Clinical Outcomes of Implementing Two Management Protocols for Acute Respiratory Distress Patients with COVID-19: A Randomized Controlled Trial

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Abstract

Background: Acute respiratory distress syndrome (ARDS) patients with COVID-19 require sedation or neuromuscular blocking agents to facilitate mechanical ventilation. **Aim:** to assess the effect of two management protocols on the clinical outcomes of ARDS patients with COVID-19. **Research design:** This randomized controlled trial included 80 patients with COVID-19 admitted in intensive care units of main hospital Assiut University in Egypt. **Sample**: A purposive sample was collected according to inclusion criteria. **Tools**: four tools were included in this study. **Methods:** ICU nurses and the researchers evaluated the clinical outcomes of administer sedatives versus muscle relaxant protocols among ARDS patients with COVID-19. Propanol and midazolam were used in the – sedatives protocol, and cisatracurium was used in the muscle relaxant protocol. The clinical outcome measures were oxygenation parameters, lung mechanics, tissue perfusion parameters, organ failure, success of weaning, and survival in 28 days. **Results:** More than two-thirds (67.5 %) of the sedation group were successfully weaned from mechanical ventilation from the first trial, while more than half (57.5 %) of the muscle relaxant group needed another trial for weaning, with a statistically significant difference between both groups. The mean duration of mechanical ventilation was not significantly between the muscle relaxant group (9.24± 5.66) and the sedation group (8.27 ± 3.91). **Conclusion:** Severe ARDS patients with COVID-19 who underwent the sedation protocol were successfully weaned from mechanical ventilation from the first attempt, compared to those who used muscle relaxants. Morality rate was significantly reduced by sedation compared to using muscle relaxant. **Recommendations**: Further studies must be applied using different type of sedation and neuromuscular agents COVID-19 patients with severe ARDS

Keywords: ARDS,COVID-19, Muscle relaxant, Sedation

Introduction

The coronavirus disease 2019 (COVID-19) is the most dangerous pandemic to date, which led to a surge in demand for curative management. The pathophysiology of acute respiratory distress syndrome (ARDS) involves the binding of S2 subunit to ACE receptors, followed by the invasion of type II pneumocytes, which are responsible for the production of surfactants. After rapid replication of virus RNA, cell apoptosis occurs, and the invasion to the surrounding pneumocytes via subsequent cytokine storm leads to infection and increases the severity of the disease [Batah and Fabro,2021].

COVID-19 can progress to ARDS, and this often requires intubation and mechanical ventilation (MV). The timing of intubation in case of acute respiratory failure in patients with COVID-19 is challenging. Moreover, the use of sedation only in intubated patients with severe ARDS with or without neuromuscular blocking agents (NMBAs) remains controversial [Ginestra and etal, 2022].

NMBAs are drugs that paralyze the skeletal muscles by blocking the transmission of nerve impulses at the myoneural junction. NMBAs indicated for patients in the intensive care unit

(ICU) eliminate ventilator–patient dyssynchrony, facilitate gas exchange by reducing intra-abdominal pressure and improving chest wall compliance, reduce the risk of lung barotrauma, decrease the contribution of muscles to oxygen consumption by preventing shivering, and controls the elevations in intracranial pressure caused by airway stimulation in patients supported with MV in ICUs [Neto and etal, 2012].

ARDS increases intracranial pressure and can be sustained by neuromuscular blockade. Appropriate indication and clinical practice have gained importance considering side effects such as ICU-acquired weakness, masking seizure activity, and longer hospital and ICU stays. NMBAs block the binding of acetylcholine (ACh) to the motor endplate. They are divided into depolarizing or non-depolarizing agents based upon their mechanism of action [Balakrishna and etal, 2021].

The LUNG-SAFE study showed the superiority of the use of early NMBAs in patient outcomes [Laffey and etal, 2016]. In contrast, the ACURASYS study showed that NMBAs have no advantage over sedation alone but they can increase the risk of ventilator-associated pneumonia, aspiration pneumonia, neuromuscular weakness, and hospital acquired pneumonia (HAP) [Dizier and etal, 2015].

A holistic nursing care for mechanically ventilated ARDS patients with COVID-19 requires teamwork to maintain airway, breathing, and oxygenation from the pre-intubation phase up until the recovery phase. Collaborative nursing interventions maintain fluid volume and acid base balance and prevent shock. Monitoring respiratory and hemodynamic stability is the mainstay of the treatment strategy to recover from respiratory distress and enhance physical and mental well-being[Papazian and etal, 2010 & Needham and Brindley, 2012].

Nursing and medical management of critically ill patients with COVID-19 are aimed at continuously monitoring them to ensure fulfilling their nutritional and elimination needs; preventing infection and controlling the spread of the disease; and preventing, promptly identifying, and managing complications. However, very little attention has been paid on the application of sedation in these patients in the field of critical care; the Society of Critical Care Medicine's COVID-19 guidelines or clinical reviews mentioned this, but only minimally[Papazian and etal, 2010 & Needham and Brindley, 2012].

Operational definition:

Clinical outcomes are measurable changes in health that result from our care such as successful of weaning and mortality rate.

Two management protocols are a set of mutually accepted and implemented rules .one group received neuromuscular blocking agents protocol and other group received sedation agents.

Acute respiratory distress syndrome. Is a serious lung condition that causes low blood oxygen

Aims of the present study:

To explore the effect of sedatives versus muscle relaxant management protocols on the clinical outcomes of ARDS patients with COVID-19.

Significant of the study

Our study studied the effect of sedatives and muscle relaxant protocols on ARDS patients with COVID-19 and the results show that Severe ARDS patients with COVID-19 who underwent the sedation protocol were successfully weaned from mechanical ventilation from the first attempt, compared to those who used muscle relaxants. Morality rate was significantly reduced by sedation compared to using muscle relaxant. The research will have impact in improving the condition of Severe ARDS patients with COVID-19 and help in weaning them from mechanical ventilation

Subjects and methods

Research design: A Randomized controlled trial was conducted in this study

Research hypothesis

The clinical outcomes of the sedation group would be significantly improved than the muscle relaxant group.

Null hypothesis

The clinical outcomes of the sedation group and the muscle relaxant group are not significantly different.

Setting

This study was conducted in the general ICU at Assiut University Main Hospital in Egypt. The general ICU is divided into four rooms and comprises 20 beds.

Subjects:

A purposive sample was collected according to inclusion criteria .The sample size was calculated using the Epidemiology Information 2000 statistical software using a 95% confidence interval, 80% study power, 95% frequency of ARDS patient with COVID-19 from previous studies, and the lowest acceptable outcome of 5%. According to the calculation, the sample size should include 92 patients. We excluded 12 patients who died between the second and third days of admission. The remaining 80 patients were randomized and assigned equally to two groups: sedation group and muscle relaxant group. Each patient was assigned a unique number generated http://www. randomization. com/ for their grouping, **Figure (1).**

Inclusion criteria: The inclusion criteria were as follows: newly admitted patients aged 18–60 years, diagnosed with COVID-19, intubated and mechanically ventilated due to severe ARDS with standard criteria (PaO2/FiO2 < 200), and resistant hypoxemia and tachypnea (RR > 40 breaths/min) not relieved by high frequency nasal cannula or CPAP mask.

Exclusion criterion

In this study, we excluded patients whose relatives refused to provide consent and those with a history of neuromuscular diseases (especially demyelinating diseases).

Ethical permission: This study was approved by the Ethics Research Committee, Faculty of Medicine, Assiut University (IRB local approval number: 17300606). An official letter from the Faculty of Nursing at Assiut University was received and delivered to the responsible personnel at Assiut University Main Hospital for their authorization to collect data. The individuals authorized by the patients provided informed consent based on their understanding the aim of the study. They were also allowed to refuse or withdraw from the study at any moment to ensure anonymity.

Tools:

Tools I,II and IV were used in this study after local and international review of literature (Papazian and etal, 2010 & Needham and Brindley, 2012)

Tool I: lung mechanics oxygenation parameters assessment tool was used to assess peak airway pressure, plateau pressure, compliance (dynamic and static), FiO_2, PEEP, and airway resistance, oxygen saturation in addition to personal characteristic & medical history.

Tool II: Assessment of tissue perfusion parameters .This tool consists of recording serum lactate, Jugular venous oxygen

pressure to assess patient's tissue perfusion.

Tool III: Modified sequential organ failure assessment score **.**This tool adopted from Grissom etal 2013, The MSOFA score eliminates the platelet count, replaces partial pressure of arterial oxygen (PaO2) with arterial oxygen saturation measured by a pulse oximetery. (SpO2), and replaces serum bilirubin with clinical assessment of scleral icterus or jaundice.

Tool IV: Clinical outcomes assessment tool included success of weaning and duration of mechanical ventilation.

Methods:

- The researchers reviewed nationally and internationally studies regarding the aim of the study.
- The validity of the study tools was verified by five specialists from the Anesthesia and Intensive Care Department and Critical Care and Emergency Nursing Department of the Assiut University. The Cronbach's alpha test was utilized to evaluate the reliability of study tools. Reliability coefficients for tools were 0.915, 0.787, and 0.940, confirming reliability.
- **A pilot study**: A pilot study was conducted on eight patients prior to the actual study to evaluate the feasibility and applicability of all items of the tools, to detect the challenges that might occur during the data collection, and to determine the needed time to record the tools. The simple modifications of tools were made and the participants' patients in the pilot study were not involved in the study sample and substituted by new patients.

Data collection

The researchers gathered the study data for each included patient. The data covered 6 months, from September 2021 to February 2022.

The research was conducted on three phases as follows:

Assessment phase:

- On admission, baseline demographic data (patient ID, age, and sex) and medical history and BMI were collected from the patients' medical records, including nursing documentation, laboratory investigation results, physician notes, and radiology reports.
- Oxygenation was assessed based on the partial pressure of oxygen in arterial blood (PaO2), the fraction of inspired oxygen (FiO2), ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (P/F ratio), and the oxygen saturation (SaO2) on admission, after 24 h, and after 48h.
- Lung mechanics were assessed by peak airway pressure plateau pressure, static compliance, dynamic compliance, required PEEP, and airway resistance on admission, after 24 h, and after 48 hr.Tissue perfusion was assessed using popular biomarkers such as serum lactate and central venous oxygen saturation. The
- Modified Sequential Organ Failure Assessment (MSOFA) score was used to assess organ dysfunction. It combines a clinical assessment of two organ systems, cardiovascular system and central nervous system, using laboratory measurements to evaluate four other organ systems: respiratory, hematologic, liver, and renal. The SOFA score assigns 0–4 points for increasing severity of acute organ failure for each of six organ systems. In this study, we calculated the SOFA score on the first day of ICU admission and after 48 h for the sedation group.

Intervention phase:

Propofol and midazolam were used as sedatives, while cisatracurium was used as the muscle relaxant. The ICU nursing team administered the drugs on a daily basis based on physician's orders.

- **Sedation group:** Propofol has a role in non-organ dependent metabolism, and its dose is titrated to avoid hemodynamic instability. The dose of infusion was 25–80 mcg/kg/min with bolus doses of 0.25–0.5 mg/kg. Morphine sulfate is introduced if propofol is not sufficient at 0.02–0.2 mg/Kg/h and at bolus doses of 0.25–0.5

mg/kg. Midazolam was used either in infusion rates of 2–6 mg/h or in shots 2–3 mg boluses.

- **Muscle relaxant group:** A muscle relaxant was administered for at least 48 h after sedation. Cisatracurium was given in short-term infusions up to 24 h at 2–3 mic/kg/min, followed by intervallic shots of 2–5 mg.

General consideration to all patients:

A strategy for lung protection was put in place for all patients in both groups. The MV options were standardized according to local guidelines of treatment of ARDS:

- Bi-PAP mode was the main mode used.
- Tidal volume was adjusted to be 4–6 mL/kg predicted body weight in kg.
- The respiratory rate controlled up to 35 breaths/min to deliver the expected minute ventilation requirement (generally, 7–9 L /min). The respiratory rate adjusted to approach normal PaCO2 in blood gases if plateau pressure was less than 30 cmH2O.
- Positive end expiratory pressure (PEEP) controlled to at least 5 cm H2O (the higher the better), and FiO2 to maintain an arterial oxygen saturation (SaO2) of 88%–92% (PaO2: 55–70 mm Hg). Titrate FiO2 to below 70% when feasible (though ARDS Net does not specify this).
- Permissive hypercapnia considered if high plateau pressure was achieved >30 cmH2O. Current consensus suggested it was safe to allow pH to fall to at least 7.20. When pH falls below 7.20, we administered sodium bicarbonate to maintain blood pH between 7.15 and 7.20. The conditions in which permissive hypercapnia for ARDS could theoretically be harmful include cerebral edema, mass lesions or seizures; active coronary artery disease; arrhythmias; hypovolemia; and GI bleeding.
- The patients were heavily sedated when necessary to minimize ventilator–patient dissynchronization.

Evaluation phase

- **Assessment of the primary clinical outcome**, which included the improvement of oxygenation (PO2/FiO2) in the first 48 h.
- **Assessment of the secondary clinical outcomes,** which included lung mechanics, tissue perfusion, organ dysfunction by measurement of the SOFA score, MV duration and percentage of success of weaning, and 48-day survival.

Statistical analysis

The one-sample Kolmogorov–Smirnov test was used to examine the distribution of the study variables. The Statistical Package for the Social Sciences version 21 was used for coding and analyzing the study data. After the entry of the study data, examination and verification processes were conducted to avert any mistakes made during study data entry. The Chi square test was used to compare qualitative data, while the Mann–Whitney test the quantitative data between two groups. The significance of the study results was adjusted at the 5% level.

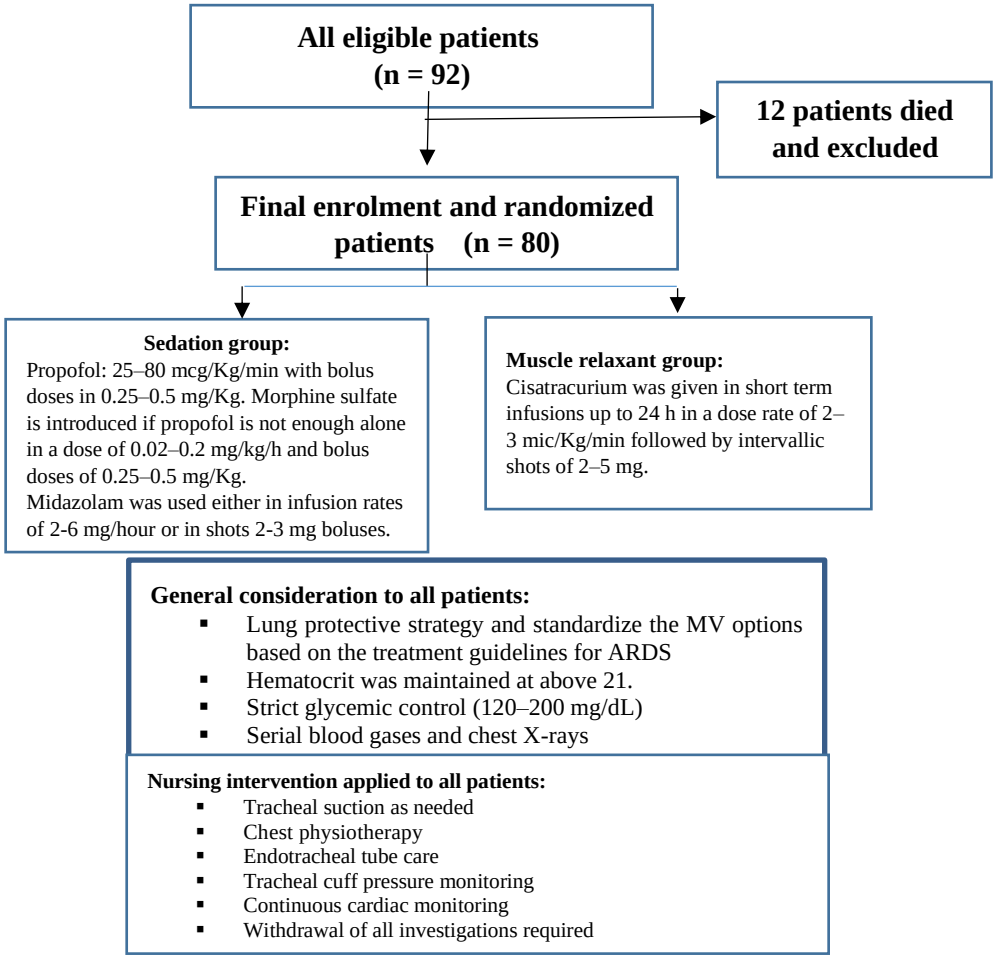

Figure (1): CONSORT flow diagram of randomized controlled trial

Results

Table 1: The characteristics of the patients in the muscle relaxant and sedation groups: It was noticed that both studied groups had an age range of between 41 and 50 years old, and more than half of them (57.5 % and 52.5%) were female. The highest percentage of studied patients had chronic diseases: (40%) COPD or asthma, (45%) diabetes and (45%) hypertension.

Table 2: The PaO2, P/F ratio, and SaO2 significantly improved in both groups, with a statistically significant difference for the sedation group versus the muscle relaxant group (P > 0.005).

Table 3: The lung **mechanics** (peak airway pressure, plateau pressure, static compliance, dynamic compliance, PEEP, and airway resistance) were similar between groups, with no significant difference in 3 days.

Table 4: Significant difference was noted on jugular venous oxygen pressure in the 1st day of admission and 2nd day of admission between groups (P > 0.002 and 0.010) as well

as on serum lactate in 2nd day of admission (P > 0.024) .

Table 5: SOFA score in the 1st day of admission was significantly different between groups (P > 0.007)

Table 6: showed that more than two-thirds of patients in the sedation group were successfully weaned from MV from the first trial, while more than half of the patients in the muscle relaxant group needed another trial for weaning, showing a significant difference between groups (P = 0.025*) .The mean duration of MV for the muscle relaxant and sedation groups were (9.24+5.66) and (8.27+3.91), respectively.

In (Figure 1) only 35% and 65% of patients in sedation and the muscle relaxant groups and the, respectively, survived for 28 days, showing a significant difference between groups (p = 0.007**)

Table (1): Demographic and medical data of the muscle relaxant and sedation groups (n = 80)

Data	**Muscle relaxant group (n = 40)**		**Sedation group (n = 40)**	
	No	**%**	**No**	**%**
Sex				
Male	17	42.5	19	47.5
Female	23	**57.5**	21	**52.5**
Age in years				
From 30 to ≤ 40 years	7	17.5	8	20.0
From 41 to ≤ 50 years	29	**72.5**	27	**67.5**
More than 50 years	4	10	5	12.5
Medical history				
COPD or asthma	15	37.5	16	**40.0**
Diabetes	16	40.0	18	**45.0**
Hypertension	17	42.5	18	**45.0**

COPD: chronic obstructive pulmonary diseases
Chi square test for qualitative data between the two groups or more
*Significant level at P value < 0.05
Mann–Whitney test quantitative data between two groups

Table (2): Oxygenation parameters between the muscle relaxant and sedation groups (n = 80)

Oxygenation parameters	Muscle relaxant group	Sedation group	Z	P-value
	Mean ± SD	Mean ± SD		
PaO2				
▪ 1st day of admission	52.68 ± 13.64	61.45 ± 10.14	−3.534	**0.000****
▪ 2nd day of admission	71.03 ± 10.17	74.2 ± 8.74	−1.990	**0.047***
▪ 3rd day of admission	69.8 ± 10.23	76.83 ± 9.48	−3.024	**0.002****
FiO2				
▪ 1st day of admission	0.82 ± 0.17	0.84 ± 0.21	−0.620	0.535
▪ 2nd day of admission	0.71 ± 0.17	0.67±0.19	−0.908	0.364
▪ 3rd day of admission	0.67 ± 0.21	0.54±0.2	−2.663	0.008**
P/F ratio				
▪ 1st day of admission	66.5 ± 20.1	77.85±22.95	−2.450	**0.014***
▪ 2nd day of admission	106.95±33.13	120.43±36.8	−1.742	0.082
▪ 3rd day of admission	117.2 ± 47.44	160.01±56.49	−3.296	**0.001****
Sao2				
▪ 1st day of admission	81.05±9.29	87.73±7	−3.357	**0.001****
▪ 2nd day of admission	92.6±3.63	96.05±2.73	−4.379	**0.000****
▪ 3rd day of admission	93.58±3.59	96.05±3.14	−3.022	**0.003****

PaO2: partial pressure of oxygen in arterial blood
FiO2: fraction of inspired oxygen SaO2: oxygen saturation
P/F ratio: ratio of partial pressure of arterial oxygen to fraction of inspired oxygen
Chi square test for qualitative data between the two groups or more
*Significant level at P value < 0.05

Table (3) Lung mechanics between the muscle relaxant and sedation groups (n = 80)

Lung mechanisms	Muscle relaxant group	Sedation group	Z	P. value
	Mean ± SD	Mean ± SD		
Peak airway pressure				
▪ 1st day of admission	34.68 ± 5	34.58 ± 4.88	−0.130	0.896
▪ 2nd day of admission	34.68 ± 5.03	35.1 ± 4.61	−0.652	0.515
▪ 3rd day of admission	35.63 ± 5.17	35.4 ± 4.76	−0.213	0.831
Plateau pressure				
▪ 1st day of admission	20.68 ± 4.43	19.9 ± 3.28	−0.860	0.390
▪ 2nd day of admission	21.13 ± 4.51	19.73 ± 3.03	−1.647	0.100
▪ 3rd day of admission	21.13 ± 5.01	19.58 ± 3.4	−1.363	0.173
Static compliance				
▪ 1st day of admission	26.2 ± 7.24	25.18 ± 5.8	−0.718	0.473
▪ 2nd day of admission	28.65 ± 7.58	25.88 ± 5.58	−1.884	0.060
▪ 3rd day of admission	28 ± 8.32	26.15 ± 5.63	−1.103	0.270
Dynamic compliance				
▪ 1st day of admission	44.53 ± 7.99	45.25 ± 6.58	−0.193	0.847
▪ 2nd day of admission	46.15 ± 8.97	45.3 ± 6.35	−0.275	0.784
▪ 3rd day of admission	47.1 ± 8.19	45.8 ± 6.43	−0.992	0.321
PEEP needed				
▪ 1st day of admission	9.3 ± 2	9.8 ± 0.76	−1.489	0.136
▪ 2nd day of admission	9.25 ± 1.48	9.85 ± 1.05	−2.061	0.039*
▪ 3rd day of admission	9.1 ± 1.63	9.5 ± 1.48	−1.143	0.253
Airway resistance				
▪ 1st day of admission	14 ± 5.78	14.68 ± 4.91	−0.728	0.466
▪ 2nd day of admission	13.55 ± 5.25	15.38 ± 4.34	−1.838	0.066
▪ 3rd day of admission	14.5 ± 4.31	15.83 ± 4.95	−1.526	0.127

Chi square test for qualitative data between the two groups or more
*Significant level at P value < 0.05
PEEP: positive end expiratory pressure

Table (4): Tissue perfusion parameters between the muscle relaxant and sedation groups (n = 80)

Tissue perfusion parameters	Muscle relaxant group	Sedation group	Z	P. value
	Mean ± SD	Mean ± SD		
SjvO2				
▪ 1st day of admission	61.15 ± 13.39	68.6 ± 7.91	−3.163	0.002**
▪ 2nd day of admission	80.78 ± 9.24	82.18 ± 5.22	−0.424	0.671
▪ 3rd day of admission	80.93 ± 7.92	85.3 ± 4.82	−2.569	0.010*
Serum Lactate				
▪ 1st day of admission	4.91 ± 2.58	4.76 ± 1.99	−0.058	0.954
▪ 2nd day of admission	2.55 ± 2.25	2 ± 0.63	−0.988	0.323
▪ 3rd day of admission	2.04 ± 1.16	1.56 ± 0.62	−2.258	0.024*

Chi square test for qualitative data between the two groups or more
*Significant level at P value < 0.05
SjvO2: Jugular venous oxygen pressure

Table (5): Modified sequential organ failure assessment score between muscle relaxant and sedation groups (n = 80)

MSOFA score	Muscle relaxant group	Sedation group	Z	P-value
	Mean ± SD	Mean ± SD		
▪ 1st day of admission	7.45 ± 3.5	9.55 ± 3.67	−2.715	0.007**
▪ 2nd day of admission	8.08 ± 3.6	9.23 ± 4.14	−1.189	0.234
▪ 3rd day of admission	8.38 ± 3.69	9.05 ± 4.66	−0.449	0.653

Chi square test for qualitative data between the two groups or more
*Significant level at P value < 0.05
Modified SOFA score: modified sequential organ failure assessment Score

Table (6): Success rate of weaning and duration of mechanical ventilation between the muscle relaxant and sedation groups (n = 80)

Clinical outcomes	Muscle relaxant group		Sedation group		P-value
	No	%	No	%	
Success of weaning					
▪ Weaned	17	42.5%	27	67.5%	0.025*
▪ Weaned at second trial	23	57.5%	13	32.5%	
Duration on MV	9.24 + 5.66		8.2 7+ 3.91		0.669

Chi square test for qualitative data between the two groups or more
*Significant level at P value < 0.05
MV: mechanical ventilation

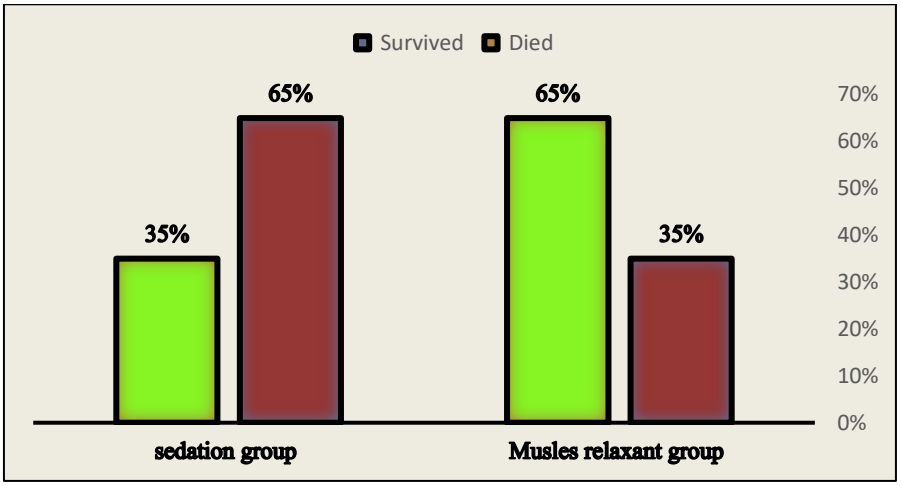

Figure 1: Survival rates of muscle relaxant and sedation groups in 28 days (n = 80)

Discussion

ARDS is developing quickly in some COVID-19 patients besides COVID-19 can lead to diffuse alveolar damage and thrombus [Batah and Fabro,2021]. The ARDS inflammatory process is associated with an increased vascular permeability and decreased lung compliance, as well as the size of the aerated lung tissue, which impairs gas exchange and results in hypoxemia [Force, 2012]. Gas exchange becomes difficult and requires invasive MV and/or extracorporeal membrane oxygenation based on the severity of the infection and the involvement of the lungs [Bellani, 2010].

The NMBAs improve arterial partial pressure of oxygen and are used to aid MV in patients with ARDS [Papazian and etal, 2010 & Needham and Brindley, 2012]. In certain studies, the effect of sedation on COVID-19 patients was examined, and the results indicated positive effect with increasing the needed doses of analgesics and sedations [Balakrishna, 2021]. To our knowledge, this is the first study trial in Egypt that compares for the effect of sedation versus NMBAs on severe ARDS patients due to COVID-19.

Management for ARDS patients with COVID-19 have been recommended to involve a combination of NMBAs and sedation to decrease the ventilator asynchrony [Balakrishna, 2021] . The doses and duration of sedation, analgesics, and NBMR on COVID-19 patients with ARDS[Balakrishna, 2021] or even non-COVID-19 patients [Wu and etal, 2021] have been evaluated. A recent retrospective study conducted in 2021[Ego and etal, 2021] aimed to assess the differences between COVID-19 ARDS (n = 39) and non-COVID-19 ARDS patients (n = 39) in terms of the use of analgesics, sedatives, and NMBAs and found that COVID-19 patients with ARDS required longer duration and higher doses of NMBAs and sedatives than the non-COVID-19 with ARDS. Another study in 2021[Wu and etal, 2021] aimed to assess the use of sedation, analgesia, and muscle relaxation therapy in eight patients with severe ARDS with COVID-19 during ECMO therapy.

However on the contrary, data were limited in order to assess the impact of NMBAs alone on COVID-19 patients with ARDS. A previous double-blind trial in 2010[Papazian and etal, 2010] studied 340 patients with severe ARDS and reported that early administration of a neuromuscular blocking agent improved the adjusted 90-day survival and increased the time off the ventilator without increasing muscle weakness.

In the current trial, we administered the muscle relaxant alone and compared its effect with sedations according to the protocol guidelines for ARDS and COVID-19 patients that applied in our hospital ICU. Generally, the findings of the present study revealed that the muscle relaxant group had poorer clinical outcomes and lower oxygenation parameters than the sedation group, which is consistent with the findings of other studies that reported that the sedation and analgesia can reduce the ventilator asynchrony, decrease the oxygen

consumption, and prevent man-machine confrontation [Chanques and etal, 2013& Coggeshall and etal, 1985].

In the present study, the measurements of oxygenation parameters (PaO2, FiO2, P/F ratio, and SaO2) from first to third day of admission were lower in the muscle relaxant group than in the sedation group, indicating the lower effects of muscle relaxants on the improvement of oxygenation in COVID-19 patients with ARDS. On the contrary, a previous study in 2006[Forel and etal, 2006] examined the impact of NMBAs on pulmonary and systemic inflammation in 36 ARDS patients and found that the P/F ratio improved steadily over time. This difference can be attributed to the characteristics of COVID-19 subjects. Another study [Marik and Kaufman,1996] involving 36 ARDS patients demonstrated the positive impact of NMBAs on oxygenation.

A review study[Hraiech and etal, 2020] explained the positive effect of NMBA on increasing the thoraco-pulmonary compliance and functional residual capacity. However, in this study, in comparing with sedation group, lung compliance declined throughout the entire of 48 h in the muscle relaxant group, but not significantly different. Our finding challenged with previous study[Gainnier and etal, 2004] conducted to evaluate the effects of early NMBA infusion on patients with ARDS, reported that administer NMBA within a 48 h improved oxygenation. This is can be attributed to the beneficial effect of NMBA on increasing the thoraco-pulmonary compliance and functional residual capacity.

In this study, jugular venous oxygen pressure and serum lactate were used to measure the tissue perfusion parameters. SjvO2 was increased toward the normal level from the first to the third day of admission in both groups, indicating that the cerebral perfusion was maintained. However, the muscle relaxant group had significantly lower SjvO2 value than the sedation group. Moreover, as the level of serum lactate is a reliable indicator of tissue hypoxia and hypo-perfusion, our findings showed an increased serum lactate level in the muscle relaxant group compared with the sedation group. However, both groups developed lactic acidosis, due to the mechanism of NMBA in reducing the whole-body oxygen consumption by 25% and reducing breathing during MV and redistribute the blood flow to the splanchnic and other non-vital vascular beds [Gainnier and etal, 2004].

In the present study, the SOFA score was lower in the muscle relaxant group than in the sedation group but not significantly. The SOFA score indicated a mortality rate of 15%–20% in both groups but without significant difference. This could be attributed to critical illness of COVID-19 and its effect on organ failure. The viral infection and the subsequent immunological cascade and inflammation may also be contributing factors. The benefit of NMBAs may also be related to the inflammation reduction process that might otherwise intensify multisystem organ failure. Moreover, the sedation might result in similar improvements [Needham and Brindley, 2011]. This is not in line with study [Arens,2011] that reported that the use of NMBAs can have no relation with organ failure as the severity of ICU illness.

The clinical outcomes of our trial were assessed based on the success of weaning, duration on mechanical ventilator, and 28 days-survival. The muscle relaxant has no better outcomes in comparison to sedation in all phases; 57.5% of patients in the muscle relaxant group failed to wean at the first trial and needed a second trail to achieve weaning. On the contrary, 67.5% of patients in the sedation group was weaned from MV effectively from the first trial. Furthermore, the duration of MV was longer in the muscle relaxant group than in the sedation group, but the 28-day survival rate was significantly higher in the sedation group than in the muscle relaxant group.

We can explain our results in respect of a previous study [Needham and Brindley, 2012] conducted in 2012 among non-COVID ARDS patients to compare early muscle relaxant with a placebo group. The 28-day mortality was significantly lower in the muscle relaxant group using cisatracurium than in the placebo group (absolute difference −9.6%; P = 0.05). This study also mentioned that muscle relaxant group had significantly more ventilator-free days, less ICU stay, and more days free of organ failure.

Field work: no limitation in this study.

Conclusion

Sedation protocol improves oxygenation in COVID-19 patients with severe ARDS in comparison with muscles relaxants. Those who underwent the sedation protocol successfully weaned from MV from the first trial, unlike those who received the muscle relaxant. In addition, the sedation protocol significantly decreased morality rate compared to the muscle relaxant protocol.

Recommendations:

Further studies must be applied using different type of sedation and neuromuscular agents COVID-19 patients with severe ARDS.

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