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Neuromuscular Blocking Agents during Mechanical Ventilation of Patients with Acute Respiratory Distress Syndrome: A Review of Clinical Effectiveness and Guidelines

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Abbreviations

RCT	randomized controlled trial
NMBA	neuromuscular blocking agent
ARDS	acute respiratory distress syndrome
PEEP	positive-end-expiratory pressure
ICU	intensive care unit
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
FIO_2	fraction of inspired oxygen
PaO_2	partial pressure of oxygen
PICO	Patient, Intervention, Comparator and Outcome

Context and Policy Issues

Acute respiratory distress syndrome (ARDS) is a form of lung injury. It is characterized by inflammation, hypoxemia, respiratory failure and alveolar opacity.[1] Patients with ARDS may develop progressive dyspnea symptoms and increasing oxygen requirements. The underlying lung injury can be caused by different conditions including, for example, pneumonia or trauma.[2] In moderate and severe ARDS, invasive mechanical ventilation is often required.[3]

Neuromuscular blocking agents (NMBA) are often used during mechanical ventilation for treatment for ARDS. This class of drugs paralyzes patients and can be non-depolarizing or depolarizing. Non-depolarizing NMBAs competitively block acetylcholine receptors, while the second works by depolarizing the sarcolemma of the muscle fibre such that it cannot be further stimulated by acetylcholine. Non-depolarizing agents are more commonly used in clinical practice.[4] A 2016 survey of Canadian practice found NMBAs were used in 42% of severe ARDS patients, with 76.6% receiving a continuous infusion. Cisatracurium is the primary choice.[5]

The paralysis induced by NMBAs can facilitate ARDS treatment. Though the exact mechanism of benefit is unclear,[6] NMBAs may prevent undue alveolar stress because they reduce patient–ventilator dyssynchrony.[7] Using NMBAs has also been found to reduce barotrauma,[1,3] improve oxygenation[3] and reduce hospital mortality.[8] They may facilitate mechanical ventilation in particular management situations; one study demonstrated NMBAs were more likely to be used in mechanically-ventilated patients with complications such as respiratory acidosis, higher positive-end-expiratory pressure (PEEP), permissive hypercapnia and in patients in prone position.[9]

Though commonly used, there are also potential harms of using NMBAs in patients with ARDS. NMBAs have previously been associated with prolonged neuromuscular weakness.[10] They may also increase depression and symptoms of post-traumatic stress, or result in cardiopulmonary complications.[11] The relative benefits and harms remain unclear. The objective of this report is to summarize the evidence regarding the clinical effectiveness, safety and guidelines for the of use NMBAs in ARDS patients.

Research Questions

1. What is the clinical effectiveness of neuromuscular blocking agents during mechanical ventilation of patients with acute respiratory distress syndrome?

2. What are the evidence-based guidelines regarding the use of neuromuscular blocking agents during mechanical ventilation of patients with acute respiratory distress syndrome?

Key Findings

Neuromuscular blocking agents may be beneficial in patients with moderate and severe acute respiratory distress syndrome. One systematic review found that using neuromuscular blocking agents is associated with lower mortality, while one randomized controlled trial did not find a significant difference in effectiveness and was stopped early due to futility. One non-randomized study did not find a difference in effectiveness between cisatracurium and atracurium, while another study found cisatracurium was more effective than vecuronium. Guidelines generally had had weakly favourable recommendations for the use of neuromuscular blocking agents in early moderate to severe acute respiratory distress patients, based on a moderate quality of evidence.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Neuromuscular blocking agents and Acute respiratory distress syndrome. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and October 10, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients with acute respiratory distress syndrome (ARDS) in the intensive care setting
Intervention	Mechanical ventilation with a continuous or bolus infusion of any neuromuscular blocking agent (NMBA) (e.g., rocuronium, cisatracurium, atracurium)
Comparator	Q1: Mechanical ventilation without a NMBA Mechanical ventilation with an alternative NMBA Mechanical ventilation with a different dose of the same NMBA (e.g. to attain a different level of paralysis) Q2: No comparator

Outcomes	Q1: Clinical effectiveness (e.g., survival, health related quality of life, skeletal muscle function, long term care needs) and safety (e.g., deaths in hospital, cardiovascular events, long term muscle weakness/myopathy, length of stay in hospital, length of stay in ICU) Q2: Evidence-based guidelines for the appropriate use of NMBA during mechanical ventilation of patients with ARDS
Study Designs	Systematic reviews, randomized controlled trials, non-randomized studies, evidence-based guidelines

NMBA = Neuromuscular blocking agent; ICU = Intensive care unit; ARDS = Acute respiratory distress syndrome.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, they were a primary study already included in a systematic review or were published prior to 2014. Guidelines with unclear methodology were also excluded, as were studies that only considered NMBA administration during the initial tracheal tube intubation without subsequent continuous infusion.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using AMSTAR,[12] randomized and non-randomized studies were critically appraised using the Downs and Black checklist,[13] and guidelines were assessed with the AGREE II instrument.[14] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 165 citations were identified in the literature search. Following screening of titles and abstracts,150 citations were excluded and 15 potentially relevant reports from the electronic search were retrieved for full-text review. 10 potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 15 publications were excluded for various reasons, and 10 publications met the inclusion criteria and were included in this report. These comprised one systematic review, one RCT, two non-randomized studies and six evidence-based guidelines. Appendix 1 presents the PRISMA[15] flowchart of the study selection.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

One systematic review with meta-analysis was included.[16] This study included RCTs only, excluding animal studies, observational studies, and trials of pediatric patients. The authors' search included articles published from database inception to April 2018 and retrieved from the Cochrane central register of controlled trials, PubMed databases, or Wanfang Data. Five RCTs with a total of 551 patients were ultimately included.[16]

One multicentre, open-label RCT[1] and two non-randomized studies were also included.[17,18] The RCT was conducted by the Prevention and Early Treatment of Acute Lung Injury

(PETAL) Clinical Trials Network of the National Heart, Lung, and Blood Institute (NHLBI) between January 2016 and April 2018. This study included 48 U.S. hospitals. Of the non-randomized studies, one was a retrospective cohort study at a single centre conducted between July 2012 and 2015.[18] The other was a prospective cohort study conducted using records from the Permier Incorporated Perspective Database between January 2010 and 2014.[17]

Finally, six guidelines were included.[6,7,19-22] They were developed by six different groups including the Société de Réanimation de Langue Française in France,[19] the Faculty of Intensive Care Medicine and Intensive Care Society in the UK,[20] the Japanese Society of Respiratory Care Medicine and the Japanese Society of Intensive Care Medicine,[7] the American College of Critical Care Medicine,[6] the Korean Society of Critical Care Medicine and Korean Academy of Tuberculosis and Lung Diseases,[21] and the Scandinavian Society of Anaesthesiology.[22]

All the guidelines used Grading of Recommendations Assessment, Development and Evaluation group (GRADE) methodology to assess the evidence and strength of the recommendations except one,[21] which instead used the Cochrane Risk of Bias tool to assess evidence and subsequently ranked recommendations as strong or weak.[21] The remaining guidelines ranked recommendations as strong or weak in accordance with GRADE. The French guideline used the terminology 'optional' rather than weak for a Grade 2 recommendation. This grade was specified as something that should "probably" (pg. 2) be done.[19] In the Korean guideline, grade 2 also represented a 'weak' recommendation and evidence was ranked as A, B or C, or high, moderate or low quality.[21]

All but one guideline also limited included literature to systematic reviews and RCTs only and reported evidence quality, while two guidelines did not explicitly state the study designs included,[19,21] and one did not describe the quality of the evidence apart from the strength of the recommendation.[19] To determine final recommendations, one used majority opinion,[20] two required full consensus within the guideline panel,[6,7] one used a modified Delphi technique and required 50% agreement with an 80% response rate,[21] in another, recommendations were iteratively reformulated and rated until 70% of experts agreed.[15] In the French guidelines, 50% of experts had to agree (with less than 20% disagreement) for consideration and recommendatioations were iteratively reformulated to reach 70% agreement.[19] The last guideline was unclear.[19,22]

Country of Origin

The systematic review authors were from China,[16] the primary studies were all based in the U.S.[1,17,18] and the guidelines were from France,[19] the UK,[20] Japan,[7] the U.S.,[6] Korea,[21] and Scandinavia, including experts from Denmark, Finland, Iceland, Norway, and Sweden.[22]

Patient Population

The systematic review included studies of adult patients with moderate to severe ARDS, the exact definition of which was PaO_2:FIO_2 ratio < 150 mm Hg in four of the included trials and PaO_2:FIO_2 ratio ≤ 200 mm Hg in one trial. The population sizes ranged from 24 to 339, but further detail on the population was not provided.[16]

The one RCT also included adult patients with moderate-to-severe ARDS defined as PaO_2:FIO_2 ratio < 150 mm Hg. These patients had to have had ARDS for 48 hours or less, a PEEP of 8 cm or more of water, bilateral pulmonary opacities on chest radiography or on computed tomography and respiratory failure.[1] 1006 patients, 501 in the intervention group

and 505 in the control group, were included with an average age of 56 and 44% were female.

Of the two non-randomized studies, one used an International Classification of Disease-9-Clinical Modification (ICD-9-CM) diagnostic of ARDS, or an ARDS risk factor including acute hypoxemic respiratory failure, pneumonia, sepsis, trauma, burns, and other diagnoses or treatments,[17] while the other required a diagnosis of ARDS with PaO_2:FIO_2 < 150 mm Hg.[18] Both studies required eligible patients to be administered an NMBA, including i) a two-day continuous infusion of cisatracurium or vecuronium[17] and ii) cisatracurium or atracurium within 72 hours of ARDS presentation.[18] The average age was 51.9 and 30.5% of a total 6925 patients in the full analysis were female in the first study, which also conducted a propensity score analysis with a smaller sample size of 1901.[17] In the other non-randomized study, the average age was 52.1 and 49% of the total sample of 76 was female.[18]

The primary cause of lung injury leading to ARDS in two primary studies was pneumonia,[1,18] while it was unclear in the other one.[17] The most common reasons for exclusion were achieving PaO_2:FIO_2 >200 mmHg before randomization,[1] having already received an NMBA at enrollment[1,18] and not meeting the diagnosis of ARDS.[18] Two studies excluded pregnant women,[1,18] while the third did not state this as an exclusion criterion.[17] All the primary studies took place in an ICU setting.

Three of the six guidelines stated intended users and target populations as health care providers caring for adult patients with ARDS,[7] clinicians treating adult patients with ARDS in medical and surgical ICUs,[6] and practitioners caring for adult patients in an early phase of ARDS and invasive mechanical ventilation[19] The remaining three guidelines[20-22] included studies of adult patients with ARDS however did not clearly state the intended guideline user.

Interventions and Comparators

The systematic review included trials of any NMBA compared to placebo or usual treatment (which excluded other NMBAs).[16] There was no restriction placed on the type, dose or duration of NMBAs.

The RCT compared cisatracurium to usual care. In the intervention group, an intravenous bolus of 15 mg cisatracurium was administered, followed by a 48-hour continuous infusion of 37.5 mg cisatracurium with deep sedation. Usual care included no routine NMBA and lighter sedation targets, however an intravenous bolus injection of 20mg cisatracurium was allowed in both groups if patients' end-inspiratory plateau pressure was sustained at greater than 30 cm water for 10 minutes.[1]

Both the non-randomized studies compared different NMBAs. One compared a 48-hour continuous infusion of cisatracurium to vecuronium. The dose was unspecified.[17] The other compared cisatracurium to atracurium. The median dose of cisatracurium was 2.5 mcg/kg/min, with a median duration of 2.6 days. The median dose of atracurium was 1.9 mcg/kg/min, with a median duration of 2.5 days.[18]

All the guidelines considered the use of NMBAs in adult patients with ARDS, without further specification of types, doses or durations.

Outcomes

All primary studies considered mortality as an outcome. The systematic review did not further specify the type of mortality but ultimately included four trials which considered 21 to 28-day mortality and ICU mortality. The systematic review also considered 48-hour improvement in PaO_2:FIO_2, reduction of plateau pressure and PEEP at 48 hours.[16]

The RCT's primary outcome was all-cause mortality at 90 days, while a secondary outcome was also in-hospital death at day 28. It further included as secondary outcomes days free of ventilation at day 28, days not in the ICU at day 28 and days not in hospital at day 28.[1] The study measured adverse events, survival at three, six and 12 months, disability (score from 0 to 10 based on 10 Katz Activity of Daily Living, Lawton Instrumental Activities of Daily Living, and Nagi scale where higher scores are worse), health-related quality of life (EuroQol-5D-5 level score), patient-reported health (five point scale where 1 was excellent health), pain interference (five point scale where 1 was no interference), post-traumatic stress symptoms (Posttraumatic Stress Symptoms-14 score which ranges from 14 to 98; higher scores mean more symptoms) and return to work at three, six and 12 months. Cardiovascular outcomes were assessed using Sequential Organ Failure Assessment scores. Physical activity was assessed using a condensed ICU mobility scale where zero was not actively moving and ten was walking independently without gait aid.[1]

Both non-randomized studies studies also measured hospital mortality.[17,18] In one of the studies, mortality was a secondary outcome while change in PaO_2:FIO_2 from baseline to 72 hours after NMBAs was the primary outcome.[18] The other study did not specify primary versus secondary outcomes. Both studies also measured ventilator days, ICU days, and hospital days.[17,18] One study additionally measured discharge to home versus elsewhere.[17]

The guidelines all considered mortality, with two further specifying 28 days,[7,20] hospital, six and 12 month mortality[20] and ICU mortality[7] The guidelines additionally considered days of mechanical ventilation,[22] hypoxemia and barotrauma,[21] barotrauma and myopathy,[7] ICU and hospital length of stay, quality of life and harms at three, six and 12 months.[20]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Systematic Reviews

The systematic review included a comprehensive search of Cochrane Central Register of Controlled Trials, PubMed databases, and Wanfang Data, supplemented with hand searching reference lists without language restrictions. Two investigators conducted the screening and extraction, however it was unclear whether this was done independently reducing the reliability of the screening. Two authors did independently assess quality using the Cochrane Risk of Bias tool. The statistical analysis accounted for heterogeneity by planning to employ a random effects meta-analysis which could account for the variation where necessary, however they did not end up detecting heterogeneity between studies when measured using I^2. A funnel plot was used to determine that there was no evidence of publication bias, however with only five trials, this interpretation is not necessarily accurate. The study did not state a clear research question in terms of Patient, Intervention, Comparator and Outcome (PICO), did not refer to a pre-published protocol and provided limited detail on the patient characteristics of the included trials.

Randomized Controlled Trials

Subjects in the RCT had similar characteristics at baseline in the intervention and control group, minimizing the risk of confounding due to unbalanced patient factors. It did not report on the drugs used for sedation between the groups which may affect outcomes. The study was underpowered because it calculated 90% power to reject the null hypothesis of no difference with 1408 patients while only 1006 were included. This suggests that the study may attribute a true difference between the intervention and control groups to chance, though given the trial was stopped early because outcomes were similar in both groups, it is unlikely that an effect would have been detected. Further, allocation to treatment groups was not concealed, and the study was unblinded. Both increase the potential for differences in the way the treatment groups' care was handled based on practitioners' knowledge of which group patients are in, which could affect their outcomes. The assessors who interviewed survivors were, however, blinded. A binomial model by treatment group was used for statistical analysis, which was an appropriate for the research question.[1]

Non-Randomized Studies

Both non-randomized studies' subjects had similar baseline characteristics across intervention and comparator groups, minimizing the risk of confounding that would explain any observed effect.[17,18] One of these employed propensity score matching, a technique that matches control patients with similar characteristics to intervention patients which the authors demonstrated improved similarity between the groups overall. This study also employed an analysis without the matching to assess the sensitivity of their results.[17]

One study conducted an appropriate statistical analysis that included the treatment hospital as a random effect in their model which would reduce the chance that hospital-specific factors could explain any observed effect.[17] The other study based treatment versus comparator differences on *P*-value statistics alone, did not present information on precision and did not adjust their *P*-value criterion for multiple comparisons.[18] The latter means that any observed effect has a greater than five percent probability of being by chance rather than a true effect. Neither study included a power calculation, however one included 6925 patients, limiting concern that they were underpowered,[17] while the other had 76 patients at a single-centre which may not have been enough subjects to detect an effect.[18]

The patient population in one study may have included non-ARDS patients because those with ARDS risk factors and not necessarily a diagnosis code were included.[17] This contamination may limit the generalizability to ARDS patients if the effects are inadvertently driven by people without ARDS. Further, the study did not list exclusion criteria or list intervention and comparator dosage, making the precise population, intervention and comparator that resulted in the observed effect unclear.[17] The other study may have had unobserved differences between intervention and control groups because treatment allocation was based on availability, i.e. the intervention, cisatracurium, was a first choice but there might have been shortages. Those given a particular drug may have been sicker if providers were rationing the drugs based on what they thought was more effective.[18]

Guidelines

All six guidelines used a well-known validated tool to guide their development process including GRADE,[6,7,19,20,22] AGREE II[21] and the Cochrane Risk of Bias Tool for evidence quality.[21] They all provided a rating of the strength of the recommendations and five of the six also provided ratings of the quality of evidence.[6,7,20-22] All guidelines had a clear purpose and clearly identifiable recommendations, however three of these did not state a clear

intended user.[20-22] One guideline did not describe a standard process for achieving consensus on the final recommendations.[22]

Two of the guidelines did not describe their literature search methodology preventing assessing comprehensiveness,[19,21] while the remaining guidelines described a comprehensive search strategy[6,7,20,22] and three explicitly stated PICO questions.[7,20,22] These suggest that the search was systematic. Two guidelines employed standard statistical methods to meta-analyse data including random effects to handle heterogeneity,[7,22] while the remaining guidelines did not describe meta-analysis methods.[6,19-21]

Patient perspectives were considered in the development of one guideline,[7] as it included a variety of stakeholders ranging from physicians to pharmacists to patients in a guideline panel discussion group.[7] For further validation, the guideline was posted online for public comment, enabling additional perspectives.[7] No other guideline stated a validation process or effort to include patients, though one highlighted that lay members were part of the guidelines group.[20] Rather, the panels included clinicians[19,21,22] or did not describe the panel's background[6,20] which could limit perspectives on deciding the final recommendations. Finally, only one guideline included a plan for updating.[22]

Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions.

The clinical effectiveness of neuromuscular blocking agents during mechanical ventilation of patients with acute respiratory distress syndrome

NMBA was found to be beneficial compared with placebo in the systematic review. It was associated with significantly reduced 21-28 day mortality and ICU mortality.[16] However, in one RCT and one non-randomized study, no difference in mortality measures was observed when comparing cisatracurium to usual care,[1] or cisatracurium to atracurium[18]. Conversely, patients administered vecuronium had significantly higher odds of hospital mortality than those given cisatracurium.[17]

Compared to vecuronium, patients in the cisatracurium group had significantly lower mean difference in ICU days, ventilator days in both the matched sample and full sample, and higher odds of discharge to home in the non-propensity score -matched analysis only.[17] However, there were no significant differences in ventilator free days, days in/not in the ICU and days in/not in hospital[1,18] when comparing NMBA to usual care[1] and cisatracurium to atracurium.[18]

The RCT found a significant difference in the mean level of physical activity up to day six in the control group as well as a lower number of serious cardiovascular events (n=14 versus n=4; $P = 0.02$). There were no other differences in three, six and 12 month outcomes.[1] This trial was stopped at the second interim analysis due to futility, (i.e. the trial would not have been able to detect a significant effect associated with cisatracurium due to the similarity between outcomes at this time point).[1]

Two studies found significant improvement in oxygenation at 48 hours measured in terms of PaO2:FIO2[16,18] and plateau pressure and PEEP[16] in the NMBA group compared to placebo[16] and the cisatracurium group compared to atracurium.[18]

Evidence-based guidelines regarding the use of neuromuscular blocking agents during mechanical ventilation of patients with acute respiratory distress syndrome

Five of six guidelines had a weak favourable recommendation to use an NMBA in patients with ARDS.[6,7,20-22] The recommendations were specific to patients with early severe ARDS,[22] moderate to severe ARDS,[20] in patients with PaO_2:FIO_2 ratio < 150[6] or < 200.[7] in four of the guidelines. Four guidelines based their recommendations on moderate evidence quality.[6,7,20-22] The remaining guideline had a Grade 2+ strong agreement recommendation, meaning an 'optional' recommendation with at least 70% agreement among experts, to use an NMBA in patients with PaO_2:FIO_2 < 150 mm Hg as long as it was administered within 48 hours of starting ARDS.[19]

Recommendations were based on significantly improvement in mortality outcomes,[6,7,19,20,22] oxygenation[6,19,21] and lower barotrauma.[6,7,21] The evidence underlying recommendations was based on the same three randomized trials conducted by one French group in four guidelines.[6,7,19,21] In addition to these trials, one guideline[19] included the same two non-randomized studies included in this rapid review.[17,18] The others identified systematic reviews as their evidence base.[20,22]

Where described, the quality was downgraded to moderate in the guidelines due to imprecision of the effect estimates,[6,22] concern about providers knowing patients' treatment allocation group,[6,20] and indirectness.[7] One guideline found that findings related to ICU-acquired weakness and duration of mechanical ventilation outcomes were at a high risk of bias.[6] In the Japanese guidelines, the recommendation was downgraded because cisatracurium, the drug used in all included trials, was unavailable in Japan.[7] One guideline was unclear about reasons for the given evidence quality rating,[21] while the other did not explicitly rate or describe evidence quality.[19]

One guideline also had a recommendation that was weakly against using NMBAs in all patients with ARDS, and weakly recommended their use in those whose ARDS was moderate or severe.[20]

Limitations

The evidence base was generally limited in quantity and quality. The five trials included in the one systematic review[16] were all considered at high or unclear risk of bias except for one, which was considered at lower risk of bias. Of the primary studies, only one was an RCT, which was stopped early due to lack of effect, while the remaining two studies were cohort studies which were at a higher risk of bias. The primary studies were both conducted in the U.S., though their results may still be generalizable to Canada.

The main reasons for the downgrading of evidence ratings that led to weak recommendations in the guidelines included imprecision and concerns about bias due to lack of blinding and indirectness. The Japanese guideline[7] downgraded evidence due to cisatracurium unavailability, which is not applicable to Canada.

Conclusions and Implications for Decision or Policy Making

This review identified one systematic review, one randomized controlled trial, two non-randomized studies and six guidelines relevant to the use of NMBAs in patients with ARDS. The guidelines, systematic review and RCT considered the use of NMBAs versus a non-NMBA comparator, while the non-randomized studies compared different NMBAs.

Overall, the findings were mixed but suggested potential benefit of using NMBAs in early moderate to severe ARDS patients. The guidelines generally had weakly favourable recommendations for the use of NMBAs, while the systematic review found that using NMBAs is associated with lower mortality. However, the studies included in the guidelines and systematic review were not consistently considered high quality.

At the same time, the RCT and a study comparing cisatracurium to atracurium did not find a significant difference in mortality measures. Findings on adverse events were limited, though the RCT suggested those on cisatracuirum were more likely to have serious cardiovascular events compared with usual care. One non-randomized study found cisatracurium was more effective to prevent hospital mortality than vecuronium; a 2016 survey suggested cisatracurium is already the most commonly used NMBA in Canada,[5] a change from a 2006 where pancuronium, rocuronium, and vecuronium were common.[23]

ICU-acquired weakness was not found to be higher among NMBA users in the RCT, a previously highlighted concern associated with NMBAs. This finding is supported by a 2010 double-blinded randomized controlled trial[24] and an earlier systematic review that both suggested that ICU-acquired weakness is not associated with NMBAs.[8]

Future research could consider longer term outcomes associated with NMBAs and adverse events. This review was unable to conclude on quality of life, cognitive or other longer-term outcomes because only one RCT planned to measure them only as secondary outcomes. Further only the RCT measured adverse events such as cardiovascular events, limiting the ability to draw conclusions on safety outcomes.

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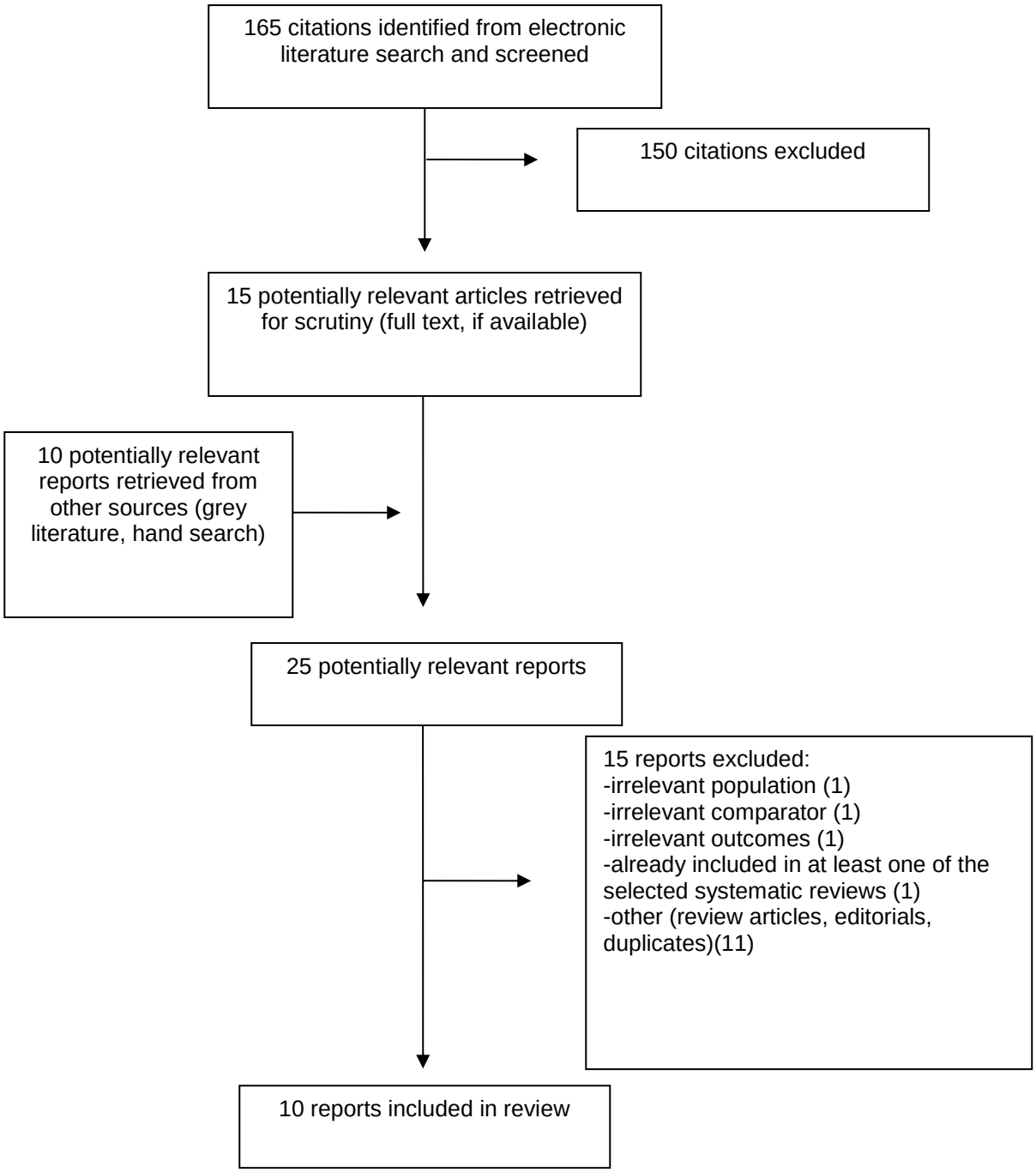
24. Papazian L, Forel J-M, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *New England Journal of Medicine.* 2010;363(12):1107-1116.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 1: Characteristics of Included Systematic Review and Meta-Analysis

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Tao, Neuromuscular blocking agents for adult patients with acute respiratory distress syndrome: A meta-analysis of randomized controlled trials, 2018, China[16]	5 RCTs (577 references searched) with 551 patients	Adult patients with moderate to severe ARDS	NMBAs with placebo or usual treatment (not defined, but excluded studies that compared different NMBAs)	Mortality (follow up not stated)

RCT = randomized controlled trial; ARDS = acute respiratory distress syndrome; NMBA = neuromuscular blocking agent

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Randomized Controlled Trials				
The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network, Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome, 2019, USA[1]	Multicentre, unblinded, randomized controlled trial	Mechanically ventilated ICU patients with moderate-to-severe ARDS for less than 48 hours with PaO_2:FIO_2 less than 150 mm Hg	*Intervention*: 48 hours of continuous cisatracurium (IV bolus of 15 mg, followed by continuous infusion of 37.5 mg for 48 hours) with deep sedation *Comparator:* Usual care with light sedation	Follow up: 12 months Primary: All-cause mortality at 90 days in-hospital Secondary: Organ dysfunction, in-hospital death at day 28, days free of organ dysfunction, days not in the ICU, days free of mechanical ventilation, and days not in the hospital at day 28. Longer-term (3,6, 12 months): survival, disability, health-related quality of life, patient-reported health, pain interference, post-traumatic symptoms, cognitive function, and return to work

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Non-randomized studies				
Sottile, 2018, An Observational Study of the Efficacy of Cisatracurium Compared with Vecuronium in Patients with or at Risk for Acute Respiratory Distress Syndrome, USA[17]	Multicentre, observational cohort study of the Permier Incorporated Perspective Database (Jan 2010 to Jan 2014)	Mechanically ventilated, ICU patients with a diagnosis of ARDS or a known ARDS risk who received at least 2 days of a continuous infusion of cisatracurium or vecuronium within the first 2 days of hospital admission	*Intervention:* Cisatracurium *Comparator:* Vecuronium	Follow up: Unclear Hospital mortality, ventilator days, ICU days, hospital days, and discharge home versus elsewhere.
Moore, Comparison of Cisatracurium Versus Atracurium in Early ARDS, 2017, USA[18]	Retrospective cohort between July 2012 and 2015	Patients with ALI/ARDS and treated with neuromuscular blocking agent, within 72 hours of ARDS presentation and PaO_2:FIO_2 < 150 mm Hg	*Intervention:* Cisatracurium (median dose 2.5 mug/kg/min; median duration 2.6 days) *Comparator:* Atracurium (median dose 1.9 mug/kg/min; median duration 2.5 days)	Follow up: 28 days Primary outcome: Difference of PaO_2:FIO_2 at 72 h Secondary outcomes: ventilator-free days at day 28, ICU and hospital lengths of stay, and hospital mortality

RCT = randomized controlled trial; ARDS = acute respiratory distress syndrome; PaO_2 =partial pressure of oxygen; FIO_2 = fraction of inspired oxygen; ICU = intensive care unit

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Papazian, 2019[19]						
Practitioners, with application to adult patients, early phase of ARDS and invasive mechanical ventilation	Administration of NMBA	Mortality	-Formulated question according to PICO format, but no description otherwise	-Literature analysed using GRADE methodology	-For consideration, at least 50% had to agree and less than 20% disagree. -For strong agreement, at least 70% of experts had to agree	Not stated

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
					-Recommendations Were iteratively reformulated and rated to reach 70% agreement	
Griffiths, 2019[20]						
Not stated but appears to be directed at practitioners	Neuromuscular blocking agents in adults with ARDS	Mortality (28 days, hospital and 6 month), 1-year mortality, ICU and hospital length of stay, quality of life and harms at 3 months, 6 months and 1 year	-Each topic developed using PICO -Search strategy developed by group information expert	-Quality of evidence rated using GRADE -Mortality outcomes had MODERATE rating due to risk of bias -Adverse events: ICU acquired weakness had VERY LOW rating due to very serious risk of bias	-Lead author present data and suggest a recommendation Using GRADE methodology -The findings were then debated among the whole expert group and a consensus was reached based on majority opinion	Not stated
Hashimoto, 2017[7]						
Health care providers caring for patients with ARDS	Adult patients with ARDS requiring mechanical ventilation	ICU mortality, 28-day mortality, rate of barotrauma and myopathy	-Systematic review question developed into PICO and outcomes selected and approved by guidelines committee, and ranked by importance -Included only systematic reviews or RCTs,	-RCTs ranked according to GRADE tool (risk of bias, inconsistency, indirectness, imprecision and other considerations)	-Recommendation determined when full panel was unanimous -Recommendations were graded according to strength (strong is 1; weak is 2) and certainty (A is high; D is low)	`-External validation panelists evaluated the draft using AGREE II checklist -Guideline was posted online for public comment
Cho, 2016[21]						
Not stated but appears to be	Use of NMBAs among adult patients with ARDS	Hypoxemia and barotrauma	-Standard PICO question developed for the topic	-Cochrane Risk of Bias tool used to assess bias in RCTs	-Recommendations drafted and graded as strong or weak based on	Not stated

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
directed at practitioners			-Studies selected through systematic searching	-Evidence characterized as as high (A level), moderate (B level), or low (includes very low) (C level) quality based on study design, risk of bias, imprecision, inconsistency, indirectness of results, and the likelihood of publication bias.	study results and cost-effectiveness -Modified Delphi technique used to arrive at consensus; panel members voted on their level of agreement -Recommendations reaching 50% agreement with response rate of at least 80% to be included, however all recommendations reached consensus	
Classon, 2016[22]						
Not stated but appears to be directed at practitonners	Use of NMBAs among patients with ARDS	Days of mechanical ventilation and mortality	-Standard PICO format used for questions -McMaster PLUS databased used find systematic reviews of RCTs -Most recent systematic review of lowest risk of bias included -Four databases searched for additional studies and meta-analysis -Excluded observational and physiological studies	Used GRADE methodology to rate evidence according to risk of bias, inconsistency, indirectness and imprecision on a scale from high to low	-Considered benefits and harms, quality of evidence, values and preferences, and cost -The group agreed on all recommendations	Not stated
Murray, 2016[6]						
Clinicians who treat adults who are patients in medical and surgical ICUs	Use of NMBAs among adult patients with ARDS	Survival (not stated otherwise)	-Performed systematic review on each question and pooled data where appropriate -RCTs were	-GRADE used to rate quality of evidence and strength of recommendation -Evidence rated	-Task force reached consensus on all the recommendations -Recommendation strength based on quality	Not stated

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
			preferentially included, and excluded abstracts and unpublished studies.	based on risk of bias, directness, consistency of results, analysis and publication bias	of evidence, outcomes, their relative importance to patients, the balance between desirable and undesirable effects, the cost, and the feasibility of implementation of the intervention for each individual question	

NMBA = neuromuscular blocking age; ARDS = acute respiratory distress syndrome; ICU = intensive care unit; PaO_2 =partial pressure of oxygen; FIO_2 = fraction of inspired oxygen; GRADE = Grading of Recommendations Assessment, Development and Evaluation; PICO = Population, intervention, comparator, outcome; RCT = randomized controlled trial

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[12]

Strengths	Limitations
Tao, 2018[16]	
-Searched several databases with appropriate search terms -Conducted hand searching of reference lists -No language restrictions -Two investigators conducted the initial screening and extraction (unclear whether it was independent) -Independent assessment of quality by investigators -Used funnel plot to check for publication bias and I^2 to assess heterogeneity -Quality assessed using Cochrane Risk of Bias tool -Appropriate statistical analysis including random effects if heterogeneity detected	-Unclear whether two investigators independently screened abstracts and full texts and how consensus was reached -No pre-published protocol -Did not state clear outcomes or interventions (PICO) question -Limited detail on patient characteristics

Table 5: Strengths and Limitations of Clinical Studies using Downs and Black[13]

Strengths	Limitations
Randomized controlled trials	
The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network, 2019[1]	
-Assessors who interviewed survivors for late sequelae were unaware of group assignment -Pre-published protocol -Power calculation done to achieve 90% power to reject the null with 1408 patients -Used absolute measure (risk difference) and appropriate statistical analysis by treatment group (binomial model) for the primary outcome, and Poisson model for adverse events -Baseline characteristics between groups were similar	-Unblinded, meaning investigator bias is possible -1:1 randomization without allocation concealment -Some contamination possible as control group could still receive cisatracurium -Underpowered (1006 vs 1408 patients required) though stopped early due to futility
Non-randomized studies	
Sottile, 2018[17]	
-Used propensity score analysis to reduce the risk of bias caused by different risk among treatment groups -Groups did not show baseline differences in demographics or other patient characteristics suggesting successful matching -Included hospital as a random effect in the regression model to reduce risk of bias associated with location of treatment -Assessed robustness of results using multivariable analysis	-Patient population may have included people without ARDS because diagnostic code was not required (only code for risk factors) -Exclusion criteria not listed -Dosage of intervention and comparator not included -Non-randomized, open-label study could mean there were remaining differences between the groups
Moore, 2017[18]	
-Intervention and comparator groups were overall comparable in terms of baseline characteristics	-No power calculation and small sample sizes, so unclear whether underpowered -The allocation to treatment groups was based on availability, with cisatracurium being the first choice, potentially meaning more severe patients had cisatracurium -Statistical analysis based only p-value without adjustment for multiple comparison or presentation of uncertainty

Table 6: Strengths and Limitations of Guidelines using AGREE II[14]

Item	Guideline					
	Papazian, 2019[19]	Griffiths, 2019[20]	Hashimoto, 2017 [7]	Murray, 2016[6]	Cho, 2016[21]	Claesson, 2016[22]
Domain 1: Scope and Purpose						
1. The overall objective(s) of the guideline is (are) specifically described.	X	X	X	X	X	X
2. The health question(s) covered by the guideline is (are) specifically described.	X	X	X	X	X	X
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	X	X	X	X	X	X
Domain 2: Stakeholder Involvement						
4. The guideline development group includes individuals from all relevant professional groups.	X	X	X	X	X	X
5. The views and preferences of the target population (patients, public, etc.) have been sought.		X	X			
6. The target users of the guideline are clearly defined.	X		X	X		
Domain 3: Rigour of Development						
7. Systematic methods were used to search for evidence.	X	X	X	X	X	X
8. The criteria for selecting the evidence are clearly described.		X	X	X		X
9. The strengths and limitations of the body of evidence are clearly described.		X	X	X	X	X
10. The methods for formulating the recommendations are clearly described.		X	X	X	X	
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	X	X	X	X	X	X
12. There is an explicit link between the recommendations and the supporting evidence.	X	X	X	X	X	X
13. The guideline has been externally reviewed by experts prior to its publication.			X		X	X
14. A procedure for updating the guideline is provided.						X
Domain 4: Clarity of Presentation						
15. The recommendations are specific and unambiguous.	X	X	X	X	X	X
16. The different options for management of the condition or health issue are clearly presented.						
17. Key recommendations are easily identifiable.	X	X	X	X	X	X

Item	Guideline					
	Papazian, 2019[19]	Griffiths, 2019[20]	Hashimoto, 2017 [7]	Murray, 2016[6]	Cho, 2016[21]	Claesson, 2016[22]
Domain 5: Applicability						
18. The guideline describes facilitators and barriers to its application.						
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.						
20. The potential resource implications of applying the recommendations have been considered.			X			X
21. The guideline presents monitoring and/or auditing criteria.						
Domain 6: Editorial Independence						
22. The views of the funding body have not influenced the content of the guideline.		X	X	X	X	X
23. Competing interests of guideline development group members have been recorded and addressed.			X	X	X	X

Appendix 4: Main Study Findings and Authors' Conclusions

Table 7: Summary of Findings Included Systematic Review and Meta-Analysis

Main Study Findings	Authors' Conclusion
Tao, 2018[16]	
NMBA versus placebo Mortality 21 to 28 day: Relative risk: 0.63; 95%CI, 0.49–0.82; p = 0.001; I2 = 0.0%; 4 trials, 527 patients ICU mortality: Relative risk: 0.73 (95% CI, 0.58–0.93; p = 0.009; I2 = 0.0%; 4 trials, 455 patients Improvement in Pa02:Fa02 ratio at 48 hours: WMD:27.98; 95% CI, 7.45–48.51; p = 0.008; I2 = 44.2%; 4 trials, 212 patients Reduction of Pplat: WMD: 0.43; 95% CI, −0.46 to 1.31; p = 0.345; 4 trials, 455 patients PEEP at 48 hours: WMD, 0.10; 95% CI, −0.47 to 0.67; p = 0.73; 4 trials, 455 patients	"Our results showed that the use of NMBAs is beneficial for patients with moderate to severe ARDS who needed mechanical ventilation…[it] reduced 21- to 28-day mortality and ICU mortality in moderate to severe ARDS patients were found in NMBA-treated group. Moreover, NMBAs improved oxygenation at 48 h after randomization." (pg 1104)

NMBA = neuromuscular blocking age; WMD = weighted mean difference; Pplat = plateau pressure; PEEP = positive end-expiratory pressure; ARDS = acute respiratory distress syndrome; ICU = intensive care unit

Table 8: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Randomized controlled trials	
The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network, 2019[1]	
Cisastracurium vs usual care (no routine NMBA) -In-Hospital death by day 90: 213 (42.5±2.2) vs 216 (42.8±2.2); RD = -0.3 (95% CI -6.4 to 5.9) percentage points Secondary Intervention vs Control -In-hospital death by day 28: 184 (36.7) vs 187 (37.0); RD = −0.3 (−6.3 to 5.7) -Days free of ventilation at day: 9.6±10.4 vs 9.9±10.9; RD = −0.3 (−1.7 to 1.0) -Days not in ICU at day 28: 9.0±9.4 vs 9.4± 9.8; RD = −0.4 (−1.6 to 0.8) -Days not in hospital at day 28: 5.7±7.8 vs 5.9±8.1; RD = −0.2 (−1.1 to 0.8) -Number of serious adverse events: 35 vs 22 (p=0.09) -In hospital recall of paralysis: 9/501 vs 10/505 (−0.2 (−1.9 to 1.5)) -Patients in the control group had higher mean levels of physical activity up to day 6. -ICU-acquired weakness: 107/226 (47.3) vs 89/228 (39.0); MD = −7.3 (−15.7 to 1.1) -Serious cardiovascular events: 14 vs 4 p=0.02 -No significant difference in artirial fibrillation or SVT, barotrauma, or pneumothorax rates, or other 3,6 and 12 month outcomes.	"In a cohort of critically ill patients identified shortly after the diagnosis of moderate-to-severe ARDS, the addition of early continuous neuromuscular blockade with concomitant deep sedation did not result in lower mortality than a usual-care approach to mechanical ventilation that included lighter sedation targets." (pg 2006)

Main Study Findings	Authors' Conclusion
Non-randomized studies	
Sottile, 2018[17]	
Cisatracurium vs Vecuronium *Propensity-score analysis* Mortality: OR= 0.93(0.79 to 1.10); p= 0.40 0.91 0.80 to 1.02 0.11 Difference in ventilator days: 1.01 (0.30 to 1.72); p= 0.005 0.78 0.31 to 1.25 0.001 Difference in ICU days: 0.98 (0.11 to 1.86); p= 0.028 0.73 0.17 to 1.30 0.011 Difference in hospital days: 0.66 (20.75 to 1.83); p= 0.41 0.57 20.29 to 1.44 0.05 Odds of discharge to home: OR 1.19 (1.00 to 1.43); ; p= 0.056 1.19 1.05 to 1.37 0.008 *Multivariable analysis (adjustment for confounders but no matching)* Mortality: OR= 0.91 (0.80 to 1.02); p= 0.11 Difference in ventilator days: 0.78 (0.31 to 1.25); p=0.001 Difference in ICU days: 0.73 (0.17 to 1.30); p=0.011 Difference in hospital days: 0.57 (20.29 to 1.44); p=0.05 Odds of discharge to home: OR= 1.19 (1.05 to 1.37); p= 0.008	"When compared with vecuronium, cisatracurium was associated with improved outcomes for patients at risk for and with ARDS. Therefore, cisatracurium may be the neuromuscular blockade agent of choice for these patients." (pg 903)
Moore, 2017[18]	
Atracurium versus Cisatracurium median (IQR): PaO2:FIO2 72 h after NMBA: 165 (77–262) vs 178 (121–255); p= .65 PaO2:FIO2 improvement at 72 h: 65 (25–162) vs 66 (16–147); p= .65 Ventilator-free days at day 28: 13 (0–22) vs 15 (8–21); p= .72 ICU length of stay: 18 (8–34) vs 15 (9–22); p= .34 Hospital length of stay: 28 (16–39) vs 18 (10–28); p= .09 Hospital mortality, n (%) 9 (50) vs 36 (62); p= .42	"The present study shows no difference between the use of atracurium and cisatracurium among subjects diagnosed with early ARDS and treated with NMBAs." (pg 950)

NMBA = neuromuscular blocking age; WMD = weighted mean difference; Pplat = plateau pressure; PEEP = positive end-expiratory pressure; ARDS = acute respiratory distress syndrome; ICU = intensive care unit; OR = odds ratio; IQR = interquartile range; RD = risk difference; PaO_2 =partial pressure of oxygen; FIO_2 = fraction of inspired oxygen

Table 9: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
Papazian, 2019[19]	
"R4.1 – A neuromuscular blocking agent should probably be considered in ARDS patients with a PaO_2/FIO_2 ratio < 150 mmHg to reduce mortality. The neuromuscular blocking agent should be administered by continuous infusion early (within 48 h after the start of ARDS), for no more than 48 h, with at least daily evaluation." pg 8-9	Optional recommendation with strong agreement among experts -Based on three randomized trials tested the effect of adding NMBA to deep sedation in early ARDS
Griffiths, 2019[20]	
"We do not suggest using NMBAs for all patients with ARDS." "We suggest the use of cisatracurium besylate by continuous 48 hours infusion in patients suffering early moderate/ severe ARDS (PaO_2/FIO_2 <20 kPa)" pg 15	Weak recommendation Moderate quality of evidence due to risk of bias -Included four systematic reviews, and two had meta-analyses which compared continuous 48 h infusion of cisatracurium versus standard of care

Recommendations	Strength of Evidence and Recommendations
Hashimoto, 2017[7]	
"We suggest the use of neuromuscular blocking agents (NMBAs) in adult patients with ARDS requiring mechanical ventilation, under certain circumstances"(pg 16)	Weak recommendation, moderate quality of evidence (grade 2B)
Cho, 2016[21]	
"We suggest using neuromuscular blockade for 48 hours after starting mechanical ventilation in patients with ARDS" (pg 222)	Weak recommendation, moderate quality of evidence (grade 2B) -Based on three RCTs and retrospective studies, and further stipulates justifiable use only for patients with moderate/severe ARDS and for less than 48 hours
Classon[22]	
"We suggest that neuromuscular blocking agents (NMBAs) may be used in the early stages of severe ARDS." (pg 703)	Weak recommendation, moderate quality of evidence -Based on three RCTs but the quality of evidence was downgraded due to imprecision of estimates
Murray, 2016[6]	
"We suggest that an NMBA be administered by continuous IV infusion early in the course of ARDS for patients with a PaO_2/FIO_2 less than 150" (pg 2084)	Weak recommendation, moderate quality of evidence -Based on three multi-center RCTs evaluating early use of 48-hour cisatracurium infusions, all by the same group in France

NMBA = neuromuscular blocking age; ARDS = acute respiratory distress syndrome; ICU = intensive care unit; PaO_2 =partial pressure of oxygen; FIO_2 = fraction of inspired oxygen; RCT=randomized controlled trial