administered when NMBAs are used, unless full neuromuscular recovery has been documented with quantitative monitoring. In clinical practice, however, less than one third of anesthesiologists routinely administer anticholinesterase agents.[19] The reasons why many anesthetists fail to routinely reverse the residual effects of NMBAs are uncertain but, no doubt, multifactorial. Many clinicians still appear to harbor concerns regarding the administration of anticholinesterase/antimuscarinic drugs and associated adverse cardiovascular and respiratory effects, as well as the potential for an increased incidence of postoperative nausea and vomiting.[19] In addition, 80 to 90% of respondents to an international survey assert that they had *never* observed patients in the PACU with residual neuromuscular weakness.[19] There also appears to be a lack of appreciation of the duration of effect of an "intubating dose" of an NMBA. Two hours after a single 2 times the ED_{95} dose of a relaxant of intermediate duration, 37% of individuals will still not have recovered to a TOF ratio of 0.9 and 10% will still have TOF values less than 0.7.[20] Furthermore, the use of qualitative neuromuscular monitors (conventional peripheral nerve stimulators) may provide reassuring but misleading information to the clinician. Once the TOF ratio exceeds 0.4, most individuals can no longer detect the presence of fade by tactile or visual observation.[21,22]

Another reason for reluctance to administer neostigmine to reverse NMBAs may be related to concerns about the potential of this drug to produce paradoxical muscle weakness when administered at full neuromuscular recovery. In an attempt to understand why the use of NMBAs appears to be associated with an increase in the incidence of POP, Bulka *et al.*[6] suggest that neostigmine may contribute to severe postoperative respiratory complications when used in an unwarranted fashion (anticholinesterase administration when neuromuscular recovery is already almost complete). They cite several recent articles as the basis for this hypothesis.[15,23,24] Their thesis is also compatible with the assertions of Gross-Sundrup *et al.*[11] and Sasaki *et al.*[15] that neostigmine reversal increases the risk of postoperative desaturations and atelectasis. We are not convinced that neostigmine-induced block is the most likely explanation for the association between NMBA administration and POP.

A bit of history may be instructive. A study from 1980 demonstrated that in patients who were not given NMBAs, one or two injections of 2.5 mg neostigmine caused a substantial reduction in the peak tetanic contraction and severe tetanic fade, which persisted for about 20 min (although single twitch height was slightly potentiated).[25] These results were subsequently confirmed by Goldhill *et al.*[26] However, the decrement in tetanic tension observed was very brief, lasting not more than 10 min. The authors concluded that "even when considerable spontaneous recovery of muscle power has occurred, a single modest dose of reversal agent is unlikely to cause clinically important muscle weakness, and any effects are probably short lived."[26]

The duration of effect (residual paralysis) appears to be of critical importance. This concept was demonstrated in the only large-scale, randomized trial designed to examine the relationship between PRNB in the PACU and longer term outcomes (POP within 6 days of surgery).[27] In patients who received atracurium or vecuronium, the incidence of POP was approximately 5% and was unrelated to the TOF ratio upon arrival in the PACU. In patients who received the long-acting NMBA pancuronium with TOF ratios of less than 0.7, the incidence of POP was almost 17%. The conclusion is that *prolonged* as opposed to a transient postoperative weakness is a risk factor for pneumonia.

Muscle relaxants are often essential components of a balanced anesthetic technique; yet, they may produce life-threatening complications if not dosed and monitored appropriately. The findings of Bulka *et al.*[6] provide further support to the concept raised more than 60 yr ago that NMBA use is associated with increased morbidity. In order to optimize patient outcomes, clinicians should only administer NMBAs when clinically necessary. If NMBAs are needed intraoperatively, the lowest dose required for surgical relaxation should be used, the depth of neuromuscular blockade should be monitored, and NMBA administration should be minimized during the last hour of the procedure.

Ideally, neostigmine should not be administered until at least the fourth response to TOF stimulation appears; however, the time to achieve acceptable neuromuscular

recovery may be as much as 15 min in this setting, even after a large dose (0.06 to 0.07 mg/kg) of neostigmine.[28,29] Unless there is quantitative evidence that the TOF ratio at the adductor pollicis has returned to a value of more than or equal to 0.9, an appropriate dose of an anticholinesterase agent or sugammadex should be administered at the end of surgery. When no tactile or visual fade is detectable with TOF stimulation, reversal agents should still be administered since the TOF ratio may be as low as 0.4.[21,22] We are unaware of any clinical evidence that suggests that doses of neostigmine of 0.03 mg/kg or less may produce adverse respiratory effects, even when neuromuscular recovery is essentially complete.[30–33]

The investigation by Bulka *et al.*[6] adds important additional insights into our growing body of knowledge about the long-term risks of failure to reverse neuromuscular blocking agents. On the basis of existing data, we believe that the well-documented hazards of postoperative residual neuromuscular blockade outweigh any theoretical risks of paradoxical muscle weakness and that reversal of neuromuscular blocking agents should be routine.

Competing Interests

Dr. Murphy has served as a consultant for Merck. The other author declares no competing interests.

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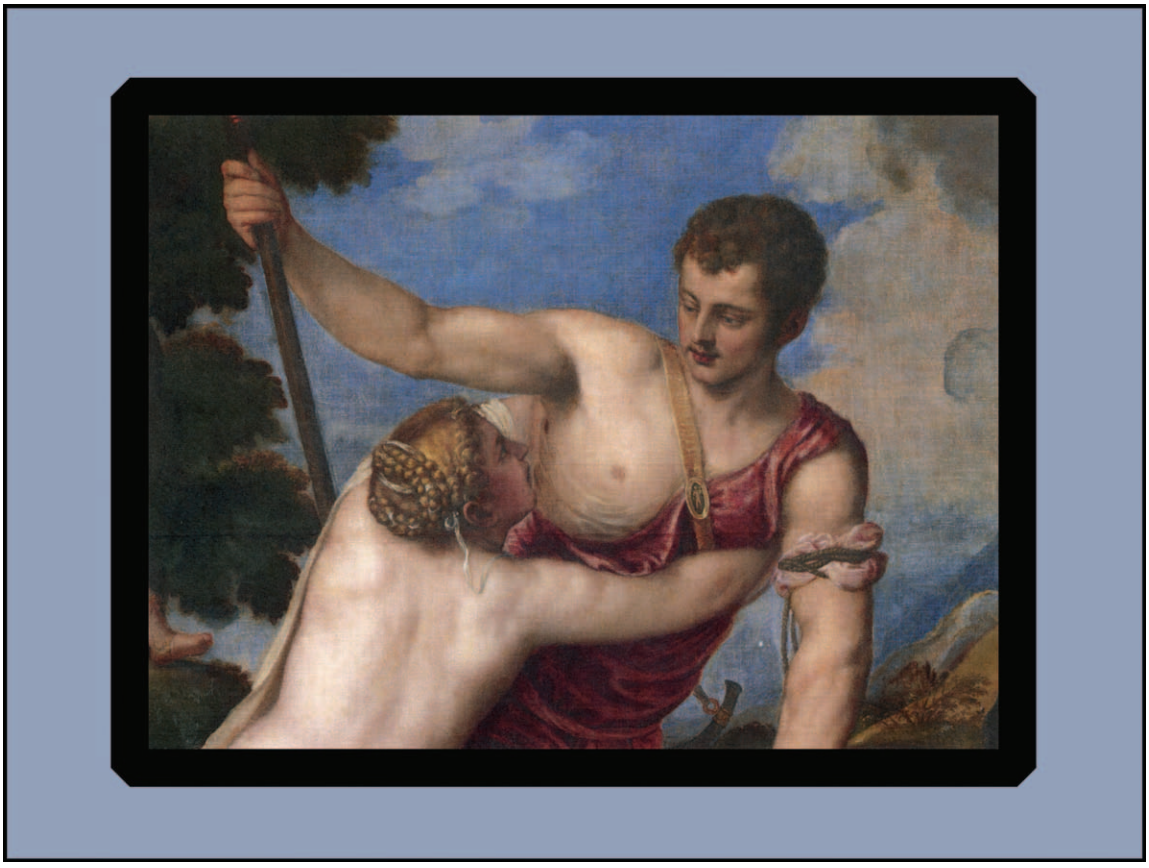
From *Venus and Adonis*: Shakespearean Inebriation and Colton Gas



As painted in 1554 by Titian, lovesick Venus (*left*) throws herself shamelessly at disdainful Adonis (*right*), her handsome foster son. In Shakespeare's narrative poem, *Venus and Adonis*, the goddess "treads the path that she untreads again" as she frets about the safety of Adonis. The Bard compares her behavior to "the proceedings of a drunken brain." The author of *Shakspeare* [sic] *and the Bible*, nitrous oxide pioneer G. Q. Colton (1814 to 1898) parlayed the American public's awareness of "drunken" behavior at recreational demonstrations of his "Colton gas" into public confidence in trying an apparently familiar agent, laughing gas, as an anesthetic for dental extraction. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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