Occasional Essay

Neuromuscular Blockade and Skeletal Muscle Weakness in Critically Ill Patients

Time to Rethink the Evidence?

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Neuromuscular blocking agents are commonly used in critical care. However, concern after observational reports of a causal relationship with skeletal muscle dysfunction and intensive care–acquired weakness (ICU-AW) has resulted in a cautionary and conservative approach to their use. This integrative review, interpreted in the context of our current understanding of the pathophysiology of ICU-AW and integrated into our current conceptual framework of clinical practice, challenges the established clinical view of an adverse relationship between the use of neuromuscular blocking agents and skeletal muscle weakness. In addition to discussing data, this review identifies potential confounders and alternative etiological factors responsible for ICU-AW and provides evidence that neuromuscular blocking agents may not be a major cause of weakness in a 21st century critical care setting.

Keywords: neuromuscular blockade; intensive care unit–acquired weakness; outcome

Neuromuscular blocking agents (NMBAs) are commonly administered to critically ill patients to induce muscular paresis. Extended administration of NMBAs is considered with caution due to the reported causal relationship with skeletal muscle dysfunction and the potential risk for development of intensive care–acquired weakness (ICU-AW) (1–3), a condition that has recently received significant clinical and research attention (4–8). This clinical integrative review complements the previous systematic review detailing the risk factors for ICU-AW (9) and evaluates the current published data on the relationship between the use of NMBAs and ICU-AW. Based on these current data, this review challenges the causal relationship between the use of NMBAs and skeletal muscle weakness. This integrative approach has distinct differences from that of a systemic review: the data have been interpreted in the context of our current understanding of the pathophysiology of ICU-AW and integrated into our current conceptual framework of clinical practice. The goal was to challenge the established clinical view and to inform clinicians that NMBA use in 21st century critical care does not have a clear causal relationship with ICU-AW.

We used PubMed and MEDLINE search engines to obtain all relevant abstracts and articles from January 1977 to December 2011. The search terms used were "depolarizing agent," "nondepolarizing agent," "neuromuscular blockade," "muscle relaxant," "intensive care unit–acquired weakness," "critical illness myopathy," "critical illness neuromyopathy," and critical illness polyneuropathy" (10). Only human studies were included in the search, and Boolean searches were performed with all search terms used alone or in combination.

NMBAs IN CLINICAL PRACTICE

Nondepolarizing agents (e.g., tubocurare, vecuronium, and atracurium) compete with acetylcholine (ACh) for binding at the nicotinic receptor level of the motor end plate. Depolarizing agents (e.g., succinylcholine) act as fixed agonists causing sustained opening of associated sodium channels, preventing further ACh-driven excitation. Bolus use of both depolarizing and nondepolarizing NMBAs facilitates endotracheal intubation, but data supporting more prolonged use of the nondepolarizing agents are limited. This is reflected by the recommendations of both the Brain Trauma Foundation and the National Institute of Clinical Excellence, which do not recommend the routine use of NMBAs in management of traumatic brain injury (11, 12). Furthermore, the data to support the use of NMBAs in the context of therapeutic hypothermia are similarly lacking (13). With the exception of a recent clinical trial investigating the effect of NMBAs on outcome in patients with adult respiratory distress syndrome, there are few randomized controlled trials to support the common indications for the use of NMBA (9, 14–16). Despite this weak evidence base, prolonged administration of nondepolarizing agents is frequent in clinical practice in the management of raised intracranial pressure after head injury and neurosurgery, patient-ventilator asynchrony, refractory respiratory failure, and therapeutic hypothermia (17–19). More recently, data detailing beneficial effects of NMBAs (14, 16) have been reported.

First reported in 1977, severe muscle weakness was described in patients exposed to a combination of mechanical ventilation, high-dose corticosteroids, and NMBAs (20–23). Based on the mode of action of NMBAs, a series of case reports continued to implicate them as causal (24–31), with more than 44 case reports

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published from 1977 to 1997 (32). Consequently, reviews and guidelines have cautioned clinicians of the risks associated with NMBA use (1, 3, 33–44). Indeed, there is biological plausibility for the proposed adverse effect. In addition to data reporting inhibition of myogenesis via the antagonism of trophic factors such as neuregulins (45, 46), animal models of denervation have demonstrated reduced sodium channel activity leading to muscle hypoexcitability (47). Furthermore, pharmacological denervation has been used repeatedly to model muscle atrophy secondary to immobilization (48, 49).

But is there a causal relationship between the use of NMBAs and skeletal muscle weakness? Weakness must be considered in terms of both the electropathophysiological process (nerve, neuromuscular junction, and muscle) and impaired muscle mass regulation during critical illness. Weakness is common in critically ill patients as a feature of (*1*) acute primary neuropathy (e.g., Guillain- Barré syndrome), (*2*) acute secondary myopathy (e.g., rhabdomyolysis [50]), (*3*) electrolyte imbalance (e.g., hypophosphatemia [51] and hypokalemia [52, 53]), (*4*) acute-on-chronic myopathy (e.g., malignancy-related [54] and as part of a preexisting cardiorespiratory disease such as chronic heart failure [55] and chronic obstructive pulmonary disease [56]). Acute primary myopathy may result from the marked reduction in muscle mass observed in the critically ill, with a 2 to 4% per day loss of fiber cross-sectional area (57, 58).

ICU-AW is the result of complex pathophysiological processes involving the nerves and muscles that determine the functional property of skeletal muscle. It can be subclassified, based on electrophysiological measurement, into critical illness myopathy, critical illness polyneuropathy, or critical illness neuromyopathy (10). Although the mechanism underlying this muscle loss remains to be clearly elucidated, protein malnutrition, systemic inflammation, and prolonged immobility are likely contributory factors (59, 60). As a result, such muscle loss will be most pronounced in the sickest patients—those most likely to require neuromuscular blockade. Thus, it is rational to consider that there is no, or at least only a weak, causal relationship between NMBA use and ICU-AW.

STUDIES AND TRIALS EVALUATING NMBAs

Table 1 describes the observational studies performed in the last 20 years reporting associations between NMBA use and ICU-AW. It must be highlighted that in addition to differences in study design (e.g., retrospective and prospective observational studies), the majority of studies included a heterogeneous critical care population and the detailed data collection across studies was variable. In particular, this is significantly notable for the collection of the illness severity data. The frequency of corticosteroid use was high in these studies. Steroid-induced myopathy is a well-described phenomenon whereby glucocorticoids induce catabolism, inhibit anabolism, and potentially exacerbate the effects of immobilization (61–63). Furthermore, the mean age between the studies is wide. Sarcopenia, or age-related skeletal muscle loss, is common in those individuals over the age of 65 years. Finally, the methodology to confirm or exclude ICU-AW varies among these studies. Current practice for diagnosing ICU-AW is to use standard electrophysiological tests and manual muscle testing (10), although the use of electrophysiological studies has limited value. Previous studies demonstrated that electrophysiological abnormalities occur early in critical illness and do not correlate with muscle function and outcome (64, 65).

Despite the current clinical concern of a causal relationship between NMBA use and skeletal muscle weakness, only 31% of the 16 studies (3 prospective and 2 retrospective) implicate NMBA use to be associated with ICU-AW. Segredo and colleagues studied 16 patients who received vecuronium infusions (longest duration of paralysis was 168 h) and demonstrated extended neuromuscular blockade after NMBA cessation (66), which is a completely different diagnosis from that of ICU-AW based on the current definitions (10). Three of the studies were performed in patients with severe life-threatening asthma, all of whom received very high dose corticosteroids (31, 67, 68). Adnet and colleagues performed a retrospective cohort study of ventilated patients with asthma in five centers (68). Despite the authors' conclusion that the use of NMBAs was the only independent predictor of ICU-AW, in a multiple regression analysis those receiving NMBAS had a greater severity of illness, demonstrated by the increased use of volatile gas ventilation to manage bronchospasm, adding a significant confounder to the appropriateness of the comparison. Douglass and colleagues reported 25 consecutive cases of acute asthma requiring mechanical ventilation (31). Twenty-one patients received vecuronium and all received corticosteroids. In this study, the use of vecuronium *per se* was not associated with myopathy. Behbehani and colleagues performed a multivariate analysis in a retrospective cohort study of patients with asthma receiving mechanical ventilation in two centers over a 10-year period (67). All 86 patients received intravenous corticosteroids and 30 patients received NMBAs for a mean of 3 days. Although 30% of patients receiving NMBAs developed ICU-AW, more than 10% of those who did not receive NMBAs also developed ICU-AW. The universal use of high dose corticosteroids was again a significant confounding factor. Although this would not wholly explain the between-group differences in prevalence of ICU-AW, review of the study design showed other important differences. Different total doses of NMBAs were used between the two recruiting centers, likely accompanied by a difference in total sedative dose, although these data were unavailable. These confounders could significantly influence the incidence of ICU-AW.

Garnacho-Montero and colleagues studied 73 critically ill patients with an electrophysiological diagnosis of ICU-AW. After multivariate analysis it was concluded that NMBA use was an independent risk factor for electrophysiological abnormality (69). In addition to the diagnostic limitations of such electrophysiological testing in critically ill patients unable to follow simple commands (5, 64, 70), in a subsequent study of 68 heterogeneous critically ill patients, undertaken by the same research group using the same diagnostic protocol, NMBA use was demonstrated not to be a cause of ICU-AW (71). In addition, and of major relevance to this discussion, was that excess sedative use was observed in those who developed ICU-AW (71).

More recently, Papazian and colleagues reported a study investigating use of cisatracurium on the outcome of patients with acute respiratory distress syndrome (14). Three hundred forty patients were randomized to receive 48 hours of cisatracurium or placebo. Although the primary outcome was 90-day survival, manual muscle testing was performed on the day of ICU discharge and on Day 28. No difference was observed between groups in the incidence of ICU-AW (29 vs. 32%, $P = 0.49$). Interestingly, in the subgroup that received corticosteroids there was no difference in the frequency of ICU-AW observed (37 vs. 30%, $P = 0.32$) (72). The other relevant randomized controlled trial involving NMBAs was performed by Forel and colleagues, albeit without an *a priori* decision to test for ICU-AW (16). In 36 patients randomized to receive 48 hours of neuromuscular blockade or placebo, there was no increased rate of ICU-AW observed. These more recent data support the view that short-term use of NMBA is not associated with in an increased incidence of ICU-AW (14, 16).

TABLE 1. OBSERVATIONAL STUDIES INVESTIGATING THE RELATIONSHIP BETWEEN NEUROMUSCULAR BLOCKING AGENTS USE AND INTENSIVE CARE–ACQUIRED WEAKNESS

Author	Year of Study	Mean Age (*yr*)	Diagnosis	Mean APACHE Score (SD)	Design	Frequency of ICU-AW	Steroid Use	Neuromuscular 1Blocking Agent Used	Mean Length of Use of Neuromuscular Blocking Agent (*d*)	Days Ventilated Prediagnosis of ICU-AW	Diagnostic Method for ICU-AW	Association with Neuromuscular Blocking Agent
Leijten *et al.* (117)	1995	<75	Heterogeneous	Not reported	Prospective observational	29/50	Not recorded	Vecuronium	Not reported	Not standardized	EP Testing	N (U)
Latronico *et al.* (70)	1996	50.2	Heterogeneous	Not reported	Prospective observational	24/24	4/24	Pancuronium or atracurium	For procedures only	Not standardized	Clinical examination	N (U)
Kesler *et al.* (98)	2009	39	Asthma	Not reported	Retrospective observational	10/74	All	Vecuronium or atracurium	2 patients	Not standardized	Clinical examination	N (U)
Leatherman *et al.* (97)	1996	38	Asthma	Not reported	Retrospective observational	20/96	All	Vecuronium or atracurium	1	Not standardized	Clinical examination	N (U)
Behbehani *et al.* (67)	1999	47	Asthma	14.3 (6.2)	Retrospective observational	9/86	All	Vecuronium or pancuronium	3.1	Not standardized	Clinical examination	Y (M)
Segredo *et al.* (66)	1992	45	Respiratory failure	Not reported	Prospective observational	7/16	None	Vecuronium	7	Not standardized	EP testing*	Y (U)
Witt *et al.* (118)	1991	43	Heterogeneous	Not reported	Prospective observational	30/43	Not recorded	Not recorded	Not reported	Not standardized	EP testing	N (M)
Douglass *et al.* (31)	1992	N/A	Asthma	Not reported	Prospective observational	9/25	All	Vecuronium	Not available	Not standardized	Clinical examination	Y (U)
Adnet *et al.* (68)	1995–1999	40	Asthma	Not reported	Retrospective observational	10/55	All	Pancuronium or vecuronium	4.2	Not standardized	Clinical examination	Y (M)
Nanas *et al.* (119)	2005–2006	55	Heterogeneous	15 (7)	Prospective observational	50/474	38/474	Not recorded	61 patients	Not standardized	Clinical examination	N (M)
De Jonghe *et al.* (5)	1999–2000	62	Heterogeneous	SAPS II 48.7	Prospective observational	23/95	26/95	Vecuronium	3.3	>7	Clinical examination	N (U, M)
Garnacho-Montero *et al.* (69)	1996–1999	62	Heterogeneous	17.5 (6.9)	Prospective observational	46/73	11/73	Vecuronium or atracurium	10/73	>10	EP testing	Y (M)
Campellone *et al.* (120)	1995–1995	53	Liver transplantation	24.4	Prospective observational	8/77	All	Pancuronium or vecuronium	Not reported	>7	Clinical examination	N (U,M)
de Letter *et al.* (121)	1994–1996	70	Heterogeneous	Not reported	Prospective observational	32/98	34/98	Vecuronium	Not reported	>15	Clinical examination	N (M)
Garnacho-Montero *et al.* (71)	1999–2002	61	Severe/sepsis	22.2	Prospective observational	34/64	Not reported	Vecuronium or atracurium	13/64	Not standardized	EP testing	N (M)
Bednarik *et al.* (122)	2000–2002	59	Multiorgan failure	SOFA 7	Prospective observational	17/61	None	Pipecuronium	Not reported	Not standardized	Clinical examination	N (M)

Definition of abbreviations: EP testing = electrophysiological testing; ICU-AW = intensive care unit–acquired weakness; M = multivariate; N = no; U = univariate; Y = yes.
*Limited to ulnar nerve stimulation.

SEDATION AS A POTENTIAL RISK FACTOR FOR ICU-AW

NMBA use, and subsequent immobilization, must always be accompanied by appropriate levels of sedation, which also sustain immobilization. Indeed, inadequate use of sedation in conjunction with NMBAs may exacerbate psychosocial morbidity in ICU survivors, although this is beyond the remit of this review. Prolonged immobilization results in electrophysiological dysfunction, decreased muscle protein synthesis, loss of muscle mass, and microvascular dysfunction (73–76). Although bed rest, antigravity, and hind limb suspension models simulate immobility, sedation should also be considered as an independent risk factor above the effects on immobilization. Propofol and benzodiazepines positively modulate the inhibitory function of the neurotransmitter γ-amino-butyric acid (GABA) (77, 78). GABA facilitates the opening of the voltage-gated chloride channels in skeletal muscle, which decreases muscle excitability (78, 79). Barbiturates and ketamine attenuate the response of excitatory neurotransmitters such as glutamate, decreasing muscle tone by acting on motor-associated neurons in the spinal cord via N-methyl-D-aspartate (NMDA) receptors (78, 80, 81). Thus, continued sedation could be expected to have a greater effect on muscle atrophy and muscle weakness than the conventional awake human and animal immobility models. This could explain the results of previous studies that have shown that ICU-AW was greater in those patients exposed to a higher sedative load (71). It is therefore reasonable to postulate the beneficial physical effects observed in studies using sedation protocols with sedation holds and reduced sedation load (82–85) are potentially the direct result of decreased frequency and severity of ICU-AW. There are no published data investigating the association of sedation level with ICU-AW or patient arousal and activity and ICU-AW. With current prevailing clinical practice favoring a more minimalistic approach to sedation and a proactive approach to mobilization (82–84, 86), clinicians may focus further on reducing the use of sedatives.

APPLICATION OF HISTORIC NMBA DATA IN THE 21ST CENTURY CRITICAL CARE SETTING

To interpret previous studies objectively, we need to consider the patient groups investigated and their clinical management. It must be acknowledged that the majority of data from previous uncontrolled studies indicating a causal relationship between NMBAs and ICU-AW were observations made during the last century (Table 1). Clinical practice has changed significantly over the last 20 years. The majority of patients included in these studies had primary ventilatory failure, and strategies of mechanical ventilation were markedly different from those currently practiced. In the 1980s and early 1990s, the most common ventilators used lacked the ability to support spontaneous ventilation through pressure-support (PS) modes, whereas others lacked a synchronized intermittent mandatory mode of ventilation. The commonest weaning mode used in the United States in the late 1980s was the use of mandatory breaths from intermittent mandatory ventilation, supplemented by

spontaneous breaths from a reservoir bag (87). In the early 1990s the use of synchronized intermittent mandatory mode of ventilation, PS, and bilevel positive airway pressure modes increased (88, 89), with PS mode finding an increasing role in weaning patients from mechanical ventilation (90, 91, 92), although individual practice differed between countries (93). With the limited technology and understanding of patients weaning from mechanical ventilation in the 1980s, critically ill patients received more prolonged periods of invasive mechanical ventilation with greater risk of ventilator-associated pneumonia and other infections combined with greater exposure to sedative agents. These risk factors, rather than a short period of NMBA *per se*, could potentially have resulted in an increase in the incidence of ICU-AW in these patients. Indeed, the use of neuromuscular blockade has decreased over time. In 1981, a survey of 34 intensive care units observed that 90% of patients were routinely administered NMBAs (94), which 12 years later had fallen to 9% (95, 96). If a causal relationship exists between NMBAs and ICU-AW, a corresponding decrease in ICU-AW should be evident. Leatherman and colleagues published a retrospective series of 96 patients with asthma requiring invasive ventilation admitted between 1983 and 1995, which found no association between NMBA use and ICU-AW (97). More importantly, the same research group, after a change in clinical practice with a goal to avoid muscle paralysis, compared the records of 74 patients with asthma admitted between 1995 and 2004. Again, there was no difference found in the incidence of ICU-AW despite this clear reduction in the use of NMBAs (20 vs. 14%, $P = 0.23$) (98). These data add support to the argument for a lack of causal relationship between NMBA use and ICU-AW.

TRANSLATIONAL PITFALLS WITH CRITICAL CARE ANIMAL MODELS

Basic mechanistic studies investigating the effect of NMBAs on peripheral skeletal muscle structure and function have been performed using critically ill rodent models. Although these animal models are necessary to provide insight in mechanistic process, the clinical usefulness of extrapolating animal work to humans is limited in some areas. Muscle physiology studies highlight the dissociation between animal models and humans (99–102). For example, total protein turnover in adult rats is three to four times greater than in humans, with approximately a 2.5-fold greater protein synthetic rate (99, 103). A recent review details animal studies in which very short periods of muscle unloading (5 h) initiate a proteolytic response in animals, whereas humans regularly unload their muscles for protracted periods (e.g., during sleep) with no such effect (104). Despite these limitations, animal studies are instructive in the mechanisms and intracellular pathways governing muscle wasting. Larsson and colleagues have led this field of animal work, building on the model developed by Dworkin (105, 106). These critical care models demonstrated loss of muscle mass, decreased myosin heavy chain to actin ratio (107), altered ubiquitin proteasome pathway signaling, and glucocorticoid receptor expression (108). Their most recent work demonstrated loss of myosin, down-regulation of transcription factors for protein synthesis, and significant muscle atrophy (109). However, their model differs significantly from current clinical management of critically ill patients, as the animal model incorporates isoflurane anesthetic and α-cobratoxin as an NMBA, which is used continuously for 6 to 14 days. Although this must be considered a major criticism of this model, this model has similarities to the observational studies in patients with asthma, which also used volatile gas anesthesia in the management of severe bronchospasm. More interestingly, a porcine model has been developed that will allow for longitudinal studies of greater time periods yielding further insights (110–114). As in human studies, it must be highlighted that these animal studies are unable to separate the effect of NMBA use from the effect of sedation use for obvious ethical reasons.

FUTURE CLINICAL AND RESEARCH PRACTICE

In 21st century critical care clinical practice, short-term use of NMBAs does not appear to be a risk factor for ICU-AW. Indeed, independent causality of ICU-AW by NMBAs has yet to be clearly demonstrated. In those clinical scenarios in which the use of NMBA may decrease mortality, the recommendation is that NMBA should be used for short periods without caution. The concerns that NMBAs cause ICU-AW need to be modified, and further evidence from observational cohort studies and randomized controlled trials is required. Meanwhile, such is the importance of muscle weakness that we consider that the assessment of peripheral skeletal muscle function an essential feature of all future critical care clinical trials. This could be as either a primary or secondary outcome measure similar to other usual measured parameters, such as illness severity score, days of mechanical ventilation, and length of stay (115).

Finally, separating neuromuscular blockade from immobilization and sedation as causative factors in the pathogenesis of ICU-AW is likely to be difficult through prospective randomized trials. However, research tools do exist that can provide greater insights. Physical activity, as measured using vector unit triaccelerometry, can quantify passive and active physical movement in patients when accompanied by detailed diary carding. It is therefore feasible to incorporate activity monitoring into clinical trials during early, recovery, and rehabilitative stages of critical illness to investigate the relationship between muscle wasting, physical activity, NMBA use, and sedative use. This would facilitate differentiating the effects of NMBAs, sedatives, immobility, and bed rest *per se*. In addition, as clinical weakness assessment requires patients to have sufficient cognitive function and motivation, we need objective measures of muscle wasting to act as biomarkers of muscle weakness. Rectus femoris cross-sectional area measured using B-mode ultrasound is a future potential tool for this (116).

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