Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
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EVIDENCE SUMMARY

Should sedation and neuromuscular blockade be done in mechanically ventilated patients with COVID-19-associated acute respiratory distress syndrome?

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RECOMMENDATIONS

We suggest light over deep sedation in COVID-19 patients who are mechanically ventilated and who are anxious or agitated. *(Very low certainty of evidence; Weak recommendation)*

We suggest against the routine use of neuromuscular blockade in mechanically ventilated patients with COVID-19 associated respiratory distress syndrome.
(Low certainty of evidence; Weak recommendation)

Consensus Issues
Light sedation for mechanically ventilated COVID-19 patients has been suggested to help in managing agitation and anxiety. Certain patients, however, who are on paralytics and prone position, as well as those who exhibit ventilator asynchrony must be considered for deep sedation. On the other hand, routine neuromuscular blockade is not recommended unless there are indications for paralysis: as supportive management to facilitate lung protective strategies or prone ventilation.

Key Findings

There are currently no available randomized clinical trials testing for the effect of sedation and neuromuscular blockade in COVID-19 patients with acute respiratory distress syndrome (ARDS). Only indirect evidence from eight studies (two randomized clinical trials (RCTs) on the use of sedation versus no sedation in mechanically ventilated patients and six RCTs on the use of neuromuscular blockade agent (NMBA) compared to light sedation alone or placebo with or deep sedation in mechanically ventilated patients with moderate to severe ARDS) showed no significant benefit in 90-day mortality, length of hospital stay, and ventilator free-days. In terms of adverse events, major thromboembolic complications were significantly observed among mechanically ventilated patients on sedation while the incidence of delirium, accidental extubation, and ventilator-associated pneumonia did not significantly differ. The use of NMBA in moderate-to-severe ARDS showed significant reduction in 28- and 90-day mortality, improvement in PaO2/FiO2 ratio at 72 hours when compared to a deep sedation strategy without NMBA. Likewise, the use of NMBA reduced the risk of barotrauma and pneumothorax compared to no NMBA.

Introduction

Acute respiratory distress syndrome (ARDS) is a life-threatening condition that complicates a variety of critical illnesses, including sepsis, pneumonia, and trauma.[1] The Coronavirus Disease 2019 ARDS (COVID-19 ARDS) has some distinguishing features that includes progressive pulmonary infiltrates and hyperinflammatory response resulting in severe refractory hypoxemia, which poses a major challenge in ventilatory management. [2,3] In critically ill patients, sedatives are frequently administered to relieve anxiety, reduce the stress of being mechanically ventilated, and prevent agitation-related harm. On the other hand, the routine use of neuromuscular blocking agents is not recommended unless indicated as supportive therapy to facilitate lung protective ventilation or prone ventilation.[4,5]. This review aims to evaluate the effects of sedation and neuromuscular blockade among mechanically ventilated COVID-19 patients with moderate to severe ARDS.

Review Methods

We performed a systematic literature search to identify relevant studies in PubMed, Cochrane Library, WHO trial Registry, and ClinicalTrial.gov databases up to November 19, 2021. Our search strategy combined concepts related to Sedation, Paralysis, COVID-19 and acute respiratory distress syndrome (i.e., “Mechanical Ventilation”, “Severe Pneumonia”, “Sedation”, “ARDS”, “respiratory distress syndrome”, “ICU”, “Randomized Trial”, and “neuromuscular blockade”). In addition, MeSH and free text search were done for the following terms: sedation, neuromuscular blockade, paralysis, ICU, mechanical ventilation, COVID-19, and acute respiratory distress syndrome. We also reviewed the references listed in each identified study and manually searched the related articles to identify all eligible studies and minimize any potential publication bias. No language or journal type restriction was applied.

Results

I. Sedation in Mechanically Ventilated Patients

Characteristics of Study Population, Interventions, and Comparators

The population, drugs used, and methodology process were similar in the two (2) studies included for sedation. Both trials were conducted to investigate whether a plan of no sedation in patients receiving mechanical ventilation would result in a better survival outcome than a plan of light sedation with daily interruption. In both studies, included patients were 18 years of age or older, had undergone endotracheal intubation within 24 hours before screening, and were expected to receive mechanical ventilation for more than 24 hours. Upon inclusion, the patients were randomly assigned in a 1:1 ratio to a plan of no sedation (non-sedation group) or to light sedation with daily interruption (sedation group).[6,7] Patients in the non-sedation group did not receive any sedatives but could receive bolus doses of morphine for analgesia while the patients in the sedation/control group received intravenous morphine in bolus doses (2.5 or 5mg) as needed, and were sedated with an infusion of propofol (20 mg/mL) titrated to reach a Ramsay score of 3–4. Ramsay Sedation Scale scores range from 1 [anxious, restless] to 6 [unresponsive], with a score of 2 indicating that the patient is cooperative and oriented. The Ramsay score was recorded every 2–3 h to ensure correct titration of the sedative infusion. Every day, sedation was interrupted until the patients were awake, starting the day after enrolment. After 48 hours, the sedative was changed to an infusion of midazolam (1 mg/mL) titrated to a Ramsay score of 3–4.[6,7] Once the ventilator settings reached an FiO2 of 40% and a positive end-expiratory pressure of 5 cm H2O, the administration of sedatives were stopped.

Mortality
Two studies [6,7] were included in evaluating the effect of sedation in 813 mechanically ventilated patients. In both studies, patients were randomly assigned in a 1:1 ratio to a plan of no sedation or to light sedation with daily interruption within 24 hours after intubation. Pooling of the results showed that among mechanically ventilated patients, the 90-day mortality outcome (RR 1.00, 95% CI 0.70-1.43; I^2=59%; very low certainty), ventilator free days (MD -1.07, 95% CI -3.05-0.91; low certainty), and length of ICU stay (MD -0.34, 95% CI -6.15-5.47; low certainty), did not differ significantly between the two groups. Significant heterogeneity in mortality could have been introduced by differences in the study population in terms of cause of respiratory failure and sedation protocols. Certainty of evidence for mortality was downgraded to very low due to indirectness of the study population, inconsistency, and imprecision, while certainty of evidence for ventilator-free days and ICU length of stay were downgraded to low due to indirectness of the study population and imprecision.

Adverse Events
Two randomized controlled trials reported adverse events between sedation and non-sedation treatment groups. Among the reported adverse events, major thrombotic events were significantly observed among patients who received sedation (RR 9.94, 95% CI 1.28-77.26; moderate certainty).[6] Delirium (RR 0.34, 95% CI 0.12-1.02; low certainty) [7], extubation (RR 0.66, 95% CI 0.26-1.66; I^2=0%; low certainty) [6,7], need for reintubation in 24 hours (RR 1.49, 95% CI 0.62-3.57; low certainty) [7], and incidence of ventilator-associated pneumonia (RR 1.11, 95% CI 0.40-3.09; low certainty) [7] were not significantly different between sedation and non-sedation treatment groups. Certainty of evidence for major thrombotic events was downgraded to moderate due to indirectness while certainty of evidence for the rest of the reported adverse events was downgraded to low due to indirectness and imprecision.

II. Use of Neuromuscular Blockade in Mechanically Ventilated Patients with ARDS
Characteristics of Study Population, Interventions, and Comparators
The studies included for NMBA met all of the following criteria: (1) the design was a parallel group RCT; (2) the population was adults with ARDS of any severity; (3) the intervention included any continuous NMBA infusion, at any dose or duration, compared to placebo or no continuous NMBA infusion but allowing the use of as needed NMBA boluses; and (4) outcomes included any of the following: mortality at 28 days, ICU discharge, or hospital discharge; long-term outcomes, ICU-acquired weakness; duration of mechanical ventilation; ventilator-free days (VFDs); ICU or hospital length of stay; barotrauma; or changes in oxygenation wherein PaO2/FiO2 ratio is specified.[8-13]

Four studies were conducted in France, and one was conducted in China, while the most recent study (PETAL/ROSE Trial), the largest RCT investigating NMBAs effect on ARDS thus far, was conducted in the United States. In all 6 studies, no significant differences were noted between the baseline characteristics of the treatment and control groups.[8-13] Four studies used a 48-hour infusion of cisatracurium [8,9,12,13] whereas the other two studies did not pre-specify a duration for NMBA infusions.[10,11] Weight-based dosing of cisatracurium was used in two of the studies [8,9] and a fixed high dose was used in three studies (15mg bolus, followed by a continuous infusion of 37.5mg per hour).[10,11,13] The study from China was the only included trial which used vecuronium, utilizing maintenance doses without boluses being reported: 0.05 mg/kg/h and 1 µg/ kg/min.[11]

The interventions used in the control arm varied between studies: three studies used a 48-hour infusion of placebo (normal saline) with deep sedation [8-10], an additional two studies did not

describe the control they used [11,13], and one study used light sedation in the control group.[12] All experimental groups received deep sedation on top of the assigned NMBA. Deep sedation was defined as a Ramsay score of 6 while light sedation was defined by a score on the Richmond Agitation–Sedation Scale of 0 or −1 (scores range from 4 [combative] to −5 [unresponsive], with a score of 0 indicating that the patient is alert and calm), a score on the Riker Sedation–Agitation Scale of 3 or 4 (scores range from 1 [unresponsive] to 7 [dangerous agitation], with a score of 4 indicating that the patient is calm and cooperative), or a score on the Ramsay Sedation Scale of 2 or 3 (scores range from 1 [anxious, restless] to 6 [unresponsive], with a score of 2 indicating that the patient is cooperative and oriented).[12,14]

In the study done by Guervilly et al., severe ARDS patient whose PaO2/FiO2 ratio was less than 100 did not get randomization but received open label NMBA infusion as per study protocol, only patients with PaO2/FiO2 ratio between 100 to 150 were randomized.[7] Most studies excluded patients with recent NMBA use prior to enrolment. In terms of neuromuscular blockade monitoring, three studies used nerve stimulators to monitor train of four (TOF) with NMBA dose adjustment accordingly. The other three studies were carried out with fixed NMBA dose. ROSE trial specifically mentioned that the reason for using a fixed dose was to replicate the dosing regimen used in the (ACURASYS) trial and to facilitate adherence to the trial protocol.[12,13] All the studies used lung protective ventilation with low tidal volume with an aim of keeping plateau pressure ≤30cmH2O. ROSE Trial used high PEEP strategy with a baseline PEEP at around 12cmH2O at enrolment.[12] ACURASYS and ROSE trials allowed any rescue therapy, and no statistical difference was found between the intervention group and control group.[12,13]

Mortality

Pooled results of studies which used deep sedation on both its control and intervention groups [8-11,13] showed that the use of NMBA infusion was associated with lower 28-day mortality (RR 0.63, 95% CI 0.49–0.82; I^2=0%; moderate certainty), a lower 90-day mortality (RR 0.72, 95% CI 0.58–0.91; I^2=0%; moderate certainty), and a lower ICU mortality (RR 0.70, 95% CI 0.55-0.89; I^2=0; moderate certainty).

The ROSE trial [12], the largest trial to date, which also applied the latest recommendation for the use of light sedation in mechanically ventilated patients in their control arm, reported no mortality benefit associated with NMBA use at 90 days regardless of ARDS severity or duration (RR 0.99, 95% CI 0.86-1.15; moderate certainty). There are a number of factors that might have contributed to the differences in results. In the ROSE/PETAL Trial, the subjects who were randomized to NMBAs received deep sedation, but for subjects in the control arm, light sedation was targeted and daily sedation interruptions were encouraged. Second, a high-PEEP strategy was utilized, which has been associated with improved recruitment and decreased lung stress and atelectrauma. Lastly, the mean time to inclusion for subjects in ROSE was earlier compared to the other five RCTs. The median time to randomization for subjects enrolled in ROSE was 6.8 to 8.2 hours compared to 21 to 22 hours in the other studies.

Improvement in Oxygenation

Improvement in oxygenation was assessed via change in the PaO2/FiO2 ratio evaluated at 48 and 72 hours of NMBA infusion. Three of the included studies [8,9,12] evaluated the effect of NMBA to oxygenation after 48 hours while four studies measured PaO2/FiO2 changes after 72 hours.[8,9,12,13] Pooled results showed no significant improvement in oxygenation after 48 hours (MD 22.2, 95%CI -4.47-48.88; I^2=64%; very low certainty). Significant benefit was observed with the PaO2/FiO2 ratio improvement after 72 hours (MD 12.9, 95% CI 3.88-21.92; I^2=32%; low certainty). Some of the proposed mechanisms leading to improvement in oxygenation include

improved ventilator synchrony, decreased work of breathing, facilitation of lung protective strategy, better lung recruitment, and improved lung compliance.[15,16]

Duration of Mechanical Ventilation and Ventilator-free Days
Three of the studies (n=431) reported on the duration of mechanical ventilation.[8,9,13] Results showed no significant difference in the duration of mechanical ventilation among those given NMBA compared to those who were not given NMBA (MD -1.21 days, 95% CI -4.23-1.81; I^2=0%; low certainty). A similar trend was observed in the pooled analysis for ventilator-free days which also showed no significant difference between the NMBA and control groups (MD 0.68 days, 95% CI -0.86-2.22; I^2=32%; low certainty).

Adverse Events
Pooled data on adverse events showed a decrease in the risk of barotrauma (RR 0.55, 95% CI 0.35-0.85; I^2=0%; moderate certainty) and pneumothorax (RR 0.46, 95% CI 0.28-0.77; I^2=0%; moderate certainty) in the NMBA group. Barotrauma was defined as new-onset pneumothorax, pneumomediastinum, subcutaneous emphysema, or pneumatocele larger than 2cm in diameter. These may be due to the increase in lung compliance and decrease in ventilatory desynchrony between the machine and the patient.[8,9,12,13] Certainty of evidence was downgraded to moderate due to indirectness of the study population.

Four of the included studies [8,9,12,13] reported on adverse events. The PETAL trial reported most of the adverse events in the pooled data.[12] Pooled analysis on the development of any adverse event showed no significant difference between those who were given NMBA infusion compared to control group (RR 1.63, 95% CI 0.97-2.71; I^2=0%; low certainty). Adverse events observed were methemoglobinemia, complete heart block, atrial fibrillation, cardiac arrest, SVT, ventricular tachycardia, new-onset pneumonia, hyperkalemia, intracranial hemorrhage, cerebrovascular accident, aspiration, hypotension, and superficial venous thrombosis. Certainty of evidence was downgraded to low due to indirectness of the study population and imprecision.

ICU-acquired weakness up to 28 days from randomization was also assessed and was evaluated with the use of the Medical Research Council (MRC) scale, a previously validated scale that assesses three muscle groups in each arm and leg.[8,9,12,13] The score for each muscle group ranged from 0 (paralysis) to 5 (normal strength), with the overall score ranging from 0 to 60.[2] The definition of ICU-acquired paresis was an MRC score of less than 48.[2] The pooled results did not show a significant difference in the rate of ICU-acquired weakness with NMBA infusion (RR 1.15, 95% CI 0.95-1.39; I^2=0%; low certainty). Certainty of evidence was downgraded to low due to indirectness of the study population and imprecision.

Recommendations from Other Groups

There are currently no guidelines regarding sedation and neuromuscular blockade specific for this patient population. At present, sedation regimens for COVID-19 ARDS patients are based on the standard guidelines in treating patients with “classic” or “pre-COVID” ARDS.

As per Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS) in Adult Patients in the ICU 2018, using light sedation in critically ill, mechanically ventilated adults is suggested in order to relieve anxiety, reduce the stress of being mechanically ventilated, and prevent agitation-related harm *(conditional recommendation, low quality of evidence)*.[17]

As of Surviving Sepsis Guidelines 2021, continuous NMBA infusion did not improve mortality when compared with a light sedation strategy with as needed NMBA boluses (RR 0.99, 95% CI 0.86−1.15). On the other hand, continuous NMBA infusion reduced mortality when compared to deep sedation with as needed NMBA boluses (RR 0.71, 95% CI 0.57−0.89).[18] Since cisatracurium is the only agent recorded to have been studied in large RCTs, it is then the preferred agent to use. In summary, it is recommended for adults with sepsis induced moderate-severe ARDS to use intermittent NMBA boluses over NMBA continuous infusion.[18]

In an ICM-RPG for the use of neuromuscular blocker by Alhazzani 2020, the panel issued one recommendation and two suggestions regarding the use of NMBA in ARDS. The current evidence does not support the early routine use of NMBA infusion in all adults with ARDS. It favors avoiding an NMBA infusion for patients who are ventilated using a lighter sedation strategy. But, for patients who require deep sedation to facilitate lung protective ventilation, prone positioning, and neuromuscular blockade, an infusion of an NMBA is a reasonable option; limiting its use to 48hrs is recommended.[19]

As for local guidelines issued by the Clinical Practice Guidelines for Sepsis and Septic Shock in Adults in the Philippines 2020, the use of either continuous or intermittent sedation in mechanically-ventilated patients with sepsis or septic shock is recommended *(conditional recommendation, low quality of evidence)* as an adjunct to short-acting non-benzodiazepine sedatives (e.g. dexmedetomidine and propofol) in order to address agitation and the need for adequate sedation to achieve protocol-based sedation targets *(conditional recommendation, low quality of evidence).* With regard to NMBA use, local guidelines recommend its early use preferably within 48 hours of ARDS diagnosis in moderate to severe ARDS *(weak recommendation, very low quality of evidence).*[20]

Research Gaps

The data specific for patients with COVID-19 with ARDS are limited, derived mainly from observational studies and clinical experiential accounts. A randomized clinical trial, if possible, is needed to further assess and evaluate optimal components of care (i.e., use of sedation and neuromuscular blockade) in this particular patient population. Though their condition is similar to “traditional” ARDS, the differences in other processes might affect the final outcome when studied strictly among the said population.

Ongoing Trials

There are four registered clinical trials in ClinicalTrials.gov as of November 20, 2021 (see Appendix 6), one of which is a randomized clinical trial comparing the effect of neuromuscular blockade with sedation vs sedation alone in intubated COVID-19 patients with ARDS but is yet to begin recruitment. The remaining three trials are related to inhaled sedatives and its possible utilization in COVID-19 ARDS patients. Two of the three trials have completed their data collection but no published article is presently available. Other than this, one registered randomized clinical trial was found comparing sedation vs non sedation in mechanically ventilated patients. No published results are available at present.

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion: sedation (N=5)

FACTORS	JUDGEMENT					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (5)				• Critically ill patients with ARDS may require sedation and neuromuscular blockade as supportive therapy to alleviate patient anxiety and improve tolerance, and as therapeutic measures to improve ventilatory synchrony and oxygenation without contributing to adverse outcomes
Benefits	Large	Moderate (1)	Small (2)	Uncertain (2)		• No significant difference in: the 90-day mortality outcome (RR 1.00; 95% CI 0.70, 1.43; I2=59%; Very Low Certainty), ventilator free days (MD -1.07; 95% CI -3.05, 0.91; Low Certainty), and length of ICU stay (MD -0.34; 95% CI -6.15, 5.47; Low Certainty).
Harm	Large (3)	Small (1)	Uncertain (1)	No response		• Reported adverse events: major thrombotic events was significantly observed among patients who received sedation (RR 9.94; 95% CI 1.28, 77.26; Moderate Certainty)
Certainty of Evidence	High	Moderate	Low (1)	Very low (4)		• Very low due to indirectness in study population, inconsistency, and imprecision
Balance of effects	Favors drug (1)	Does not favor drug (3)	Uncertain (1)			

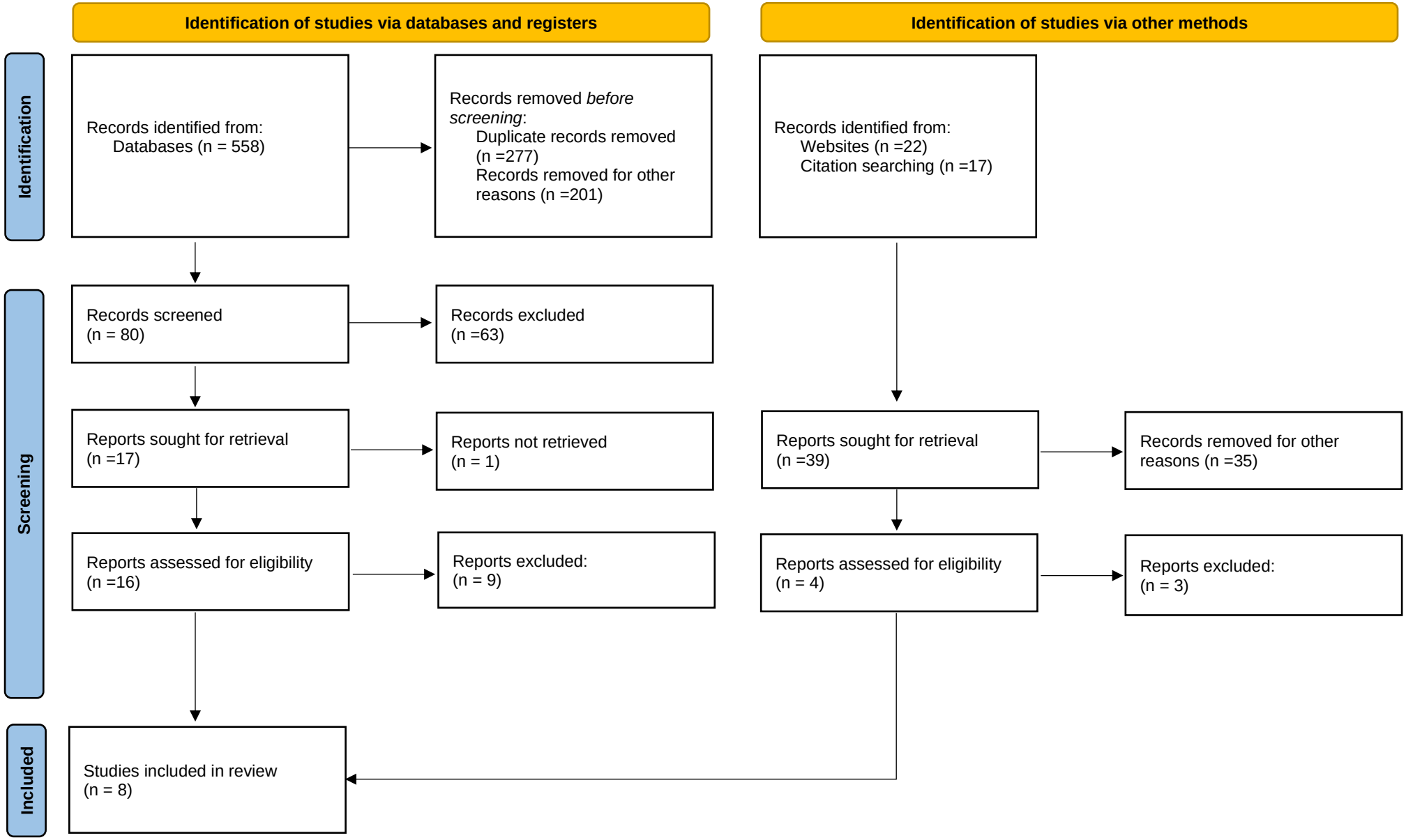
Values	Important uncertainty or variability (4)	Possibly important uncertainty or variability (1)	Possibly NO important uncertainty or variability	No important uncertainty or variability			
Resources Required	Uncertain (4)	Large cost (1)	Moderate Cost	Negligible cost	Moderate savings	Large savings	
Certainty of evidence of required resources	No included studies (5)	Very low	Low	Moderate	High		
Cost effectiveness	No included studies (5)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention			
Equity	Uncertain (0)	Reduced (1)	Probably no impact (4)	Increased			
Acceptability	Uncertain (1)	No (4)	Yes (0)				
Feasibility	Uncertain	No	Yes (5)				

Table 2. Summary of initial judgements prior to the panel discussion: neuromuscular blockade (N=5)

FACTORS	JUDGEMENT					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (5)				• Critically ill patients with ARDS may require sedation and neuromuscular blockade as supportive therapy to alleviate patient anxiety and improve tolerance, and as therapeutic measures to improve ventilatory synchrony and oxygenation without contributing to adverse outcomes
Benefits	Large	Moderate (5)	Small	Uncertain		• A lower 28-day mortality (RR 0.63; 95% CI 0.49–0.82; I^2=0%; Moderate Certainty), a lower 90-day mortality (RR 0.72; 95% CI 0.58–0.91; I^2=0%; Moderate Certainty), and a lower ICU mortality (RR 0.70; 95% CI 0.55-0.89, I^2=0; Moderate Certainty). • Significant benefit was observed with the PaO2/FiO2 ratio improvement after 72 hours (MD 12.9; 95% CI 3.88, 21.92; I^2=32%; Low Certainty).
Harm	Large (3)	Small (2)	Uncertain	No response		• Decreased risk of barotrauma (RR 0.55; 95% CI 0.35, 0.85; I^2=0%; Moderate Certainty) and pneumothorax (RR 0.46; 95% CI 0.28, 0.77; I^2=0%; Moderate Certainty) in the NMBA group
Certainty of Evidence	High	Moderate	Low (5)	Very low		• Certainty of evidence was low due to indirectness in study population, and imprecision
Balance of effects	Favors drug (5)	Does not favor drug	Uncertain			

Values	Important uncertainty or variability	Possibly important uncertainty or variability (1)	Possibly NO important uncertainty or variability (2)	No important uncertainty or variability (2)			
Resources Required	Uncertain (5)	Large cost	Moderate Cost	Negligible cost	Moderate savings	Large savings	
Certainty of evidence of required resources	No included studies (5)	Very low	Low	Moderate	High		
Cost effectiveness	No included studies (5)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention			
Equity	Uncertain (1)	Reduced (1)	Probably no impact (3)	Increased			
Acceptability	Uncertain	No	Yes (5)				
Feasibility	Uncertain	No	Yes (5)				

Appendix 2. Search Yield and Results



Appendix 3. Characteristics of Included Studies

3.1 Study Characteristics of Included Studies on Sedation (n=2)

Study ID Title Author	Study Design	Setting/Country	Total number of Patients Included	Population	Intervention	Comparator/ Control	Outcome Monitored or Observed	Result
Olsen et.al.[9] (2020) DOI: 10.1056/NEJMoa1906759 Non sedation or Light Sedation in Critically Ill, Mechanically Ventilated Patients	Randomized Clinical Trial, open label	Multicenter 5 in Denmark; 2 in Norway; 1 in Sweden	n= 700	-18 years of age or older - Underwent endotracheal intubation within 24 hours before screening - Expected to receive mechanical ventilation for more than 24hours	-non sedation	-interrupted sedation (Using Propofol for the first 48hours followed by midazolam infusion thereafter)	**Primary outcome**: 1. all-cause mortality at 90 days after randomization. **Secondary outcomes:** 1. Number of days until death up to 90 days after randomization 2. Number of thromboembolic events (pulmonary embolus or deep vein thrombosis) 3.Number of days free from coma or delirium 4. The highest score on the Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease (RIFLE) 5. Length of stay in the ICU 6. The number of days without mechanical ventilation	-48 patients (42.4%) in the non sedation group had died and 130 patients (37.0%) in the sedation group -Number of days until death up to 90 days was 13 days (interquartile range, 6 to 27) in the non sedation group and 12 days (interquartile range, 5 to 28) in the sedation group -A major thromboembolic event (pulmonary embolus or deep-vein thrombosis) within 90 days after randomization occurred in 1 patient (0.3%) in the non sedation group and in 10 patients (2.8%) in the sedation group -The number of days free from coma or delirium was 27 in the non sedation group and 26 in the sedation group -The highest measured RIFLE score within 28 days after randomization was 2 in both groups -All other secondary outcomes did not differ significantly between the trial groups: Length of stay in the ICU (13 vs 14) and

								Median number of days without mechanical ventilation (20 vs 19).
Strom et. al.[12] (2010) DOI: 10.1016/S0140-6736(09)62072-9 A Protocol of No Sedation for Critically Ill Patients Receiving Mechanical Ventilation: A Randomised Trial	Randomized Clinical Trial, open label	Single Center; Denmark	n=113	-18 years of age or older - Underwent endotracheal intubation within 24 hours before screening - Expected to receive mechanical ventilation for more than 24hours	-non sedation	-interrupted sedation (Using Propofol for the first 48hours followed by midazolam infusion thereafter)	**Primary outcome**: 1. Number of days without mechanical ventilation in a 28-day period **Secondary outcomes:** 1. Length of stay in the ICU (28 days) 2. Length of stay in the hospital (90 days) 3. Mortality in the ICU (28 days) 4. Mortality in the Hospital (90 days) 5. Occurrences of need for CT or MRI brain scans 6. Number of accidental removal of endotracheal tube 7. Number of ventilator-associated pneumonia 8. Incidence of delirium	-The no sedation strategy was associated with a significantly higher number of days without ventilation -Length of stay in the intensive care unit was significantly shorter in the no sedation group than in the sedation group, with a difference of 9·7 days -Length of hospital stay was substantially shorter in the no sedation group than in the sedation group, with a difference of 24 days -No difference was recorded in the occurrence of complications between both groups: >Accidental removal of the endotracheal tube (n=7 vs n=6; p=0·69); >Need for CT or MRI brain scans (n=5 vs n=8; p=0·43); >Ventilator-associated pneumonia (n=6 vs n=7; p=0·85) >Need for intubation again within 24 h (n=7 vs n=11; p=0·37). -Delirium was recorded in 11 (20%) patients in the no sedation group and 4 (7%) in the sedation group (p=0·04)

3.2 Study Characteristics of Included Studies on Neuromuscular Blockade (n=6)

Study ID Title Author	Study Design	Setting/Country	Total number of Patients Included	Population	Intervention	Comparator/ Control	Outcome Monitored or Observed	Result
Gainnier et. al.[5] (2004) DOI: 10.1097/01.CCM.0000104114.72614.BC Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome	Randomized Clinical Trial	Multicenter (4), France	n=56	-Adult patients >18 years old -Intubated <48hrs -AECC definition of ARDS; PaO2/FIO2 ratio ≤150; PEEP≥5 cm H20	NMBA infusion (Cisatracurium) for 48hrs + Deep sedation [Midazolam and Sufentanil]	Standard of care (Deep Sedation) [Midazolam and Sufentanil] + Placebo (Sodium chloride 0.9%)	**Primary outcome:** 1. f PaO2/FIO2 ratio (p 0.021) **Secondary outcome:** 1. Decrease in positive end-expiratory pressure 2 Adverse events	-Patients randomized to the NMBA group had a higher PaO2/FIO2 at 48, 96, and 120 hrs. -A decrease in positive end-expiratory pressure (p0.036) was found in the NMBA group. -Only one patient (from the control group) developed pneumothorax
Forel et. al.[4] (2006) DOI: 10.1097/01.CCM.0000239435.87433.0D. Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome	Randomized Clinical Trial	Multicenter (3), France	n=32	-Adult patients >18 years old -Intubated <48hrs -AECC definition of ARDS; PaO2/FIO2 ratio ≤150; PEEP≥5 cm H20	NMBA infusion (Cisatracurium) for 48hrs + Deep sedation [Midazolam and Sufentanil]	Standard of care (Deep Sedation) [Midazolam and Sufentanil] + Placebo (Sodium chloride 0.9%)	**Primary outcome**: 1. Effects of a 48-hr period of NMBA infusion on pulmonary and systemic inflammatory response (measured by IL-6, IL-8, IL-1B) **Secondary outcome:** 1.Improvement in oxygenation, measured with the PaO2/FIO2 ratio	-At 48 hrs, pulmonary concentrations of IL-1 (p 0.005), IL-6 (p 0.038), and IL-8 (p 0.017) were lower in the NMBA group as compared with the control group. -A decrease over time in IL-6 (p 0.05) and IL-8 (p 0.003) serum concentrations in the NMBA group. -Sustained improvement in PaO2/FIO2 ratio in the NMBA group (p < .001).
Papazian et. al.[11] ACURASYS (2010)	Randomized Clinical Trial	Multicenter (20), France	n=340	-Adult patients >18 years old -Intubated <48hrs	NMBA infusion	Standard of care	**Primary outcome**:	The hazard ratio for death at 90 days in the cisatracurium group, as compared with the

DOI: 10.1056/NEJMoa1005372 Neuromuscular blockers in early acute respiratory distress syndrome		(Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)		-AECC definition of ARDS; PaO2/FIO2 ratio ≤150; PEEP≥5 cm H20	(Cisatracurium) for 48hrs + Deep sedation [Midazolam, Propofol, Ketamine, and Sufentanil]	(Deep Sedation) [Midazolam, Propofol, Ketamine, and Sufentanil] + Placebo	1.Reduction of the mortality rate of ARDS patients at d90 **Secondary outcome:** 1. Mortality at day 28, day 60, day 180 and ICU mortality 2. Ventilator-free days and alive at day 28 and day 60 3. Exposure time to FIO2 > 80% or PEEP > 10 cmH2O during the first 7 days 4. Sedatives and analgesics requirements during the first 7 days 5.Organ failure-free days and alive at day 28 6.Incidence of barotrauma 7.Incidence of critical illness neuromyopathy 8.Incidence of ventilator-associated pneumonia 9.Quality of life at day 180	placebo group, was 0.68 (95% confidence interval [CI], 0.48 to 0.98; P=0.04), after adjustment for both the baseline PaO2:FIO2 and plateau pressure and the Simplified Acute Physiology II score. The crude 90-day mortality was 31.6% (95% CI, 25.2 to 38.8) in the cisatracurium group and 40.7% (95% CI, 33.5 to 48.4) in the placebo group (P=0.08). Mortality at 28 days was 23.7% (95% CI, 18.1 to 30.5) with cisatracurium and 33.3% (95% CI, 26.5 to 40.9) with placebo (P=0.05). The rate of ICU-acquired paresis did not differ significantly between the two groups
Lyu et. al. [7] (2014) DOI: 10.3760/cma.j.issn.2095-4352.2014.05.008 Clinical study of early use of neuromuscular blocking agents in patients with severe sepsis and acute respiratory distress syndrome	Randomized Clinical Trial	Single Center, China	n=96	-Adult patients >18 years old -Severe sepsis -Intubated -Moderate to severe ARDS (Berlin Criteria) PaO2/FiO2<200	NMBA infusion (Vecuronium) for 48hrs + Deep sedation	Standard of care (Deep Sedation)	**Primary outcome**: 1. 21-day mortality rate **Secondary outcomes:** 1.acute physiology and chronic health evaluation II (APACHEII) score 2.Sequential organ failure assessment (SOFA) 3.Arterial oxygenation index (PaO2/FiO2)	-For both moderate and severe ARDS group, there were no statistically significant difference in APACHEII score, SOFA score, PaO2/FiO2, ScvO2, Lac and CRP *before* treatment between two groups. -48hrs *afte*r treatment APACHEII score, SOFA score, PaO2/FiO2, ScvO2, and Lac were

							4.Central venous oxygen saturation (ScvO2) 5.Arterial blood lactate (Lac) 6.C-reactive protein (CRP) levels at 48 hours after treatment	significantly improved in *severe* ARDS group compared with control group, while the value of CRP showed no significant difference -21-day mortality in treatment group was significantly lower than that in control group -In moderate ARDS group, the clinical parameters were improved in both groups except for CRP at 48 hours *after* treatment -The 21-day mortality rate in the treatment group was slightly lower than that in the control group but showed no statistically significant difference.
Guervilly et. al.[6] (2016) DOI: 10.1007/s00134-016-4653-4 Effects of neuromuscular blockers on transpulmonary pressures in moderate to severe acute respiratory distress syndrome	Randomized Clinical Trial	Multicenter (2), France	n=24	-Adult patients >18 years old -Intubated <48hrs -ARDS Berlin definitions. PaO2/FiO2≤150, PEEP≥5 cm H20	NMBA infusion (Cisatracurium) for 48hrs + Deep sedation [Midazolam, Ketamine, and Sufentanil]	Standard of care (Deep Sedation) [Midazolam, Ketamine, and Sufentanil]	**Primary outcome**: 1. To assess the effects of a 48-h infusion period of NMBA on respiratory mechanics (Pplat, total PEEP, driving pressure, inspiratory and expiratory PL and ∆PL) in moderate to severe ARDS. **Secondary outcome:** 1. To assess and compare the percentages of positive expiratory PL during the 48 h of the study	-NMBA infusion was associated with an improvement in oxygenation in both moderate and severe ARDS, accompanied by a decrease in both plateau pressure and total positive end-expiratory pressure -The mean inspiratory and expiratory PL were higher in the moderate ARDS group receiving NMBA than in the control group -No change was observed in either driving pressure or ∆PL related to NMBA administration.
PETAL [8] (2019)	Randomized Clinical Trial	Multicenter (48), USA	N=1,006	ARDS, PaO2/FiO2≤150 PEEP≥8 cm H2O,	NMBA infusion	Standard of care	**Primary outcome**: 1. Hospital Mortality to Day 90 [Time Frame:	-The trial was stopped at the second interim analysis for futility.

DOI: 10.1056/NEJMoa1901686 Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome		Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label)		Criteria met in <48 hours	(Cisatracurium) for 48hrs + Deep sedation	(Light Sedation)	90 days after randomization] **Secondary outcomes:** 1. Mean Ventilator Free Days to Day 28 2. Mean Organ Failure Free Days to Day 28 3. ICU Free Days to Day 28 4. Mean Hospital Free Days to Days 28 5. Katz Activities of Daily Living (ADL)/Lawton Instrumental Activities Of Daily Living Scale (IADL) [3mos,6mos,12mos] 6. EuroQol (EQ-5D-5L): Health Related Quality of Life. [3mos, 6mos, 12mos] 7. PTSS-14: Post-traumatic Stress-like Symptoms Scores >/= 45. [3mos,6mos,12mos] 8. MoCA-Blind: Montreal Cognitive Assessment [3mos,6mos,12mos]	- At 90 days, 213 patients (42.5%) in the intervention group and 216 (42.8%) in the control group had died before hospital discharge (between group difference, −0.3 percentage points; 95% confidence interval, −6.4 to 5.9; P=0.93). - In the hospital, patients in the intervention group were less physically active and had more adverse cardiovascular events than patients in the control group. -There were no consistent between-group differences in end points as assessed at 3, 6, and 12 months.

Appendix 4. Risk of Bias Table

Study	Sequence generation	Allocation concealment	Blinding	Withdrawal; loss to follow-up	Selective outcome reporting	Free of other bias	Overall Risk of Bias
Gainnier et. al. (2004)	Low risk	Low risk Centralized	Low risk Nurses aware of assignment; infusion covered by sheet.	Low risk None	Low risk None	Low risk None	**Low**
Forel et. al. (2006)	Low risk	Low risk Centralized	Low risk Nurses aware of assignment; infusion covered by sheet.	Low risk None	Low risk None	Low risk None	**Low**
Papazian et. al. (2010)	Low risk .	Low risk Centralized, using undisclosed block sizes.	Low risk Blinding of patients, clinicians, evaluators, investigators, analysts.	Low risk None	Low risk None	Low risk None	**Low**
Lyu et. al. (2014)	Low risk	Unclear risk Not reported	High risk Probably only patients blinded.	Unclear risk Not reported	High risk Incomplete reporting	High risk Unclear	**High**
Guervilly et. al. (2016)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	**Low**
ROSE (2019)	Low risk	Low risk Process Not specifically explained	Low risk -Primary end point unblinded. -uncertainty about In-hospital assessors of end points being unaware of treatment group, but all post-discharge end points were assessed by trial personnel who were unaware of the group assignment.	Low risk	Low risk	Low risk Although trial was topped early for futility it included a very large number of events	**Low**

Appendix 5. GRADE Evidence Profile

5.1 GRADE PROFILE: Sedation vs Non Sedation

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sedation	No Sedation	Relative (95% CI)	Absolute (95% CI)		
90-Day Mortality												
2	randomised trials	not serious	serious[a]	serious[b]	serious[c]	none	157/409 (38.4%)	168/404 (41.6%)	RR 1.00 (0.70 to 1.43)	0 fewer per 1,000 (from 125 fewer to 179 more)	⨁⨁◯◯ Low	CRITICAL
Length of ICU Stay												
2	randomised trials	not serious	not serious	serious[b]	serious[c]	none	409	404	-	MD 0.34 lower (6.15 lower to 5.47 higher)	⨁⨁◯◯ Low	IMPORTANT
Ventilator Free Days												
2	randomised trials	not serious	not serious	serious[b]	serious[c]	none	409	404	-	MD 1.07 lower (3.05 lower to 0.91 higher)	⨁⨁◯◯ Low	IMPORTANT
Adverse Event: Delirium												
1	randomised trials	not serious	not serious	serious[b]	serious[c]	none	4/58 (6.9%)	11/55 (20.0%)	**RR 0.34** (0.12 to 1.02)	**132 fewer per 1,000** (from 176 fewer to 4 more)	⨁⨁◯◯ Low	CRITICAL
Adverse Event: Extubation												
2	randomised trials	not serious	not serious	serious[b]	serious[c]	none	7/409 (1.7%)	11/404 (2.7%)	**RR 0.66** (0.26 to 1.66)	**9 fewer per 1,000** (from 20 fewer to 18 more)	⨁⨁◯◯ Low	CRITICAL
Adverse Event: Major Thrombotic Event (Pulmonary Embolism & Deep Vein Thrombosis)												
1	randomised trials	not serious	not serious	serious[b]	not serious	none	10/351 (2.8%)	1/349 (0.3%)	**RR 9.94** (1.28 to 77.26)	**26 more per 1,000** (from 1 more to 219 more)	⨁⨁⨁◯ Moderate	CRITICAL
Adverse Event: Reintubation												
1	randomised trials	not serious	not serious	serious[b]	serious[c]	none	11/58 (19.0%)	7/55 (12.7%)	**RR 1.49** (0.62 to 3.57)	**62 more per 1,000** (from 48 fewer to 327 more)	⨁⨁◯◯ Low	CRITICAL
Adverse Event: Ventilator-Associated Pneumonia												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sedation	No Sedation	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious[b]	serious[c]	none	7/58 (12.1%)	6/55 (10.9%)	**RR 1.11** (0.40 to 3.09)	**12 more per 1,000** (from 65 fewer to 228 more)	⊕⊕◯◯ Low	CRITICAL

CI: confidence interval; MD: mean difference; **RR:** risk ratio

Explanations

a. Significant heterogeneity (I^2>50%)
b. Study population were mechanically ventilated patients with ARDS but of non-COVID etiology
c. Risk estimates crossed the line of no effect

5.2. GRADE PROFILE: Neuromuscular Blockade vs Standard of Care (Sedation Only)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With SoC	With NMBA		Risk with SoC	Risk difference with NMBA
Duration of Mechanical Ventilation											
431 (3 RCTs)	not serious	not serious	serious[b]	not serious	none	⊕⊕⊕◯ Moderate	208	223	-	The mean duration of Mechanical Ventilation was **-1.21**	MD **1.21 lower** (4.23 lower to 1.81 higher)
Mortality Outcome by Level of Sedation (Light) at 90 days											
1006 (1 RCT)	not serious	not serious	serious[b]	serious[c]	none	⊕⊕◯◯ Low	216/505 (42.8%)	213/501 (42.5%)	**RR 0.99** (0.86 to 1.15)	428 per 1,000	**4 fewer per 1,000** (from 60 fewer to 64 more)
Mortality Outcome by Level of Sedation (Deep) at t 90 days											
431 (3 RCTs)	not serious	not serious	serious[b]	not serious	none	⊕⊕⊕◯ Moderate	98/208 (47.1%)	76/223 (34.1%)	**RR 0.72** (0.58 to 0.91)	471 per 1,000	**132 fewer per 1,000** (from 198 fewer to 42 fewer)
Mortality Outcome at 21-28days											
503 (5 RCTs)	not serious	not serious	serious[b]	not serious	none	⊕⊕⊕◯ Moderate	98/245 (40.0%)	65/258 (25.2%)	**RR 0.63** (0.49 to 0.82)	400 per 1,000	**148 fewer per 1,000** (from 204 fewer to 72 fewer)
ICU Mortality											

Certainty assessment							Summary of findings				
455 (4 RCTs)	not serious	not serious	serious[b]	not serious	none	⊕⊕⊕◯ Moderate	98/221 (44.3%)	73/234 (31.2%)	**RR 0.70** (0.55 to 0.89)	443 per 1,000	**133 fewer per 1,000** (from 200 fewer to 49 fewer)
Improvement in Oxygenation after 48hours (assessed with: PaO2/FiO2)											
821 (3 RCTs)	not serious	serious[a]	serious[b]	serious[c]	none	⊕◯◯◯ Very Low	394	427	-	The mean improvement in Oxygenation after 48hours was **0**	MD **22.2 higher** (4.47 lower to 48.88 higher)
Improvement in Oxygenation after 72hours (assessed with: PaO2/FiO2)											
1011 (4 RCTs)	not serious	not serious	serious[b]	serious[c]	none	⊕⊕◯◯ Low	469	542	-	The mean improvement in Oxygenation after 72hours was **0**	MD **12.9 higher** (3.88 higher to 21.92 higher)
Ventilator Free Days (Day 28)											
1437 (4 RCTs)	not serious	not serious	serious[b]	serious[c]	none	⊕⊕◯◯ Low	713	724	-	The mean ventilator Free Days (Day 28) was **0**	MD **0.68 higher** (0.86 lower to 2.22 higher)
Barotrauma											
1437 (4 RCTs)	not serious	not serious	serious[b]	not serious	none	⊕⊕⊕◯ Moderate	52/713 (7.3%)	29/724 (4.0%)	**RR 0.55** (0.35 to 0.85)	73 per 1,000	**33 fewer per 1,000** (from 47 fewer to 11 fewer)
Pneumothorax											
1401 (3 RCTs)	not serious	not serious	serious[b]	not serious	none	⊕⊕⊕◯ Moderate	45/695 (6.5%)	21/706 (3.0%)	**RR 0.46** (0.28 to 0.77)	65 per 1,000	**35 fewer per 1,000** (from 47 fewer to 15 fewer)
ICU Acquired Weakness											
714 (4 RCTs)	not serious	not serious	serious[b]	serious[e]	none	⊕⊕◯◯ Low	115/351 (32.8%)	136/363 (37.5%)	**RR 1.15** (0.95 to 1.39)	328 per 1,000	**49 more per 1,000** (from 16 fewer to 128 more)
Adverse Events											
1437 (4 RCTs)	not serious	not serious	serious[b]	serious[f]	none	⊕⊕◯◯ Low	22/713 (3.1%)	36/724 (5.0%)	**RR 1.63** (0.97 to 2.71)	31 per 1,000	**19 more per 1,000** (from 1 fewer to 53 more)

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Significant heterogeneity (I2>50%)

b. The population included in the studies are Non-Covid ARDS patients. Based on latest studies, there are some considered differences between the pathology of Non- Covid and Covid ARDS which may change the actual results if the said population was studied.

c. CI included both small benefit and harm

d. Downgraded by 1 due to serious imprecision. CI included extreme benefit and harm

e. CI included substantial harm and trivial benefit.

f. The CI included both substantial harm and small benefit. Also, the number of events is small (n=58).

Appendix 6. Characteristics of Ongoing Studies

6.1 Study Characteristics of Ongoing Studies on Sedation and Neuromuscular Blockade on COVID-19 patients (n=4)

Title Identifier Expected Completion Date	Intervention	Comparator/Control	Patients/Population Recruited	Outcomes
Comparison for the Effect of Neuromuscular Blocking Agents Versus Sedation Alone on Severe ARDS Patients Due to COVID-19 NCT04922814 August 1, 2022	**Experimental:** Muscle relaxant group (group B) They will receive muscle relaxation treatment for at least 48 hours. Cisatracurium will be given. Short term infusions up to 24 hours will be given in a dose rate of 2-3 mic/Kg/min followed by intervallic shots of 2-5 mg.	**Control:** No Intervention (Group A) Only sedation for mechanically ventilated COVID patients	-18 Years to 75 Years -With Severe ARDS: PaO2/FiO2 <200, resistant hypoxemia and tachypnoea (RR > 40 breath/minute) Not relieved by high frequency nasal canula or CPAP. -Need for invasive mechanical ventilation (uncooperative) ***NOT YET RECRUITING***	**Primary Outcome Measures:** -PaO2/FiO2: Ratio of arterial oxygen pressure in milliliters mercury to fraction of inspired oxygen at same time within the arterial blood gas **Secondary Outcome Measures:** -Change in lung mechanics -SOFA score -Measurement of tissue perfusion: -Monitoring of Alveolar - Arterial Oxygen difference -28 days survival -Recording risk factors -Recording complications
Sevoflurane Sedation in COVID-19 ARDS Patients to Reduce Lung Injury: a Randomized Controlled Trial NCT04355962 July 16, 2021 *(Final data collection date for primary outcome measure)* (No results posted yet)	**Experimental**: Sevoflurane Sedation Sedation with sevoflurane (etSevo 0.5-1.5 Vol %) for 48 hours in patients with COVID-19 ARDS	**Control:** Intravenous No use of sevoflurane, but current intravenous sedation at discretion of the ICU physician in charge, e.g. with propofol, fentanyl, midazolam and dexmedetomidine	-Male and female patients -18 to 85 years -Positive SARS-CoV-2 test or CTscan suspected of COVID-19 ARDS -On sedation and mechanical ventilation in ICU	**Primary Outcome Measures:** -Composite outcome of death rate (rate of patients that did not survive) -Organ failure rate (rate of patients surviving with persistent organ dysfunction) at day 28 **Secondary Outcome Measures:** -The effect of sevoflurane -Plasma Inflammatory markers -Length of stay at hospital -Sex-related differences in complications
Inhaled Sedation in COVID-19-related Acute Respiratory Distress Syndrome (ISCA): an International Research Data Study in the Recent Context of Widespread Disease	**Experimental:** Inhaled sedation	**Control:** Intravenous sedation	- >18years old - Admitted in ICU requiring invasive mechanical ventilation - -	**Primary Outcome Measures:** -Number of days off the ventilator **Secondary Outcome Measures:** -All-cause mortality

Resulting From the 2019 (SARS-CoV2) Coronavirus Pandemics (COVID-19)NL8523 NCT04383730 April 30, 2021 *(Final data collection date for primary outcome measure)* (No results posted yet)			-Suspected or confirmed COVID19	-Ventilator-free days -ICU-free -Number of days alive and not in the ICU from inclusion to day 28 -Duration of invasive mechanical ventilation -Duration of controlled mechanical -Physiological measures of lung function -Development of complications -Duration of vasopressor -Duration of renal replacement therapy -Duration (in days) of any adjuvant therapies -Number of days with continuous neuromuscular blockade -Type of sedation practices
SedAting With Volatile Anesthetics Critically Ill COVID-19 Patients in ICU: Effects On Ventilatory Parameters And Survival. Multicentre Open-label, Pragmatic, Randomized Controlled Trial and a Parallel Prospective (Non-randomized) Cohort Study NCT04415060 June 15, 2023	**Experimental:** Inhaled - volatile anesthetic The ICU patient will be randomized to either Isoflurane or Sevoflurane, whichever is available at the hospital. Dosage will be modified as per health care team guidance for the best treatment of the participant. **Interventions:** Drug: Isoflurane Inhalant Product Drug: Sevoflurane inhalant product	**No Intervention:** Standard Care The ICU patient will be randomized to standard of care, which is any IV sedation supplied by the hospital. Dosage will be modified as per health care team guidance for the best treatment of the participant. **No Intervention:** Non-randomized ICU patients who cannot be randomized will receive inhaled or IV sedation as per available in their unit. This is done to try to obtain the maximum amount of information available from the patients present to our ICUs.	-≥ 18 years of age; Mechanically ventilated -Receiving IV sedation by infusion or bolus for ≤72 hours to facilitate mechanical ventilation - Proven or suspected (under investigation) COVID-19 infection	**Primary Outcome Measures:** -Hospital Mortality -Ventilator-Free -ICU-Free Days -Participant Quality of Life at 3 and 12 months after discharge **Secondary Outcome Measures:** -Median Daily Oxygenation -Delirium and Coma Free Days -Adjunctive ARDS therapies -Hospital-Free Days -Disability -Cost Utility Analysis -Quality of Life

6.2 Study Characteristics of Ongoing Studies on Sedation on NON COVID patients (n=1)

Title Identifier Expected Completion Date	Intervention	Control Intervention: Comparator/Control	Patients/Population Recruited	Outcomes

Non-sedation versus sedation with a daily wake-up trial in critically ill patients receiving mechanical ventilation (NONSEDA Trial): study protocol for a randomised controlled trial NCT00196768 June 2018 *(Final data collection date for primary outcome measure)* (No results posted yet)	**Experimental:** The experimental group will not receive sedatives. Patients are thoroughly and repeatedly informed by the staff of where they are, what has happened, and what type of treatment they are going to receive.	**Control:** The control group will be sedated with continuous infusion of sedatives to Ramsay score 3 to 4. The first 48 hours the patients will be sedated with propofol, after 48 hours midazolam will be used.	-Endotracheally intubated within the last 24 hours -Expected time on ventilator >24 hours as estimated by the attending physician -Age ≥18 years	**Primary Outcome Measures:** -All-cause mortality at 90 days after randomization **Secondary Outcome Measures:** -Days until death throughout the total observation period -Coma- and delirium-free days -Highest RIFLE score days until discharge from the intensive care unit (within 28 days) -Days until the participant is without mechanical ventilation (within 28 days); and) -Proportion of patients with a major cardiovascular outcome. Explorative outcomes: -All cause mortality at 28 days after randomization -Days until discharge from the intensive care unit -Days until the participant is without mechanical ventilation -Days until discharge from the hospital - Incidence of organ failure

Appendix 7. Forest Plots

A. SEDATION IN MECHANICALLY VENTILATED PATIENTS

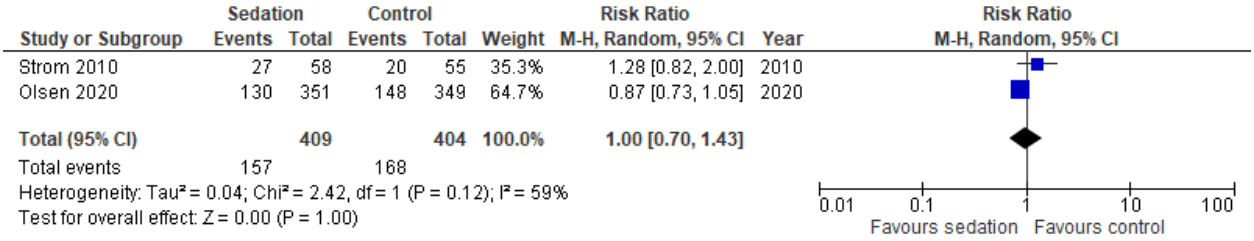


Figure 1: 90-day Mortality Outcome for Sedation versus No Sedation

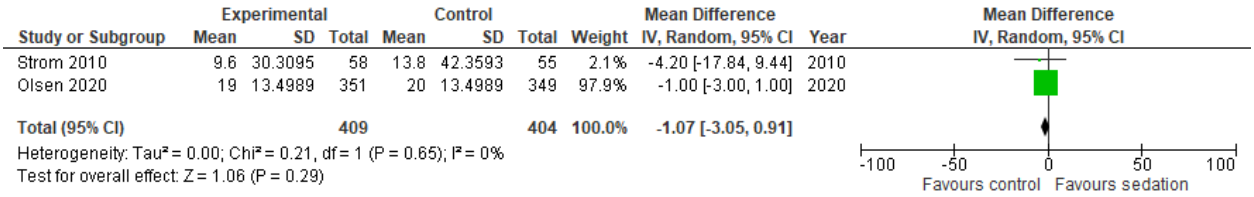


Figure 2: Ventilator Free Days for Sedation versus No Sedation

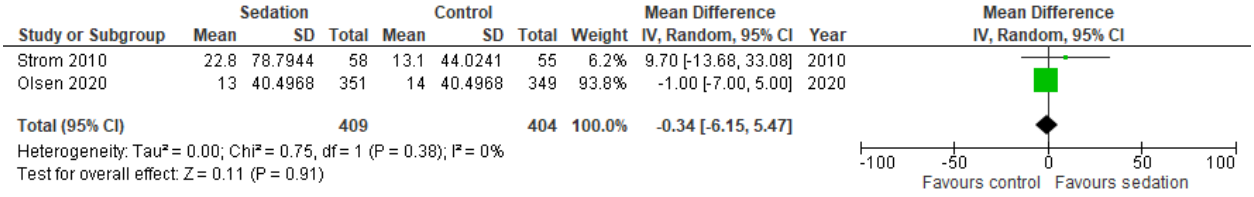


Figure 3: Length of ICU Stay for Sedation versus No Sedation

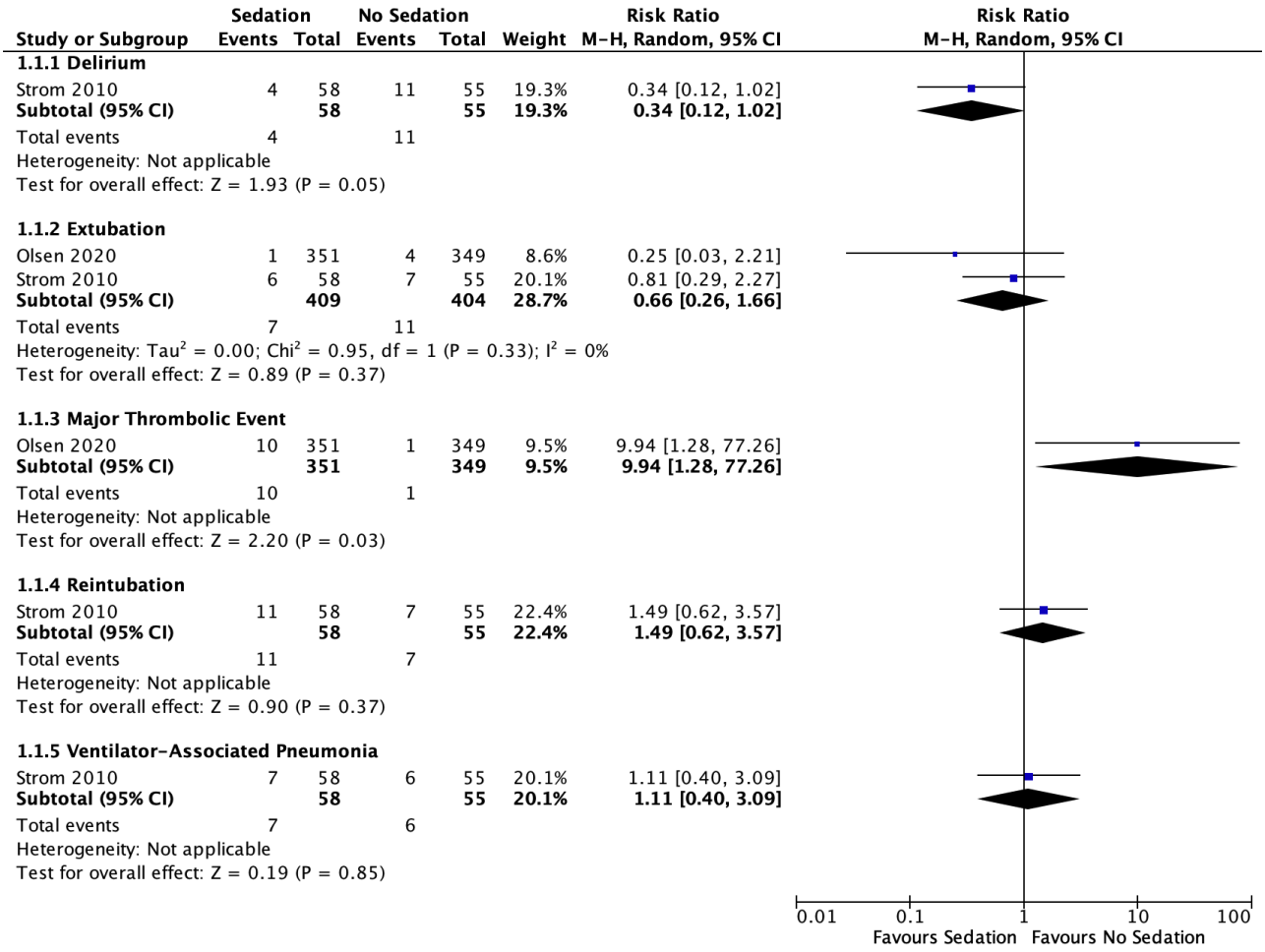


Figure 4: Adverse Events for Sedation versus No Sedation

B. NMBA IN MECHANICALLY VENTILATED PATIENTS WITH ARDS

Figure 5: Mortality at 21-28 days

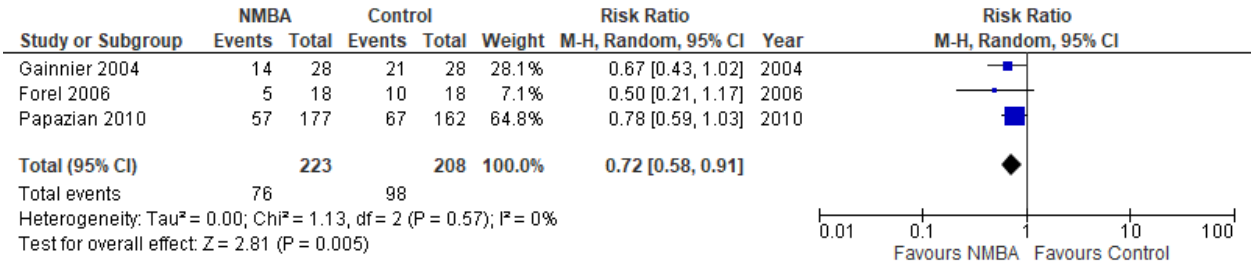


Figure 6: Mortality at 90 days

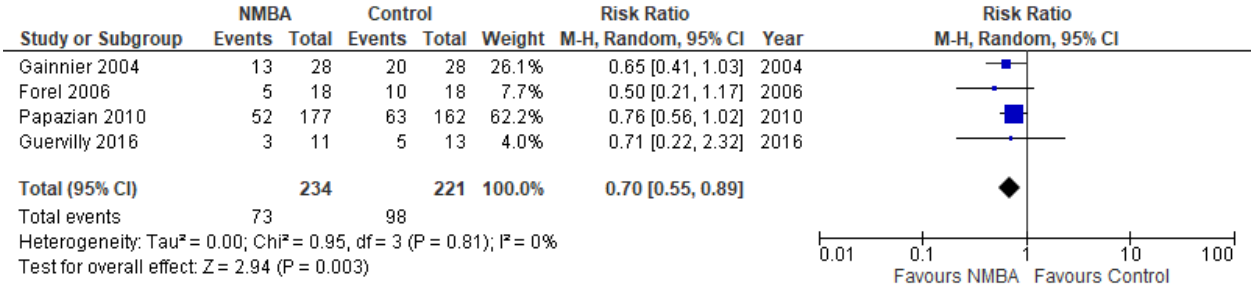


Figure 7: ICU Mortality

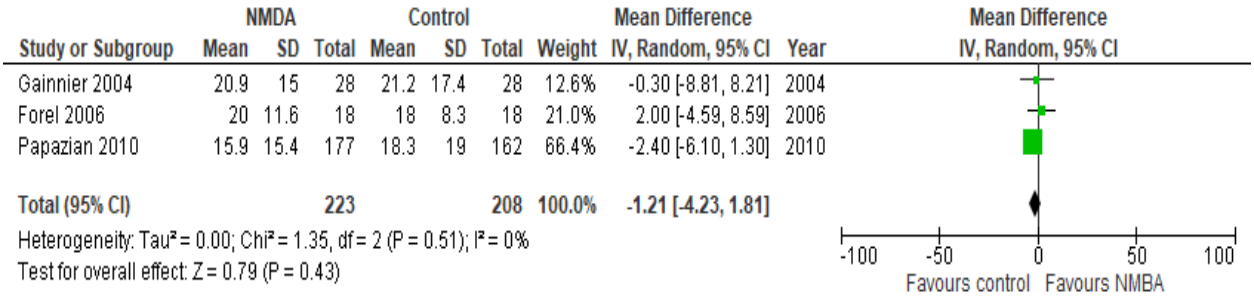


Figure 8: Duration of Mechanical Ventilation

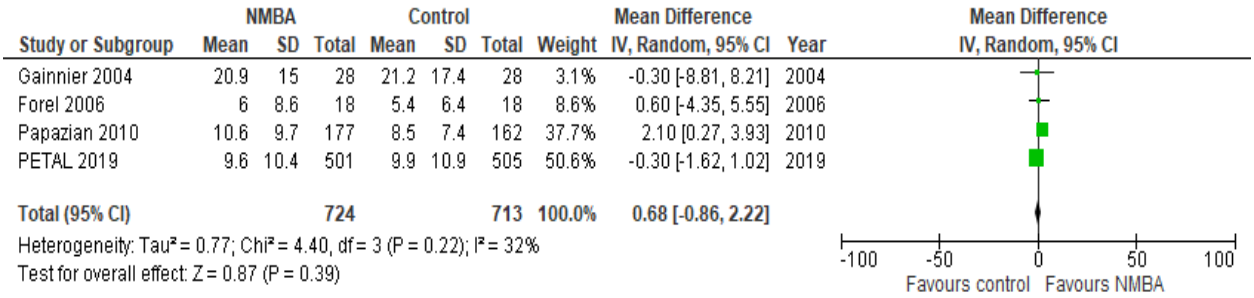


Figure 9: Ventilator Free Days at day 28

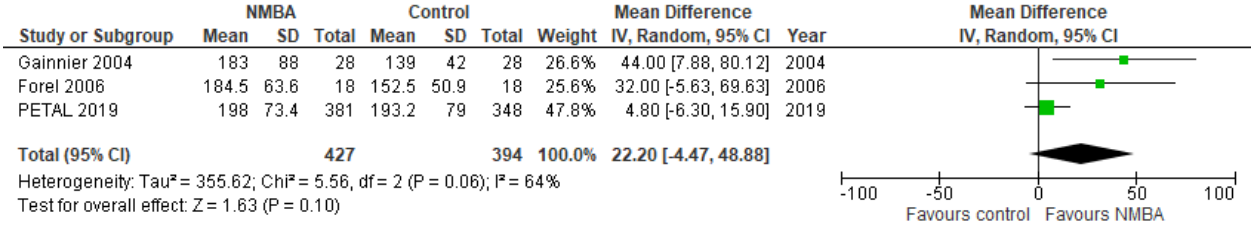


Figure 10: PaO_2/FiO_2 Changes after 48hours

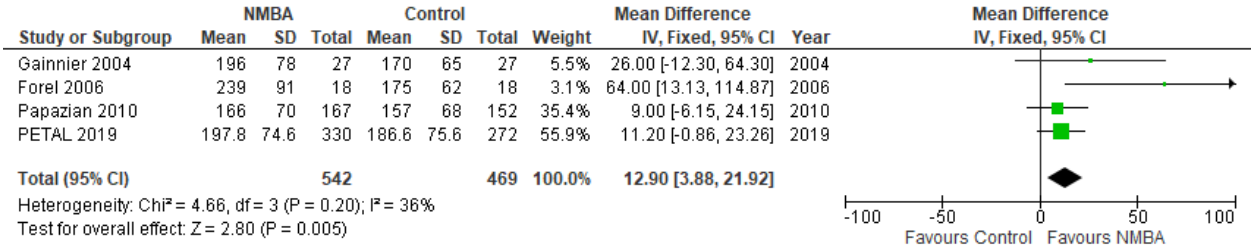


Figure 11: PaO_2/FiO_2 Changes after 72hours

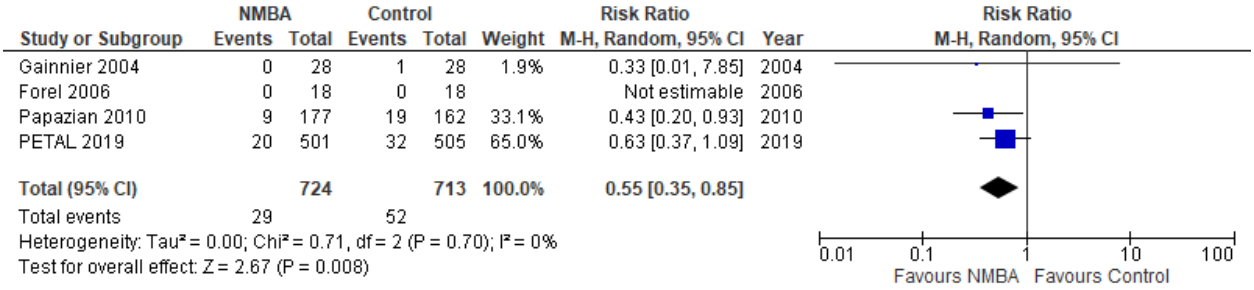


Figure 12: Barotrauma

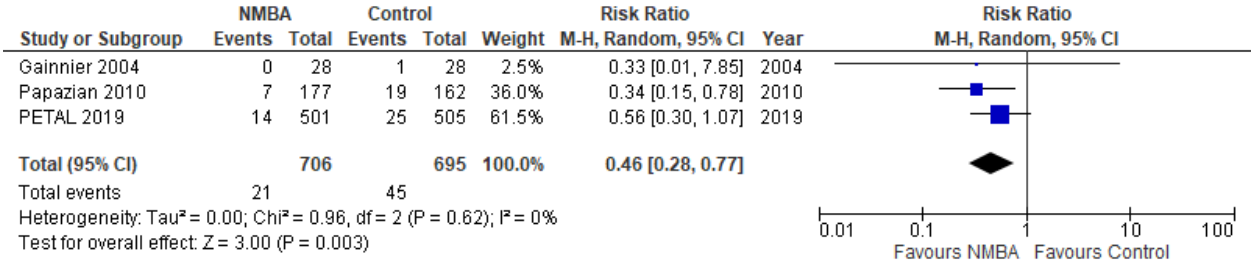


Figure 13: Pneumothorax

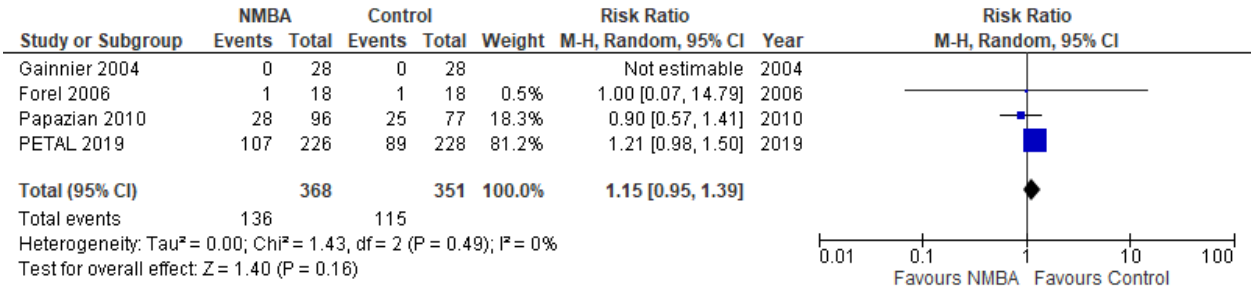


Figure 14: ICU Acquired Weakness

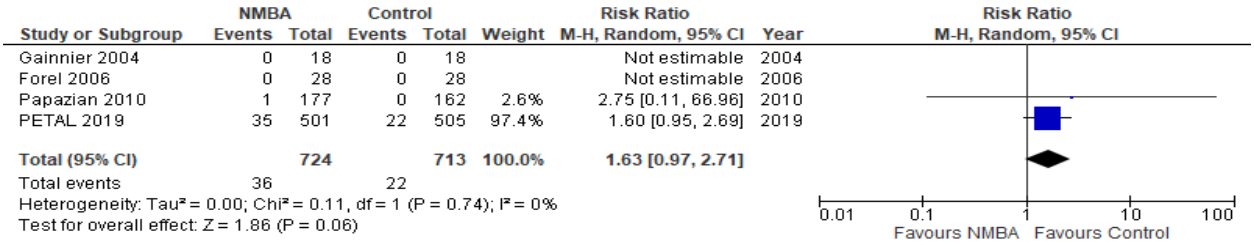


Figure 15: Adverse Events

Appendix 8. Other Tables

Table 7. Adverse Events with NMBA infusion

System/disorder	Event	Severity	Intervention	Control	Overall
Blood/lymphatic	Methemoglobinemia	Serious	2	0	2
Cardiac	Complete atrioventricular block	Serious	1	0	1
	Atrial fibrillation (paroxysmal)	Non-Serious	1	0	1
	Atrial fibrillation w/ rapid vent response	Serious	1	0	1
	Bradycardia	Serious	1	0	1
		Non-Serious	1	0	1
	Cardiac arrest	Serious	6	2	8
		Non-Serious	0	2	2
	Cardiac arrhythmia (NOS)	Non-Serious	1	0	1
	3rd degree atrioventricular block	Serious	0	1	1
	Myocardial infarction	Serious	1	1	2
	Serious prolonged bradycardia	Non-Serious	1	0	1
	Tachycardia	Non-Serious	1	0	1
	Supraventricular tachycardia	Serious	1	0	1
	Torsades De Pointe	Serious	1	0	1
	Vasovagal reaction	Non-Serious	0	1	1
	Ventricular tachycardia	Serious	2	0	2
Gastrointestinal	Ileus	Non-Serious	0	1	1
General	Death *	Serious	1	0	1
Infection	Pneumonia	Non-Serious	0	1	1
Injury	Paralysis awareness	Non-Serious	1	0	1
Metabolism/nutrition	Hyperkalemia	Serious	0	1	1
Musculoskeletal	Myopathy	Non-Serious	1	0	1
Nervous system	Intracranial bleed	Serious	0	1	1
	Cerebral infarction	Serious	1	1	2
	Cerebrovascular accident	Serious	1	0	1
	Brain hemorrhage	Serious	1	1	2
	Polyneuropathy	Serious	0	1	1
	Seizure	Serious	1	0	1
	Stroke	Serious	3	1	4
	Subarachnoid hemorrhage	Serious	0	1	1
	Subdural effusion	Serious	1	0	1
Respiratory tract	Aspiration	Serious	0	1	1
		Non-Serious	0	1	1
	Airway obstruction	Serious	1	0	1
Vascular disorders	Hematoma	Serious	0	1	1
	Retroperitoneal hemorrhage	Non-Serious	0	1	1
	Hypotension	Serious	1	1	2
		Non-Serious	6	2	8
	Superficial venous thrombosis	Non-Serious	1	0	1