Review Article

Neuromuscular Blocking Agents and Neuromuscular Dysfunction Acquired in Critical Illness: A Systematic Review and Meta-Analysis

David R. Price, MD[1,3]; Mark E. Mikkelsen, MD, MSCE[2,3]; Craig A. Umscheid, MD, MSCE[1,3]; Ehrin J. Armstrong, MD, MSc[4,5]

Objective: The relationship between neuromuscular blocking agents and neuromuscular dysfunction acquired in critical illness remains unclear. We examined the association between neuromuscular blocking agents and ICU-acquired weakness, critical illness polyneuropathy, and critical illness myopathy.

Data Sources: PubMed, EMBASE, Web of Science, Cochrane Central Register of Controlled Trials, Cumulative Index of Nursing and Allied Health Literature, and bibliographies of included studies were searched from database inception until September 24, 2015.

Study Selection: Randomized controlled trials and prospective observational studies examining the association between neuromuscular blocking agents and ICU-acquired weakness, critical illness polyneuropathy, or critical illness myopathy.

Data Extraction: One author screened titles/abstracts. Two authors independently reviewed full text and extracted data from included studies. Meta-analysis was performed using the DerSimonian-Laird random effects model (OpenMetaAnalyst 10.10 for OS.X). We assessed reporting bias with funnel plots and heterogeneity with the I^2 statistic.

Data Synthesis: Of 2,170 titles/abstracts screened, 99 full texts were selected for review, yielding one randomized controlled trial and 18 prospective observational studies, for a total of 2,254 patients. The randomized controlled trial did not show an association between neuromuscular blocking agents and neuromuscular dysfunction acquired in critical illness (odds ratio, 1.21; 95% CI, 0.67–2.19), but pooled data from all included studies suggested a modest association (odds ratio, 1.25; 95% CI, 1.06–1.48; $I^2 = 16\%$). Funnel plots suggested reporting bias, and sensitivity analyses showed a disproportionate contribution from critical illness polyneuropathy/critical illness myopathy and severe sepsis/septic shock studies.

Conclusions: This meta-analysis suggests a modest association between neuromuscular blocking agents and neuromuscular dysfunction acquired in critical illness; limitations include studies with a high risk of bias and a disproportionate contribution from studies examining patients for critical illness polyneuropathy/critical illness myopathy and those with severe sepsis/septic shock. (*Crit Care Med* 2016; 44:2070–2078)

Key Words: acquired polyneuropathies; agents, neuromuscular blocking; critical illness polyneuropathy; neuromuscular blockers; nondepolarizing muscle relaxants; polyneuropathy

The association between neuromuscular blocking agents (NMBAs) and neuromuscular dysfunction acquired in critical illness remains unclear. The possibility of an association led to diminished usage of NMBAs (1) and recommendations for cautious use of these agents in select patient populations, such as those with severe sepsis (2). More recently, after NMBAs were shown to improve oxygenation (3) and mortality (4) in patients with moderate to severe acute respiratory distress syndrome (ARDS), this controversial topic reemerged as a relevant and important one to the practice of critical care medicine.

Clinicians and researchers attempting to parse this literature face a daunting task. First, there is great "variation in terminology and nosology" that characterizes the literature examining neuromuscular dysfunction acquired in critical illness, inclusive of ICU-acquired weakness (ICUAW), critical illness polyneuropathy (CIP), and critical illness myopathy (CIM) (5).

[1]Division of General Internal Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA.

[2]Division of Pulmonary, Critical Care and Sleep Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA.

[3]Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA.

[4]Division of Cardiology, University of Colorado, Denver, CO.

[5]Department of Medicine, University of Colorado, Denver, CO.

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For information regarding this article, E-mail: drp9007@nyp.org

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Although we agree that ICUAW is presently the most clinically relevant umbrella term for weakness syndromes acquired in critical illness (5–7), this term fails to capture early studies that detected neuromuscular abnormalities in patients prior to awakening when clinical strength testing could not be attempted (8–12). The aim of this review is to better understand if NMBAs adversely impact neuromuscular function, from clinical weakness to clinically undetectable nerve and muscle dysfunction. Thus, we use neuromuscular dysfunction acquired in critical illness as an umbrella term inclusive of ICUAW, CIP, and CIM.

Second, heterogeneity of findings exists across the studies that have examined the association between NMBAs and neuromuscular dysfunction acquired in critical illness. Several studies have shown an association between NMBAs and neuromuscular dysfunction acquired in critical illness independent of potential confounders (9, 13), whereas others have failed to support this finding (10, 14, 15). A recent randomized trial also failed to demonstrate an association (4). Reviews of this topic have similarly failed to agree (7, 16, 17). These previous reviews had limitations: the 2007 review by Stevens et al (7) and the 2012 review by Puthucheary et al (16) did not meta-analyze individual studies and the 2013 review by Alhazzani et al (17) only reviewed randomized controlled trials (RCTs) of NMBAs in early ARDS from one study group.

Since a systematic review inclusive of observational studies was last published in 2007 (7), nine studies, including one RCT, were published. In this review, we provide an updated systematic review and the first meta-analysis inclusive of observational studies to examine the association between NMBAs and neuromuscular dysfunction acquired in critical illness.

METHODS

Data Sources

PubMed, EMBASE, Web of Science, Cochrane Central Register of Controlled Trials, and CINAHL were searched from inception until September 24, 2015, for RCTs and prospective observational cohort studies by linking keywords and structured language for NMBAs and for neuromuscular dysfunction acquired in critical illness. The search strategy is provided in **Supplemental Table 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/B849). Bibliographies of included studies were reviewed for additional citations.

Study Selection

One study investigator (D.P.) screened the initial titles/abstracts (**Fig. 1**). Studies were included for full-text review if they were RCTs or prospective observational cohort studies and reported on the association of NMBAs and objective measures of ICUAW, CIP, or CIM. Two study authors (D.P.; M.M.) then independently screened all full text for inclusion and exclusion criteria (**Supplemental Table 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/B850). Disagreements on study inclusion and exclusion were resolved by consensus. If consensus could not be reached, a third author (C.U.) resolved the disagreement.

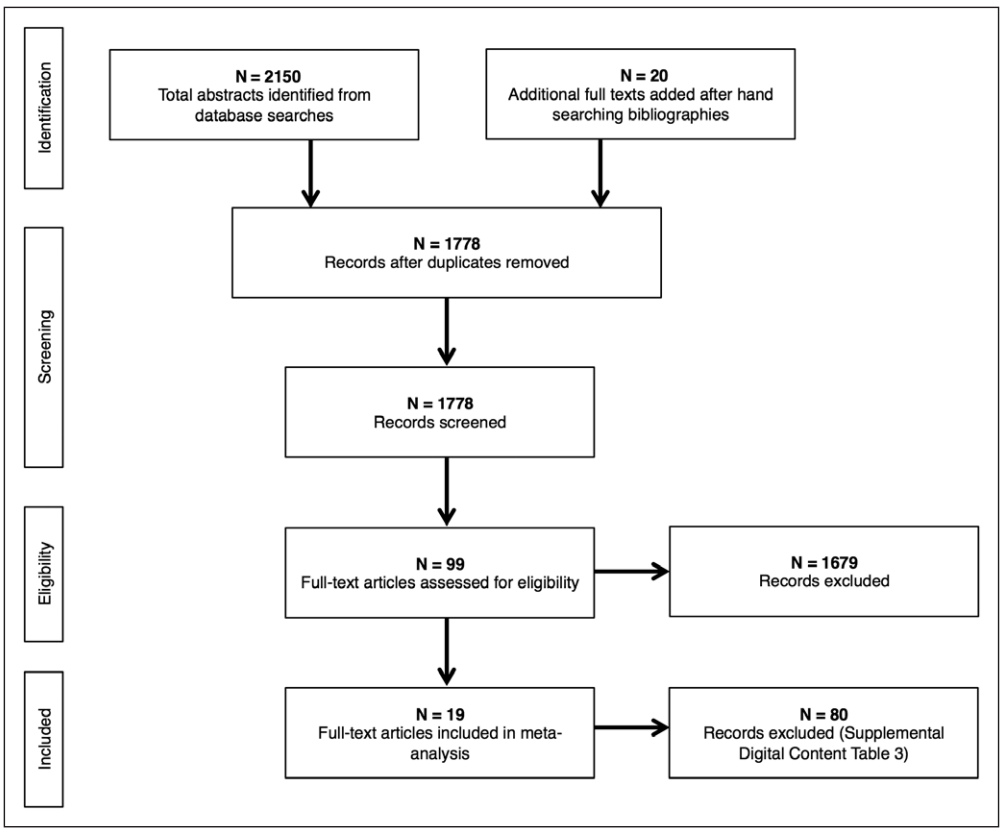

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. To access **Supplemental Table 3**, please use this link: Supplemental Digital Content 3, http://links.lww.com/CCM/B851.

Data Extraction and Risk of Bias Assessment

Data were extracted independently by study authors (D.P.; M.M.). Unadjusted event rates of ICUAW, CIP, and CIM were calculated by dividing the number of patients with neuromuscular dysfunction who were given a NMBA by the total number given an NMBA. When data were not available, study authors were contacted. Disagreements on data extraction were resolved by consensus with C.U. resolving the disagreement if needed.

The risk of bias assessment was performed using standard tools for those study designs examined, including the Cochrane Collaboration tool (18) for RCTs and the Newcastle-Ottawa Scale for prospective cohort studies (18).

TABLE 1. Study Characteristics

Study	Country	Setting	Study Design	Study Population
Fan et al (20)	United States	ICU	Cohort	MV and acute lung injury
Hermans et al (36)	Belgium	Cardiac ICU, MICU, SICU	Cohort	ICU > 8 d
Derde et al (12)	Belgium	MICU, SICU	Cohort	MV
Brunello et al (13)	Switzerland	ICU	Cohort	MV > 48 hr and systemic inflammatory response syndrome
Papazian et al (4)	France	ICU	Randomized controlled trial	MV < 48 hr and acute respiratory distress syndrome
Ali et al (25)	United States	ICU	Cohort	MV > 5 d and awake
Nanas et al (27)	Greece	MSICU	Cohort	ICU > 10 d
De Jonghe et al (19)	France	MICU, SICU, MSICU	Cohort	MV > 7 d and awake
Hermans et al (35)	Belgium	MICU	Cohort	MV > 7 d
Amaya-Villar et al (37)	Spain	ICU	Cohort	MV, chronic obstructive pulmonary disease, and corticosteroids
Bednarik et al (26)	Czech Republic	ICU, neurologic ICU	Cohort	2 organ failures
Garnacho-Montero et al (10)	Spain	MSICU	Cohort	MV ≥ 7 d and sepsis or septic shock
De Jonghe et al (14)	France	MICU, SICU	Cohort	MV > 7 d and awake
de Letter et al (15)	The Netherlands	MSICU	Cohort	Day 4 of MV
Garnacho-Montero et al (9)	Spain	MSICU	Cohort	MV >1 d and sepsis with multiple-organ failure
Leijten et al (11)	The Netherlands	MSICU	Cohort	MV > 7 d
Verheul et al (38)	The Netherlands	ICU	Cohort	MV
Coakley et al (42)	England	ICU	Cohort	> 7 d and organ failure
Douglass et al (31)	Australia	ICU	Cohort	MV for severe asthma

– = not reported, CIM = critical illness myopathy, CIP = critical illness polyneuropathy, ICUAW = ICU-acquired weakness, MB = muscle biopsy, MICU = medical ICU, MSICU = medical surgical ICU, MV = mechanical ventilation, NMD = neuromuscular dysfunction, SICU = surgical ICU.

[a]Ranges included when study provided patient characteristics by the study group instead of by total patients.

Data Analysis

OpenMetaAnalyst version 10.10 for OS.X (Center for Evidence-based Medicine, Brown University, Providence, RI; http://www.cebm.brown.edu/openmeta/index.html) was used to calculate odd ratios and conduct meta-analyses using the DerSimonian-Laird random effects model. When a trial included both univariate and multivariate data, the multivariate data were used. Heterogeneity was quantified using the I^2 statistic with an I^2 less than 40% considered low heterogeneity (18). Rev-Man 5.3 (Cochrane Review Manager Software; Nordic Cochrane Center, Copenhagen, Denmark) was used to create funnel plots to assess for reporting bias. Sensitivity analyses examined 1) the RCT and prospective cohort studies with the lowest risk of bias, 2) the RCT and prospective cohort studies with multivariate adjustment, 3) observational studies with multivariate adjustment, 4) studies examining ICUAW as an outcome, 5) studies examining CIP as an outcome, 6) studies examining CIM as an outcome, 7) studies examining CIP or CIM, and 8) studies with severe sepsis or septic shock as an inclusion criteria. p values less than 0.05 were considered statistically significant.

RESULTS

The initial title/abstract screen yielded 94 studies for full-text review; further review of the bibliographies of these studies yielded five additional studies. Nineteen studies met inclusion criteria and served as the basis for this study; interrater agreement between study authors evaluating full texts for inclusion was 94%. Thirteen authors were contacted for unpublished data with six responding; additional data from three included studies (8, 19, 20) were provided by the contacted authors. The most common reasons for study exclusion were insufficient data reported and study design not RCT or prospective observational cohort (**Supplemental Table 3**, Supplemental Digital Content 3, http://links.lww.com/CCM/B851).

n	NMD	Examination	NMD	No NMD	ICU/Hospital Length of Stay (d) [a]	Septic Shock (%)	ICU Mortality (%)
173	ICUAW	Clinical	63	110	13/–	–	–
244	ICUAW	Clinical	122	122	3–6/23–36	–	4–7
57	CIM	MB	18	39	10–27/–	–	–
39	ICUAW	Clinical	13	26	10–17/–	–	–
201	ICUAW	Clinical	68	133	–/–	–	52–63
136	ICUAW	Clinical	35	101	12–21/20–34	24	–
185	ICUAW	Clinical	44	141	–/–	–	20–36
116	ICUAW	Clinical	76	40	24/45	50	16
412	CIP	Electromyography	188	224	14/–	–	36–42
26	CIM	MB	9	17	11–24/21–33	–	18–33
61	CIP	Electromyography	35	26	–	–	–
64	CIP	Electromyography	34	30	23–47/33–85	–	10–21
95	ICUAW	Clinical	24	71	26–45/–	30–38[a]	6–17
96	CIP	Electromyography	36	60	–/–	–	–
73	CIP	Electromyography	50	23	–/–	100	52–66
38	ICUAW	Clinical	18	20	–/–	–	20–44
19	ICUAW	Clinical	9	10	–/–	–	–
23	CIM	MB	22	1	–/–	–	–
25	ICUAW	Clinical	9	16	–/–	–	–

Description of Included Studies

Characteristics of included studies are listed in **Table 1**. The 19 included studies included 2,254 patients. One trial was a RCT, whereas 18 were included as prospective observational cohort studies. Five observational studies performed multivariate adjustment when examining the association between NMBAs and neuromuscular dysfunction acquired in critical illness. Ten studies (one RCT and nine observational) evaluated ICUAW with eight using the Medical Research Council scale for weakness. Six studies (all observational) evaluated CIP, and three (all observational) evaluated CIM. Each study's neuromuscular evaluation, including scale used to evaluate weakness, electrophysiologic outcomes, and use of muscle biopsy, is listed in **Supplemental Table 4** (Supplemental Digital Content 4, http://links.lww.com/CCM/B852).

ICU mortality differed significantly across studies. Fourteen studies were limited to patients on mechanical ventilation, whereas the other five included both ventilated and nonventilated patients. Two studies focused on patients with severe sepsis or septic shock, two focused on patients with multiple-organ failure, and two studies were limited to patients with acute lung injury or ARDS. Fifteen of the 19 studies excluded patients with preexisting weakness. Four of the 19 studies reported cumulative dosing of NMBAs, whereas seven reported the number of days NMBAs were given; reporting of dosing and duration of therapy were inadequate to allow for sensitivity analyses.

The overall risk of bias of the randomized trial was low (**Supplemental Table 5*a***, Supplemental Digital Content 5, http://links.lww.com/CCM/B853). The risk of bias of the prospective observational cohort studies was high in general (**Supplemental Table 5*b***, Supplemental Digital Content 5, http://links.lww.com/CCM/B853). Thirteen of the 18 observational studies received no points for comparability, as they did not report multivariate data for NMBAs. Ten observational studies also did not comment on who assessed the primary outcome (i.e., who did the

weakness examination) and whether those assessments were independent of the patient care team. Four observational studies were low risk of bias as they satisfied all quality criteria.

Neuromuscular Dysfunction Acquired in Critical Illness

When pooled together (**Fig. 2**), the 19 studies included 2,254 people and showed an unadjusted event rate of neuromuscular dysfunction acquired in critical illness of 51% in patients exposed to NMBAs and 39% in the unexposed control group; this difference was statistically significant (odds ratio [OR], 1.25; 95% CI, 1.06–1.48; I^2 = 16%) with low heterogeneity between studies. The funnel plot for these studies (**Fig. 3**) suggests a reporting bias possibly resulting from small studies with strong associations (Amaya-Villar et al (37), Leijten et al (11), Verheul et al (38), and Douglass et al [31]), as well as studies requiring severe sepsis or septic shock for patient inclusion (Garnacho-Montero et al [10] and Garnacho-Montero et al [9]).

Studies at the Lowest Risk of Bias

A summary of the sensitivity analyses is listed in **Table 2**. The one RCT enrolled 340 patients of whom 201 were able to receive a weakness examination and did not show an association between NMBAs and ICUAW (OR, 1.21; 95% CI, 0.67–2.19). Rates of ICUAW were 27% in those exposed to NMBAs versus 26% in the unexposed control group. Four observational studies satisfied all the low risk of bias criteria and were meta-analyzed with the RCT (**Supplemental Fig. 1*a***, Supplemental Digital Content 6, http://links.lww.com/CCM/B854; **legend**, Supplemental Digital Content 7, http://links.lww.com/CCM/B855) to show the pooled effect size of studies with the lowest risk of bias. The pooled OR was not statistically significant (OR, 1.31; 95% CI, 0.92–1.86; I^2 = 48%). A subsequent sensitivity analysis (**Supplemental Fig. 1*b***, Supplemental Digital Content 6, http://links.lww.com/CCM/B854; legend, Supplemental Digital Content 7, http://links.lww.com/CCM/B855) included the RCT and five studies that performed multivariate adjustment for confounding variables, as this was the most important risk of bias criteria for the observational studies. The pooled OR again was not statistically significant (OR, 1.24; 95% CI, 0.99–1.54; I^2 = 38%). Heterogeneity in both analyses was driven by a point estimate of 16.34 in the 2001 observational study by Garnacho-Montero et al [9]; this study was given minimal weight in the pooled analyses secondary to its wide CI.

Studies Examining Severe Sepsis or Septic Shock

The two studies (all observational, **Supplemental Fig. 1*h***, Supplemental Digital Content 6, http://links.lww.com/CCM/B854; legend, Supplemental Digital Content 7, http://links.lww.com/CCM/B855) that required severe sepsis or septic shock for inclusion included 139 patients and showed an unadjusted event rate in the exposed group of 83% versus 57% in the unexposed group. This was the largest pooled effect size of all the subgroups studied with a significant OR of 5.36 (95% CI, 1.56–18.46; I^2 = 1%) with minimal heterogeneity between studies.

ICUAW, CIP, and CIM

Ten studies (one RCT and nine observational studies) had data on ICUAW with 1,404 patients included. These studies showed an unadjusted event rate of 48% in those exposed to NMBAs versus 35% in the unexposed control group (OR, 1.21; 95% CI, 1.03–1.41; I^2 = 0%) with no heterogeneity between studies. The six studies (all observational) that included data on CIP showed a higher unadjusted event rate of 61% in those exposed to NMBAs versus 45% in the unexposed group (OR, 2.03; 95% CI, 1.33–3.09; I^2 = 0%) with no heterogeneity between studies. Finally, three studies (all observational) included data on the outcome of CIM with 106 total patients. The unadjusted event rate in those exposed to NMBAs was 48% versus 43% in the unexposed group with a nonsignificant pooled effect size (1.07; 95% CI, 0.77–1.49; I^2 = 1%) and low heterogeneity.

DISCUSSION

Interest in NMBAs has been revitalized because these agents were shown to confer a mortality benefit in patients with moderate to severe lung injury (4). Because patients with neuromuscular dysfunction acquired in critical illness wean more slowly from the ventilator (8–10, 14, 19, 21–23), have longer recovery periods (13, 24), and have higher mortality rates (9, 23–25), it is critical to understand the association between NMBAs and these acquired neuromuscular disorders. In this meta-analysis, our primary analysis found that patients who receive NMBAs experience a 25% greater odds of ICUAW, CIP, or CIM than those not exposed. Although our meta-analysis revealed a modest association, this finding should be viewed within the context of our sensitivity analyses and the limitations of the included studies.

First, our sensitivity analyses revealed a possible survivor bias: specifically, the odds of neuromuscular dysfunction when given an NMBA were increased 73% in CIP/CIM studies compared with 21% in ICUAW studies. ICUAW studies require patient participation and as a result systematically exclude more severely ill patients who are known to have a higher incidence of neuromuscular dysfunction (13, 15, 26, 27) As an example, the study by Ali et al (25), which measured ICUAW, excluded 38 patients. The 38 excluded patients had higher mortality rates (68% vs 13%) and higher average APACHE III scores (102 vs 66) than patients included in the trial. Conversely, CIP and CIM studies include the most severely ill patients.

An alternative explanation for this stronger association seen in CIP and CIM studies is that electrophysiologic studies and muscle biopsy are more sensitive for detecting neuromuscular dysfunction than clinical examinations. The increased sensitivity of electromyography was demonstrated by Fletcher et al (28) in their 2003 long-term follow-up study of survivors of critical illness. Despite normal Barthel indices in 15 of 22 patients and normal strength examinations in 18 of 22 patients, 21 of 22 had electromyography evidence of chronic partial denervation.

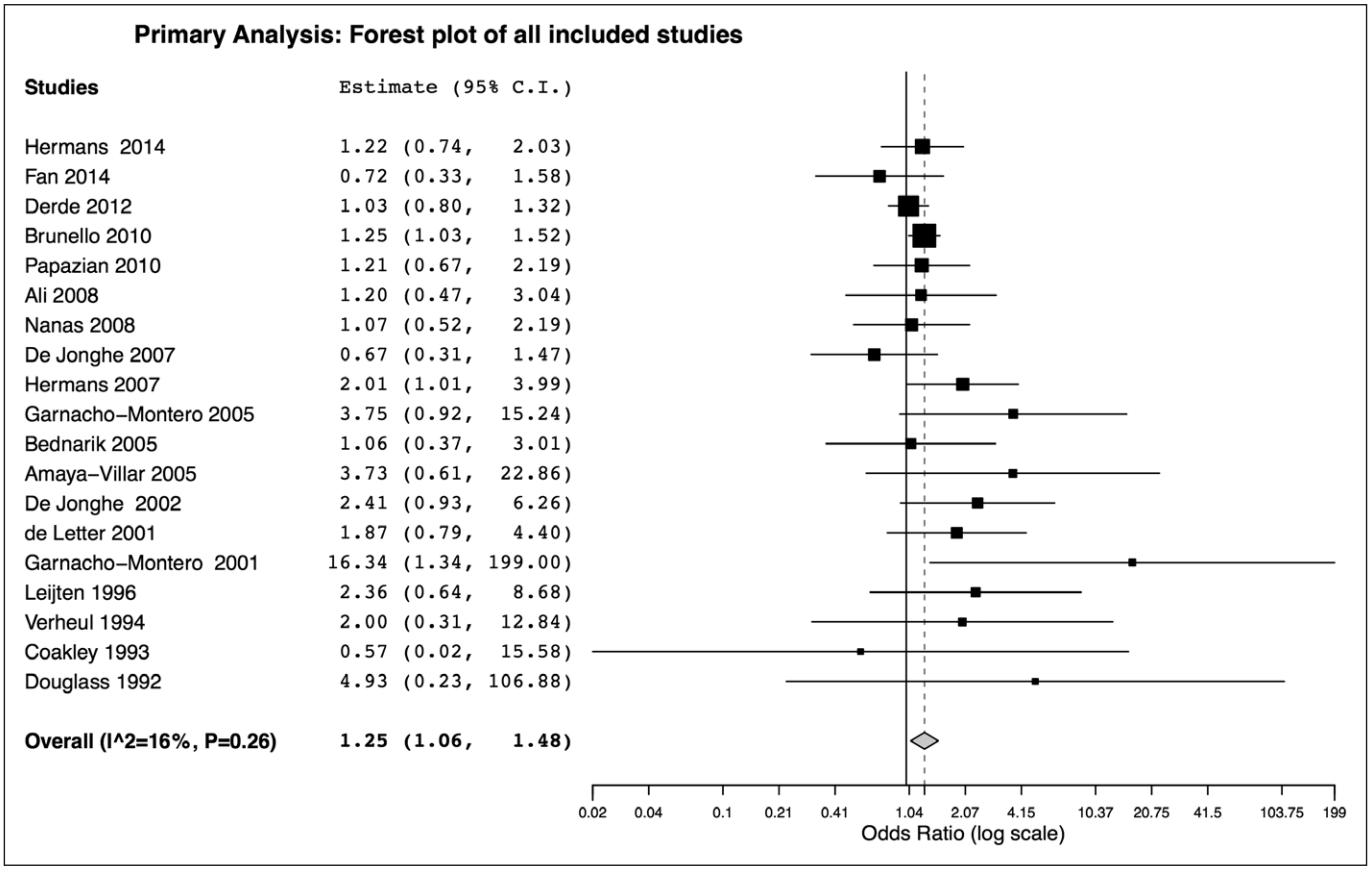

Figure 2. Primary analysis: Forest plot of all included studies.

Second, our sensitivity analyses found that studies limited to patients with severe sepsis or septic shock demonstrated the strongest association between NMBAs and neuromuscular dysfunction acquired in critical illness; inadequate reporting of patients with sepsis (as opposed to severe sepsis or septic shock) precluded this group from being included in this analysis. Both of the studies in the severe sepsis or septic shock sensitivity analysis evaluated for CIP. The first case series to describe CIP, published by Bolton et al (34) in 1984, implicated sepsis in its pathogenesis. Subsequent analyses that adjusted for confounders (13) also supported sepsis as an independent risk factor. Our analysis provides additional support that an association between NMBAs given to patients with sepsis and neuromuscular dysfunction acquired in critical illness exists, and consistent with prior work (9, 29), the association may be proportional to the severity of sepsis. Specifically, as demonstrated in Supplemental Figure 1*h* (Supplemental Digital Content 6, http://links.lww.com/CCM/B854; legend, Supplemental Digital Content 7, http://links.lww.com/CCM/B855),

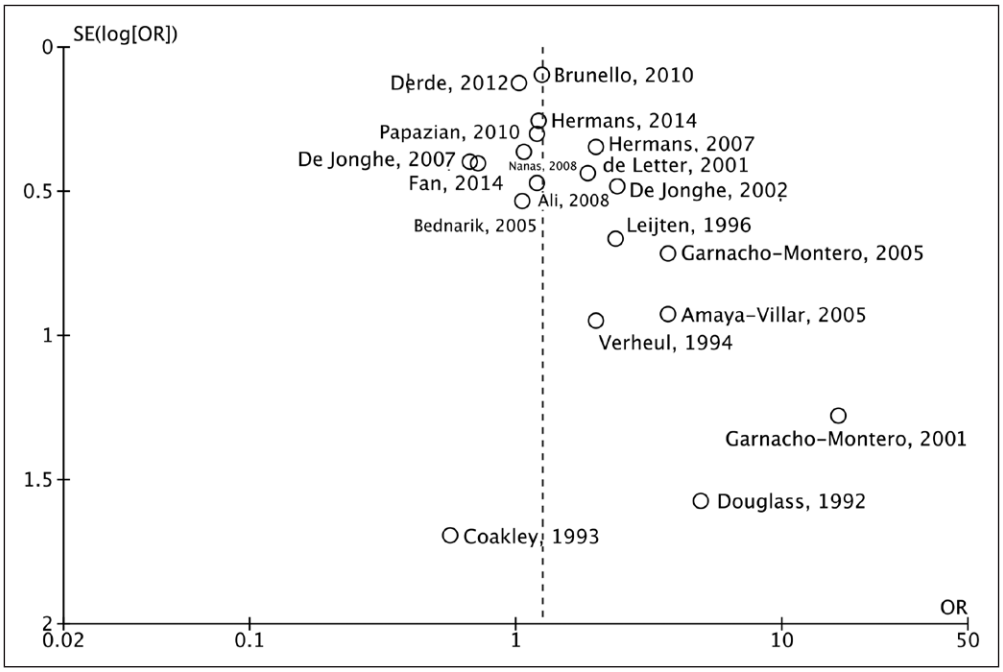

Figure 3. Primary analysis: Funnel plot of all included studies. OR = odds ratio.

TABLE 2. Sensitivity Analyses

Analyses	RCT	Observational Studies	*n*	Event Rate,[a] Neuromuscular Blocking Agents (%)	Event Rate,[a] Control (%)	OR	95% CI	I^2 (%)
Primary analysis	1	18	2,254	51	39	1.25	1.06–1.48	16%
Randomized controlled trial	1	0	201	27	26	1.21	0.67–2.19	
RCT and studies with the lowest risk of bias	1	4	1,320	54	41	1.31	0.92–1.86	48
RCT and studies with multivariate data	1	5	1,359	54	40	1.24	0.99–1.54	38
Observational studies with multivariate data	0	5	1,158	60	41	1.26	0.98–1.64	50
ICU-acquired weakness	1	9	1,404	48	35	1.21	1.03–1.41	0
CIP	0	6	744	61	45	2.03	1.33–3.09	0
CIM	0	3	106	48	43	1.07	0.77–1.49	2
CIP or CIM	0	9	850	58	45	1.73	1.11–2.69	43
Severe sepsis or septic shock	0	2	139	83	57	5.36	1.56–18.46	1

CIM = critical illness myopathy, CIP = critical illness polyneuropathy, OR = odds ratio, RCT = randomized controlled trial.
[a]Event rates are unadjusted. ORs reflect adjusted data when available as outlines in the *Methods* section of the article.

the study enrolling more severely septic patients (Garnacho-Montero et al [9]) found a larger association on multivariate analysis (OR, 16.34; 95% CI, 1.34–199) than the one study that enrolled less severely ill patients (Garnacho-Montero et al [10]; unadjusted OR, 3.75; 95% CI, 0.92–15.25).

Paradoxically, a recent retrospective cohort study using propensity matching conducted by Steingrub et al (30) observed a 12% reduction in in-hospital mortality among patients with severe sepsis requiring mechanical ventilation who received NMBAs during the first 48 hours of their ICU course compared with those receiving NMBAs after 48 hours. The patients who benefited from NMBAs received the drug for an average of 1.5 days. The risk reduction seen with NMBAs was lost if patients received the drug for more than 2 days or as a continuous infusion. Because the ARDS et Curarisation Systematique trial (4) showed the benefit of NMBAs in early ARDS, it is possible that clinicians are limiting NMBAs to short (e.g., 48 hr) intervals to improve short- and long-term outcomes. Our forest and funnel plots (Figs. 2 and 3) support this argument; studies published after ACURASYS show a consistently weaker association between NMBAs and neuromuscular dysfunction acquired in critical illness.

Our study should be interpreted in the setting of the limitations of the studies included in the systematic review. First, 18 of the 19 studies were observational studies that performed limited to no adjustment for potential confounders between NMBAs and neuromuscular dysfunction acquired in critical illness. Neuromuscular dysfunction acquired in critical illness has been associated with severity of illness (8, 11, 13–15, 27), glucocorticoids (12–14, 31–33), vasopressors (13), sepsis (8, 13, 15, 34), aminoglycoside antibiotics (27), hyperglycemia (27), female sex (14), duration of mechanical ventilation (14), hyperosmolality (9), parenteral nutrition (9), and neurologic failure (9). Of the 18 included observational studies, only five performed adjustment for these potential confounders.

When adjustments for severity of illness and other relevant confounders were performed, the pooled effects from these studies demonstrated either no association or a small nonstatistically significant association between NMBAs and neuromuscular dysfunction acquired in critical illness. These studies (Fig. 2, Hermans et al (36), Derde et al (12), Brunello et al (13), Hermans et al (35), and Garnacho-Montero et al [9]) had the most narrow CIs, likely reflecting low variance after adjustment for confounders was performed. Our study suggests that adjustment for these factors, through randomization (4, 12), multivariate analysis (9, 12, 13, 35, 36), or stratification to examine effect modification, is necessary to more precisely understand the association between NMBAs and neuromuscular dysfunction acquired in critical illness.

Another limitation of this review was the apparent reporting bias resulting from the publication of smaller studies with strong associations (11, 31, 37–39). Amaya-Villar et al (37), Leijten et al (11), Verheul et al (38), and Douglass et al (31) were small studies with high risk of bias (Supplemental Table 5*b*, Supplemental Digital Content 5, http://links.lww.com/CCM/B853) published in the early years of defining neuromuscular dysfunction acquired in critical illness. The studies by Douglass et al (31) and Amaya-Villar et al (37) were also performed in intubated asthmatics or patients with chronic obstructive pulmonary disease who received high-dose glucocorticoids, a pharmacotherapy previously associated with CIM (40).

CONCLUSION AND RECOMMENDATIONS

Our review suggests a modest association between NMBAs and neuromuscular dysfunction acquired in critical illness; however, this conclusion requires qualification. First, NMBAs were less commonly associated with clinical weakness (ICUAW) than they were with electromyography (CIP) or muscle biopsy (CIM) evidence of neuromuscular dysfunction. Although this may reflect a survivor bias, we, and others (5, 6, 41), believe that ICUAW is a more important patient-centered outcome. Second, our analysis suggests an increased risk of CIP in severely septic or septic shock patients or more severely ill patients exposed to NMBAs. In this population, clinicians should be cautious with NMBAs and target early use and limited exposure to limit the harm of these drugs while reducing the risk of CIP. Last, we found that studies in our review at the lowest risk of bias, including the RCT and the prospective cohort studies that performed multivariable adjustment, suggested a small but not statistically significant 24–31% increased odds of developing neuromuscular dysfunction acquired in critical illness. RCTs, such as the Re-evaluation of Systemic Early Neuromuscular Blockade trial (https://clinicaltrials.gov/ct2/show/NCT02509078) or prospective observational studies designed to adjust for variables previously associated with neuromuscular dysfunction acquired in critical illness are urgently needed to address this fundamental question.

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