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Neuromuscular blockade management in patients with COVID-19

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This narrative review evaluates the evidence for using neuromuscular blocking agents (NMBA) in patients being treated for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). While large prospective randomized-controlled trials (RCTs) are lacking at this point in time, smaller observational studies and case series are reviewed to ascertain the indications and utility of NMBAs. Additionally, large RCTs that address similar clinical scenarios are reviewed and the authors translate these findings to patients with COVID-19. Specifically, NMBAs can be helpful during endotracheal intubation to minimize the risk of patient coughing and possibly infecting healthcare personnel. NMBAs can also be used in patients to promote patient-ventilator synchrony while reducing the driving pressure needed with mechanical ventilation (MV), particularly in patients with the severe clinical presentation (Type H phenotype). Prone positioning has also become a cornerstone in managing refractory hypoxemia in patients with SARS-CoV-2 acute respiratory distress syndrome, and NMBAs can be useful in facilitating this maneuver. In the perioperative setting, deep levels of neuromuscular blockade can improve patient outcomes during laparoscopic operations and may theoretically reduce the risk of aerosolization as lower insufflation pressures may be utilized. Regardless of the indication, quantitative neuromuscular monitoring remains the only reliable method to confirm adequate recovery following cessation of neuromuscular blockade. Such monitors may serve a unique purpose in patients with COVID-19 as automation of measurements can reduce healthcare personnel-patient contact that would occur during periodic subjective evaluation with a peripheral nerve stimulator.

Keywords: COVID-19; Neuromuscular blockade; Neuromuscular blocking agents; Neuromuscular monitoring; Respiratory distress syndrome; SARS-CoV-2.

Introduction

Coronavirus disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) started in December 2019 as an outbreak of pneumonia in Wuhan, Hubei, China [1]. The disease spread rapidly to other areas in China, as well as other countries around the world, becoming a public health problem of international concern [2]. In March 2020, the World Health Organization (WHO) declared the outbreak a pandemic with more than 1,700,000 confirmed cases and 111,600 deaths in more than 210 countries [3].

The Center for Systems Science and Engineering (CSSE) at Johns Hopkins University reported a total global case number of 78,420,543 and deaths of 1,725,057 by December

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2020 [4,5]. In the beginning, the experience in Wuhan demonstrated that approximately 3.2% of patients with COVID-19 required intubation and mechanical ventilation (MV) [6]. Since then, frontline health workers face a considerable challenge in providing adequate airway management and preventing the spread of infection due to the high transmission risk of SARS-CoV-2 during aerosol-generating procedures (AGPs) such as endotracheal intubation [7].

Neuromuscular blocking agents (NMBA) are a routinely utilized class of medications in the operating room and intensive care unit (ICU) to facilitate MV, optimize endotracheal intubating conditions, and improve surgical conditions [8–11]. However, prolonged neuromuscular blockade is associated with complications such as patient awareness during paralysis, critical illness myopathy, and residual neuromuscular weakness [11]. The exact efficacy and indications of neuromuscular blockade in patients with COVID-19 remains unclear given the paucity of available literature. The purpose of this review is to summarize the current evidence regarding neuromuscular blockade management in patients with COVID-19 and provide a description of the neuromuscular blockade management strategies available to consider during the global pandemic. In addition, we will review optimal methods for neuromuscular blockade monitoring to aid in determining the level of the blockade and confirm adequate neuromuscular recovery while avoiding complications due to residual neuromuscular blockade.

Indications and methods

The use of NMBAs in patients with COVID-19 typically involves optimizing conditions for endotracheal intubation, facilitating MV, and positioning patients with refractory hypoxia in prone. It is important to note that there is no specific guideline regarding the indication for NMBAs in patients with COVID-19. As such, the decision to establish neuromuscular blockade must be individualized by the clinician based on the specific patient and clinical characteristics (Table 1).

The present literature review investigates recent published studies concentrating on the role of NMBAs in patients with COVID-19. The literature search was done in PubMed, Medline, Scopus, and Google Scholar between December 2019 and January 2021. The search used keywords related to the population of interest (SARS-CoV-2, coronavirus, COVID-19 patients) and the intervention of interest (neuromuscular blockade, NMBA, MV, laparoscopy). We also screened references from included studies. Papers that appeared relevant to the topic of interest were retrieved as full texts and were reviewed independently. We included small-scale observational studies and case series as the primary source of information due to the lack of large-scale randomized control trials related to COVID-19.

Endotracheal intubation

Although the benefit of establishing an advanced airway is well-recognized in patients with COVID-19, initial respiratory

Table 1. Indications for NMBA Use in Patients with COVID-19

Indications	Benefits of NMBA use	Evidence
Endotracheal intubation	Improves intubation conditions and minimizes risk of coughing during airway manipulation.	Consensus guidelines from various societies [12].
Facilitate MV	Minimization of ventilator dyssynchrony, breathing effort, driving pressure, and P-SILI.	Evidence from ARDS and expert opinion [23,57].
AGPs such as endotracheal suctioning and bronchoscopy	Avoidance of physical movement and coughing during procedure and thus minimizing risk to healthcare providers.	Expert opinion [56].
Improve oxygenation	Particularly useful in Type H phenotype, improves ventilator synchrony, inhibits inflammatory cytokines.	Meta-analysis from ARDS literature [20].
Prone positioning	Reduction of complications such as accidental extubation, coughing, endotracheal tube obstruction, main-stem bronchus intubation.	ARDS literature and case reports [30,37].
Laparoscopic surgery	Deep levels of neuromuscular blockade may facilitate lower pneumoperitoneum insufflating pressures and reduce risk of aerosolization [46,47].	RCTs from surgical literature, expert opinion

NMBA: neuromuscular blocking agents, COVID-19: coronavirus disease 2019, MV: mechanical ventilation, P-SILI: patient-self-induced lung injury, ARDS: acute respiratory distress syndrome, AGP: aerosol generating procedure, RCT: randomized controlled trial.

approach can be directed towards non-invasive therapies [3,6]. This can be accomplished with high-flow nasal cannula, continuous positive airway pressure, or bilevel positive airway pressure (BiPAP). However, respiratory instability can progress rapidly and the need for advanced airway management may be required. While the exact timing remains unclear, patients in respiratory distress showing no improvement, tachypnea with a respiratory rate > 30/min, and poor oxygenation ($\text{PaO}_2/\text{FiO}_2 < 150$ mmHg) after a trial of high-flow oxygen therapy or noninvasive ventilation should be considered for endotracheal intubation and invasive MV [8]. Most experts advocate performing a rapid sequence induction and intubation with rocuronium as this allows for pharmacologic rescue with sugammadex in the catastrophic 'can't intubate/can't ventilate' scenario. This technique, in conjunction with manual maneuvers to restore airway patency, can facilitate ventilation faster than waiting for succinylcholine-induced neuromuscular blockade to subside [12–14].

Meng et al. [6] described their experience with intubating patients in Wuhan, China. This group stressed that cough suppression in an effort to minimize aerosolization was a top priority to protect clinicians instrumenting the airway. Preoxygenation proved paramount in this vulnerable population and was accomplished with either high-flow nasal cannula or BiPAP [6]. After preoxygenation for at least 3 min, this group proceeded with modified rapid sequence induction using midazolam (1–2 mg) for those extremely anxious patients and lidocaine (> 1.5 mg/kg) to suppress coughing [15]. Etomidate (0.2–0.3 mg/kg) was used for induction for those with hemodynamic instability or propofol (1–1.5 mg/kg) for those with stable hemodynamics. This group then utilized rocuronium (1 mg/kg) or succinylcholine (1 mg/kg) immediately after loss of consciousness. Finally, the airway was secured with video laryngoscopy within 60 s of NMBA administration [6].

On the other hand, in an effort to shorten the time to onset of neuromuscular blockade, a priming dose of rocuronium has been described when intubating patients with COVID-19 [15]. Utilizing 0.03–0.04 mg/kg rocuronium 3 min before intubating, Hoshijima et al. [15] evaluated this technique when intubating patients with COVID-19. Not surprisingly, these patients became hypoxic with oxygen saturations as low as 55% prior to securing the airway as even low levels of neuromuscular blockade proved deleterious to patients with COVID-19 prior to intubation. As such, we discourage the use of a priming dose of a non-depolarizing NMBA in patients with or without COVID-19 as such a practice exposes patients to weakness and its associated complications prior to securing the airway.

In order to avoid patient complications and exposure to health-

care workers during endotracheal intubation, most of the current literature suggests the use of fitted respirator masks plus other personal protective equipment [16]. Some experts advocate for 5 min of preoxygenation with a good mask seal and no bag-mask ventilation, a rapid sequence induction under video laryngoscopy by experienced personnel limiting close distance from clinicians to the patient's oral cavity, and avoiding awake fiberoptic intubation [17]. Finally, adequate neuromuscular blockade can not only lower the risk of viral transmission by avoiding coughing while also providing optimal conditions to instrument the airway [8,18,19].

Patient self-induced lung injury

Patient self-induced lung injury (P-SILI) should be considered as a possible complication in SARS-CoV-2-induced acute respiratory distress syndrome (ARDS) [20]. The mechanism of P-SILI is based on three factors: increased lung stress, increased lung perfusion, and patient-ventilator asynchrony [21]. Lung stress is a function of the increase in transpulmonary pressure (barotrauma) and global lung stress resulting in larger tidal volumes (volutrauma). Increases in lung perfusion are associated with an increase in transmural vascular pressure associated with spontaneous effort, as this will cause a more negative pleural pressure and result in increased perfusion to intrathoracic vessels. This phenomenon can cause pulmonary edema, particularly when a vigorous spontaneous effort is made by the patient. Lastly, patient-ventilator asynchrony is associated with significant mortality based on the presence of the reverse triggering effect in which patient effort triggers the ventilator after a ventilator-initiated breath. This dyssynchrony increases the transpulmonary pressures, tidal volumes, and ultimately, lung stress [21].

NMBAs provide a pharmacologic intervention to combat spontaneous effort, lung stress, and ventilator dyssynchrony [22–24]. Therefore, early administration of NMBAs might also play an important role in decreasing devastating pulmonary outcomes. In a cohort of 56 patients with ARDS comparing conventional therapy vs. conventional therapy plus NMBA, Gannier et al. [22] reported improvement in $\text{PaO}_2/\text{FiO}_2$ ratio at 48, 96, and 120 h after establishing an adequate neuromuscular blockade ($P < 0.001$). Also, the early administration of NMBA in patients with ARDS with a lung-protective ventilation strategy has brought benefits in terms of inflammatory marker reduction, demonstrating a decrease in IL-8, IL-1beta, IL-6, and IL-8 [23]. Additionally, in those patients with severe ARDS ($\text{PaO}_2/\text{FiO}_2 < 150$ mmHg), the hazard ratio (HR) for death at 90 days using cisatracurium compared with placebo was 0.68 (95% CI, 0.48, 0.98, $P = 0.04$) [24]. Consequently,

early administration of NMBAs might be a potential therapy utilized to improve survival rate, ventilator-free days, days outside the ICU, and barotrauma [24,25]. While NMBAs have not been comprehensively studied in patients with COVID-19 developing P-SILL, expert opinion, and extrapolating data from similar conditions suggest that this class of medication could be an important option for either prophylactic or supportive therapy in COVID-19 [16].

MV in refractory hypoxia

While the Berlin criteria applies to COVID-19-induced ARDS, the current literature emphasizes there are different COVID-19 clinical presentations (Types L and H) and therapy strategies depend on the severity of lung injury and the MV requirements. Specifically, the severity of infection, host response, physiological reserve, comorbidities, ventilatory responsiveness of the patient to hypoxemia, and the time elapsed between the onset of the disease and clinical deterioration between the two phenotypes. Type L involves a milder presentation and is characterized by low elastance, high compliance, low ventilation-to-perfusion ratio, low lung weight, and low alveoli recruitability. Type H involves high elastance, high right-to-left shunt, high lung weight, and high recruitability due to a larger proportion of non-aerated pulmonary tissue [26]. Authors document an initial non-invasive MV management for Type L, guiding the respiratory support on parameters such as esophageal and central venous pressure swings, while treating Type H in a similar fashion to patients with severe ARDS [26].

While NMBAs can play a valuable role in managing patients with both Type H and L COVID-19 phenotypes, patients with type H may be associated with a better response to neuromuscular blockade given the poorer compliance [26,27]. Traditionally, NMBAs have been used early in the course of ARDS when the $\text{PaO}_2/\text{FiO}_2 < 150$ mmHg in order to improve oxygenation and reduce patient-ventilator dyssynchrony with a goal of reducing ventilator-induced lung injuries and inflammatory cytokines [28]. The largest multicenter trial regarding the effectiveness of neuromuscular blockade in ARDS is the ARDS et Curarisation Systematique (ACURASYS) published in 2010. This effort concluded that treatment with cisatracurium for 48 h early in the course of severe ARDS improved the adjusted 90-day survival rate versus placebo (30.8% vs. 44.6%, $P = 0.04$, respectively), increased the numbers of ventilator-free days (1–28 days [$P = 0.04$]; 1–90 days [$P = 0.03$]) and days outside the ICU (1–90 days [$P = 0.03$]), and decreased the incidence of barotrauma during the first 90 days [24]. Conversely, the Reevaluation of Systematic Early Neuromus-

cular Blockade (ROSE) trial found the addition of early administration of cisatracurium with concomitant deep sedation did not result in lower mortality than a usual-care approach to MV that included lighter sedation targets demonstrating a mortality rate of 42.5% vs. 42.8% (95% CI, -6.4, 5.9, $P = 0.93$), respectively [20]. However, these authors stated possible causes for such results including a higher positive end expiratory pressure strategy in both groups, deeper sedation in the intervention group (higher risk of hypotension, bradycardia, and other cardiovascular effects), and lower prone positioning rate compared to ACURASYS study [20]. As such, the timing of initiating NMBA therapy in patients with hypoxia from SARS-CoV-2-induced ARDS must be individualized.

Prone positioning

Prone positioning has been implemented as part of the non-pharmacological management in cases of moderate and severe ARDS. This technique allows for redistribution of consolidation from dorsal to ventral areas of the lung, removal of the heart's weight and mediastinum from the lung, improving alveolar ventilation, and minimizing pulmonary inflammatory cytokine production [29]. The Proning Severe ARDS Patients (PROSEVA) trial described the findings of 466 patients with severe ARDS that underwent prone and supine-positioning sessions for at least 16 h [30]. A total of 237 patients were assigned to the prone group, whereas 229 to the supine group, demonstrating 28-day mortality of 16% and 32.8% ($P < 0.001$), and an unadjusted 90-day mortality rate of 23.6% and 41% ($P < 0.001$), respectively. Most of the complications and causes of mortality were cardiac arrest in the supine group [30]. Additionally, six other randomized trials also concluded that prone positioning had a reduction in mortality (33.7%) compared to non-prone-positioning cases in moderate to severe ARDS for a longer duration of 12 h [30–36]. Proning patients can be safely accomplished with adequate levels of neuromuscular blockade as such agents might help minimize complications including inadvertent extubation, endotracheal-tube obstruction, and main-stem bronchus intubation [30,37]. Although NMBA use is not mandatory in all prone patients, the utilization of adequate neuromuscular blockade during this vulnerable time could facilitate prone positioning in patients with COVID-19 and minimize complications related to this labor-intensive and potentially dangerous technique.

Laparoscopy in COVID-19 patients

Viral studies have detected fragments of SARS-CoV-2 in a vari-

ety of bodily specimens from patients with COVID-19 [38]. Detection in fecal samples appears to be the result of an ingestion of the virus from the nasopharynx into the gastrointestinal tract. Interestingly, there is a lower incidence of viral detection in blood samples, ranging from 1% to 15% of confirmed cases, and other studies suggest almost zero incidence in the female genital tract in women with proven COVID-19 [39]. With this in mind, the specific risk of aerosolization during laparoscopic surgery may be procedure dependent with operations of the nasopharynx, respiratory, and gastrointestinal tract carrying more risk than gynecologic surgery [39]. However, it remains unclear if creation of an artificial pneumoperitoneum might be associated with an increased risk of aerosol exposure to the operating team when caring for patients with COVID-19 [40–44].

Conventionally, NMBAs are used in laparoscopic surgeries to improve surgical conditions by achieving abdominal wall relaxation and prevention of sudden muscle involuntary muscle contractions [45]. When comparing deep vs. mild or moderate neuromuscular blockade, the current evidence supports reduction of shoulder pain (28.6% vs. 60%, $P < 0.002$), as well as the avoidance of higher intra-abdominal pressure (18% vs. 43%, $P = 0.031$) and spontaneous breathing or ventilator dyssynchrony intraoperatively (6% vs. 50% cases, $P < 0.001$) [46,47]. Ikramuddin et al. [48] have proved the presence of whole cells carried as aerosols and correlated higher number of cells with increasing pneumoperitoneum pressure. As such, we propose that establishing and maintaining at least a moderate level of neuromuscular blockade (train-of-four count 1–3) represents a reasonable strategy to increase the chances for completing laparoscopic operations successfully with lower pneumoperitoneum pressures and therefore a lower potential risk of viral spread. Brief periods of deep levels of neuromuscular blockade (train-of-four count < 1) can be temporarily utilized during critical portions of the operation; however, we recommend quantitative monitoring in this setting to provide guidance on the dose of neuromuscular blockade antagonists required (i.e., neostigmine or sugammadex) and confirm adequate recovery at the conclusion of the operation. While there is no data that confirms lower insufflation pressures reduce viral spread of SARS-CoV-2, our recommendations are based on optimal neuromuscular blockade management for any patient undergoing laparoscopic surgery.

Neuromuscular blockade monitoring

Objective neuromuscular blockade monitoring is not routinely performed in the ICU as subjective evaluation with a peripheral nerve stimulator is the primary assessment method. Nonetheless,

a recent international panel of experts released a consensus statement that recommended that quantitative (objective) monitoring should be used whenever NMBAs are administered as such devices are the only means of confirming adequate recovery [49]. Leaving patients with COVID-19 with residual weakness at the time of extubation could have catastrophic consequences given their potentially tenuous clinical status.

While recovery is important, placing objective monitors on the adductor pollicis prior to NMBA administration and endotracheal intubation and waiting for this muscle to reach a train-of-four count of zero can minimize the risk of coughing during airway manipulation. Using monitors in this fashion relies upon an understanding of different muscle sensitivities to neuromuscular blockade. Relying on an objective data that reflects the patient's current state of neuromuscular blockade has the potential to briefly delay endotracheal intubation as clinicians confirm adequate paralysis rather than relying on expected responses; however, this additional time to ensure adequate neuromuscular blockade could prove to be the difference in a patient with COVID-19 coughing during airway manipulation. Monitoring facial muscles can prove challenging as direct muscle stimulation occurs easily; however, the corrugator supercilii muscle has been reported to have a similar response to NMBA as that of the diaphragm and laryngeal muscles while the orbicularis oculi can respond similarly to the extremities [50]. We agree with other experts [51,52] that monitoring facial muscles should be discouraged as there is a more than five-fold higher risk of residual paralysis when monitoring is performed at the eye muscles than those assessed at the hand muscles [53].

Quantitative monitoring can also be used to confirm adequate paralysis prior to proning a patient. Whether clinicians are utilizing intermittent boluses or continuous infusions of NMBA, the depth of neuromuscular blockade should be assessed and documented during regular intervals with a prone patient. As frequent assessments with a peripheral nerve stimulator can increase direct patient contact, the use of automated quantitative monitors can serve as an innovative method for measuring the level of blockade and reducing the risks to the healthcare team [54]. Such devices also have the ability to be seamlessly incorporated into the electronic medical record — a feature that could improve work-flow efficiency in challenging patients with COVID-19.

We certainly recognize the use of quantitative monitoring is inconsistent in modern anesthesia practices and rarely used in the critical care setting. However, a recent review article has called for objective monitoring in this setting as an innovative approach to critical care medicine [8]. While a comprehensive review of quantitative neuromuscular monitors is beyond the scope of this re-

view, these devices are often categorized by the method they obtain objective data. Acceleromyography measures the acceleration of a muscle, usually the adductor pollicis, to neurostimulation. Similarly, kinemyography measures the degree of bend of a piezoelectric sensor placed between the thumb and index finger following neurostimulation. Electromyography does not rely on an unrestricted, freely-moving thumb as it measures action potentials across the neuromuscular unit and has the advantage of working on ICU patients who may have wrist-restraints to prevent the accidental removal of invasive catheters [54]. These devices allow for automated measurements at a user-defined time interval and can perform various patterns of neurostimulation including train-of-four, single twitch, double burst, and post-tetanic potentiation [55].

Conclusions

NMBAs can prove very useful when caring for patients with COVID-19. This class of medications has particular utility when caring for critically ill patients that require endotracheal intubation, MV, proning, and avoidance of self-induced lung injury. The focus of therapy in these types of patients must integrate multidisciplinary management, including pharmacologic and non-pharmacologic techniques (e.g., MV, AGPs, prone positioning) [56]. Despite the lack of evidence in using NMBAs in COVID-19, some authors have described pragmatic approaches that rely on literature from similar clinical scenarios such as ARDS [57]. Such strategies were designed under duress with the goal of reducing healthcare exposure to SARS-CoV-2 while enhancing patient outcomes. Similarly, NMBAs can play a role in patients with COVID-19 undergoing laparoscopic surgery in an effort to allow for lower pneumoperitoneum insufflating pressures and potentially reducing aerosolization. We also advocate for quantitative monitoring whenever NMBAs are used to avoid complications associated with neuromuscular blockade, independent of whether patients are in the perioperative or critical care setting. Finally, we recognize the need for prospective, RCTs to better elucidate the actual role of NMBAs in this setting.

Conflicts of Interest

JRR has completed Merck-funded research with funds to employer. HCC, VHT, and SK have nothing to disclose.

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