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ORIGINAL ARTICLE

Neuromuscular dysfunction associated with delayed weaning from mechanical ventilation in patients with respiratory failure

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KEYWORDS

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Abstract *Background:* Mechanical ventilation offers essential ventilatory support, while the respiratory system recovers from acute respiratory failure. Yet, invasive mechanical ventilation is associated with risks and complications that prolong the duration of mechanical ventilation and increase the risk of death. Neuromuscular dysfunctions acquired during intensive care unit (ICU) stay are considered to be one of the important factors that impair the weaning process.
The aim of this work: To evaluate the role of the neuromuscular factors responsible for difficult weaning from mechanical ventilation.
Methods: The study included 19 patients with difficult weaning from mechanical ventilation from the Alexandria medical respiratory intensive care unit (ICU) during the period from May 2009 till May 2010. The selected patients included patients who need mechanical ventilation for medical reasons, Patient fulfilling the parameters for weaning, (59) with failed spontaneous breathing trial. In the present study EMG and sensory–motor nerve conduction study was done.
Results: 26% show normal study, 63% showed moderate to severe axonal sensory–motor peripheral neuropathy and 11% showed a picture of myopathy. The study revealed that 33% of the patients with peripheral neuropathy failed weaning trials and finally died. It is also found that drugs

Abbreviations: ICU, intensive care unit; EMG, electromyography

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taken during ICU stay as corticosteroids and electrolyte disturbances (hypocalcaemia, hypophosphatemia, and hypomagnesaemia) may be related to the occurrence of neuromuscular dysfunctions. The present work also revealed a significant relationship between hypoalbuminemia and neuromuscular dysfunction.

Conclusions: The present study stresses on the importance of neuromuscular assessment in all cases with difficult weaning as this may be an important contributing factor for difficult weaning and prolonged mechanical ventilation (neuropathic or myopathic in origin). EMG and nerve conduction study may be of help for the detection of such disturbances. So, proper assessment of the neuromuscular apparatus and the management of any disorder may be a great step toward successful weaning.

1. Introduction

Mechanical ventilation offers essential ventilatory support, while the respiratory system recovers from acute respiratory failure. Yet, invasive mechanical ventilation is associated with risks and complications that prolong the duration of mechanical ventilation and increase the risk of death.[1,2] Therefore, safely weaning the patient from the ventilator as soon as possible is paramount. Difficult weaning is considered when the patients fail initial weaning and require up to three spontaneous breathing trials (SBT)or as long as 7 days from the first SBT to achieve successful weaning. Weaning attempts that are repeatedly unsuccessful usually signify incomplete resolution of the illness that precipitated mechanical ventilation, or the development of one or more new problems.[3,4]

The indications for invasive mechanical ventilation in patients with acute respiratory failure include apnea or impending respiratory arrest, acute exacerbation of chronic obstructive pulmonary disease with dyspnea, tachypnea and acute respiratory acidosis, plus one of the following (acute cardiovascular instability, altered mental status, or persistent uncooperativeness, inability to protect the lower airway, copious or unusually viscous secretions, abnormalities of the face or upper airway preventing effective ventilation, progressive respiratory acidosis or other deterioration despite intensive therapy. Invasive mechanical ventilation should be considered when PaO_2 remains <45 mm Hg despite maximum tolerated fraction of inspired oxygen, or pH remains <7.20. Other causes include acute ventilatory insufficiency in neuromuscular diseases, in the presence of acute respiratory acidosis, progressive decline in vital capacity to less than 10–15 mL/kg, progressive decline in maximum inspiratory pressure to less than 20–30 cm H_2O. Acute hypoxemic respiratory failure with tachypnea, respiratory distress, and persistent hypoxemia despite administration of high fraction of inspired oxygen via high flow system, or in the presence of any of the following (acute cardiovascular instability, altered mental status or persistent uncooperativeness, inability to protect the lower airway). Other causes include the need for endotracheal intubation to maintain or protect the lower airway or to manage secretions, especially in patients with an endotracheal tube with an internal diameter of $\leqslant 8$ mm.[5]

There are innumerable factors responsible for failure of weaning from mechanical ventilation. Pulmonary factors that should be considered in all difficult-to-wean patients include ventilator settings, infections, airway patency, posture, and respiratory muscle performance. Malnutrition, which is common in ventilator-dependent patients, has detrimental effects on the respiratory system. Heart failure or coronary ischemia can be induced by the reduction of ventilatory support and cause weaning failure. A number of electrolyte imbalances can impact the process of weaning from mechanical ventilation. Psychological problems (e.g. anxiety) can be an impediment to successful weaning.[5,6]

Neuromuscular dysfunctions acquired during ICU stay are considered to be one of the important factors that impair the weaning process. Up to 62% of difficult-to-wean patients, who do not have preexisting neurologic disorders, show evidence of neuromuscular dysfunction that is significant enough to account for these patients' persistent respiratory failures.[7] Ventilator-induced diaphragm dysfunction and critical illness oxidative stress are defined as loss of diaphragm force-generating capacity that is specifically related to use of controlled mechanical ventilation.[8] Critical illness neuromuscular abnormalities (CINMA) are the most common peripheral neuromuscular disorders encountered in the intensive care unit (ICU) setting and usually involve both muscle and nerve.[9]

The pathophysiology of the neuromuscular dysfunction is attributed to the depressed central drive, central ventilatory command which leads to the failure of the neuromuscular respiratory system and the peripheral dysfunction which is considered the primary cause of neuromuscular weakness; critical illness neuromuscular abnormalities (CINMA). Liberation from mechanical ventilation requires the resumption of neuromuscular activity to overcome the impedance of the respiratory system, to meet metabolic demands and to maintain carbon dioxide homeostasis. This requires an adequate signal generation in the central nervous system, intact transmission to spinal respiratory motor neurons, respiratory muscles and neuromuscular junctions. Disruption of any portion of this transmission may contribute to weaning failure.[10] Central drive may be impeded by metabolic alkalosis, mechanical ventilation itself or the use of sedative/hypnotic medications.[10] The importance of the contribution of daily awakening and heightened awareness over sedation to prolonged weaning and ICU stay has been established in the literature.[11] Failure of the neuromuscular respiratory system to maintain homeostasis results in an increased central drive to breathe, which in turn may cause ventilatory failure. This pattern may be observed in response to an increased resistive load from upper airway obstruction, an imbalance between mechanical load and respiratory muscle capacity or isolated muscle weakness.

Abnormalities of upper airway motor control are potential causes of extubation failure. These neuromuscular disorders may be common and have been reported in up to 62% of patients in some studies.[12] Primary causes of neuromuscular weakness such as Guillain–Barré syndrome, myasthenia gravis and motor neuron disease are usually apparent before weaning difficulties are encountered. However, occasionally these new diagnoses will be made in the course of investigating the difficult-to-wean patient. Most neuromuscular dysfunction that complicates weaning is acquired during the ICU stay.[10]

CINMA are the most common peripheral neuromuscular disorders encountered in the ICU setting and usually involve both muscle and nerve.[9] These disorders were first described in Canada and France in 1984.[13,14] The reported prevalence of CINMA in the literature has varied between 50–100% and this has been associated with severity of illness, multiple organ dysfunction, exposure to corticosteroids, presence of hyperglycemia and prolonged ICU stay.[15,16] CINMA presents as a motor deficit where muscle weakness is bilateral, symmetrical and most marked in the proximal muscles. Electroneuromyographic studies of the limbs show sensorimotor axonopathy with preserved velocities and the decreased amplitude of compound action potentials. Neuromuscular transmission is normal except in the case of prolonged neuromuscular blockade. In patients with severe muscle involvement, decreased motor action potentials and fibrillation potentials may resemble a motor axonopathy and a true distinction between a nerve and/or muscle lesion may be difficult. Myopathy may be confirmed on muscle biopsy and type II fiber drop-out with a loss of myosin filaments is a consistent finding.[13,14]

The most common form of intensive care unit (ICU)-acquired myopathy is critical illness myopathy (CIM). This disorder is also known by other names, including acute quadriplegic myopathy and thick filament myopathy. The strongest risk factor for CIM is the use of IV glucocorticoids in the ICU setting, and there is some correlation between the likelihood of occurrence and severity of disease with glucocorticoid dose. Associated and perhaps triggering factors may include a higher illness severity index, hyperglycemia, hyperthyroidism, and possibly the systemic inflammatory response syndrome.[17]

The major histopathologic finding in CIM is relatively the selective loss of myosin, which can be identified as a lack of reactivity to myosin ATPase in non-necrotic fibers. This finding can be confirmed with immunohistochemical studies for myosin and by utilizing electron microscopy to identify the loss of thick filaments. There is usually atrophy of myofibers, type 2 more than type 1. There is often evidence of myofibrillar disorganization, which may be partly manifested as abnormal basophilic stippling on hematoxylin and eosin stains, purplish staining with Gomori trichrome, and irregular clumping of the reaction product with NADH-TR. Some degree of necrosis may occur.[18–20]

Oxidative stress may also play a role in the development of CIM, as illustrated by the finding that sarcolemmal immunostaining of the nitric oxide synthase isoform NOS1 was reduced or absent in six patients with CIM.[21] While the significance of this finding is not clear, it is hypothesized that the loss of sarcolemmal NOS1 could lead to muscle fiber inexcitability by reducing nitric oxide release at the muscle membrane.[21]

The bedside evaluation of respiratory neuromuscular weakness is difficult. Maximum inspiratory pressure and vital capacity are dependent on patient comprehension and cooperation and are hindered by the endotracheal tube.[22–24] In the intubated patient maximal pressure generation can be assessed during occluded maximal maneuvers and this can be simply performed as the endotracheal tube is easily accessible.[23,24] Subsequent investigators have not found (maximum inspiratory pressure (PImax) to provide such clear separation between weaning success and weaning failure patients.[22,25–32] Sensitivity was approximately 0.80, meaning that approximately 80% of patients who succeeded in a weaning trial had a PImax value that predicted success (i.e., more negative than -30 cm H_2O). However, specificity was approximately 0.25, meaning that only a minority (25%) of patients who failed a weaning trial had a PImax that predicted weaning failure (i.e., less negative than -30 cm H_2O). Moreover, the ability to predict outcome was not improved by employing a standardized method of measuring PImax. Based on these data, PImax measurements appear to be more helpful in understanding the reason why a particular patient failed a weaning trial rather than in deciding whether to attempt a weaning trial.[22,30]

Twitch transdiaphragmatic pressure in response to bilateral stimulation of the phrenic nerves can give a measure of diaphragmatic contractility. Clinical applicability is limited as this requires the placement of both an esophageal and gastric balloon. The airway pressure at the end of the tracheal tube in response to phrenic nerve stimulation has been proposed to be a noninvasive alternative measure and may have a role in monitoring inspiratory muscle contractility as its correlation to twitch transdiaphragmatic pressure is weak.[33,34]

The aim of this work: was to evaluate the role of the neuromuscular factors responsible for delay weaning from mechanical ventilation.

2. Patients

The study included 19 patients with delay weaning from mechanical ventilation from the Alexandria medical respiratory intensive care unit (ICU) during the period from May 2009 till May 2010. In revising the existing literature, this has been defined as >14 days,[35] of mechanical ventilation. In the present study, delay mechanical ventilation was considered as duration $\geqslant 14$ days. For those patients who failed weaning after 14 days of MV, tracheostomy was done to guard against the occurrence of complications as trachea–esophageal fistula.

2.1. Selection criteria

- Patients who need mechanical ventilation for medical reasons.[5]
- Patient fulfilling the parameters for weaning,[10] with failed spontaneous breathing trial.

2.2. Exclusion criteria

- Patients with central nervous system disorders as cerebrovascular stroke, brain tumors and encephalopathy.

– Traumatic lesions that necessitate mechanical ventilation.
– Post-operative patients who need mechanical ventilation.
– Patients less than eighteen year old.
– Patients who were discharged before seven days after the first attempt of weaning will be excluded from this study.
– Patients who are mechanically ventilated due to malignant lung tumors either primary or secondary.

The primary diagnosis of the studied patients was as follows; 13 patients (42%) with acute exacerbation of Chronic Obstructive Pulmonary Diseases, five (16%) with Interstitial Lung Diseases, four (13%) with Obesity Hypoventilation Syndrome, three (10%) with Obstructive Sleep Apnea Hypopnea Syndrome and Hypoventilation, two (6%) with ARDS, two (6%) with bronchiectasis, one case (3%) with pulmonary embolism, and one patient (3%) with thalassemia major and pleural effusion.

3. Methods

3.1. The following data were recorded on admission

3.1.1. Clinical evaluation

- History taking {name, age, sex, residency, occupation and smoking history}.
- General examination.
- Vital signs (temperature, pulse, respiratory rate, and blood pressure).
- Thorough chest examination.
- Neurological evaluation (Glasgow Coma Score).
- Assessment of Body Mass Index (BMI): weight/height in m^2.

3.1.2. Ventilator data

Data included tidal volume (ml/kg of predicted body weight), respiratory rate, fractional inspired oxygen (FiO_2), and inspiratory flow rate. Data were adjusted according to the diagnosis of the patient to protect the lung from ventilator induced lung injury. After correction of the initial cause of mechanical ventilation, follow up routine laboratory investigations were done (complete blood picture, serum K, serum Na, renal and hepatic functions) for the assessment of readiness to wean from mechanical ventilation. All the patients were put on pressure support ventilation (PSV) mode of mechanical ventilation with a gradual decrease of the pressure support then the patients are reevaluated for readiness to wean from mechanical ventilation using the following parameters:

– Arterial gasometry and acid –base state on PSV.
– PImax measurement: using a tube connected to a pressure gauge through the endotracheal tube. The patient is asked to do his maximal inspiratory effort and the pressure is measured during brief occlusion of the airways. The test was repeated several times to reach the best readings.
– Rapid shallow breathing index (RSBI): respiratory rate divided by tidal volume (breaths/min per L).[10]
– Compliance-respiratory rate-arterial oxygenation-maximum inspiratory pressure index (CROP index.)[22]
– Physical examination to assess respiratory rate, paradoxical motion of the rib cage and abdomen, recession of the suprasternal and intercostal spaces, and accessory muscle recruitment.

Neuromuscular evaluation: This was done after failure of weaning on PSV and this included:

– Motor nerve conduction studies of median and peroneal nerves and sensory nerve conduction studies of ulnar and superficial peroneal nerves as well as electromyogram (EMG) of biceps, extensor digitorum, vastus medialis and tibialis anterior muscles.

3.1.3. Assessment of some serum electrolytes

Potassium (k^+), calcium (Ca^{+2}), phosphorus (Ph) and magnesium (Mg) levels and evaluation of their relation with the neuromuscular findings.

4. Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS ver.17 Chicago, IL, USA). Quantitative data were described using median, minimum and maximum. Qualitative data were described using number and percent. Association between 2 qualitative variables done using Chi-square test and comparing quantitative variables between 2 groups conducted using Mann Whitney U test.

5. Results

The Age, sex, BMI, smoking and co-morbid illness of the studied patients are shown in Table 1.

5.1. Neuromuscular dysfunctions and their relation to the outcome and duration of mechanical ventilation

In the present study EMG and sensory–motor nerve conduction study was done in 19 cases. It was normal in 5 patients; four (22%) were successfully weaned and one (5%) failed the weaning trial and finally died. While in relation to the duration of MV, two patients (10%) with normal study required a duration of MV $\geqslant$ 14 days and 3 (17%) required $<$ 14 days. Two patients showed a picture of myopathy in EMG and nerve conduction study; both (10%) were successfully weaned and one (5%) required a duration of MV $\geqslant$ 14 days. In twelve patients EMG and sensory–motor nerve conduction study showed a picture of moderate-severe axonal sensory–motor peripheral neuropathy. Eight patients (42%) were successfully weaned and 4 (21%) failed weaning trials and finally died. While in relation to the duration of MV, 10 (55%) required a duration

Table 1 Age, sex, BMI and smoking of the studied patients.

Age (mean ± SD)	57.7 ± 15
Sex (No. and %)	
Male	10 (52%)
Female	9 (48%)
BMI (mean ± SD)	30 ± 7.9
Smoking (No. and %)	
Smokers	10 (48%)
Non-smokers	9 (52%)

SD: standard deviation, BMI: body mass index (kg/m^2).

Table 2 Relation between electromyography (EMG) and nerve conduction study findings and the outcome and duration of mechanical ventilation (MV).

EMG and nerve conduction	Outcome of mechanical ventilation			Monte-Carlo-Chi-square (*P*)	Duration of mechanical ventilation			Monte-Carlo-Chi-square (*P*)	Total
	Final weaning	Failed weaning and Death	Total		⩾14 days	<14 days	Total		
Normal	4 (22%)	1 (5%)	5 (27%)	0.798	2 (10%)	3 (17%)	5 (27%)	0.184	5 (27%)
Myopathy	2 (10%)	0 (0%)	2 (10%)		1 (5%)	1 (5%)	2 (10%)		2 (10%)
Sensory–motor peripheral neuropathy	8 (42%)	4 (21%)	12 (63%)		10 (55%)	2 (10%)	12 (63%)		12 (63%)
Total	14 (73%)	5 (27%)	19 (100%)		13 (6%)	6 (31%)	19 (100%)		19 (100%)

By Monte Carlo-Chi-square test ($P < 0.05$ = significance).

of MV ⩾ 14 days and 2 (10%) required < 14 days. There were no significant differences in the outcome and duration of mechanical ventilation in relation to the presence of neuromuscular dysfunction using EMG and nerve conduction study, ($P > 0.05$) (Table 2).

5.2. Relation between corticosteroid intake during ICU stay and neuromuscular dysfunction

Among those cases that showed positive EMG and nerve conduction study (myopathy or peripheral neuropath); two (14.3%) were not receiving corticosteroids, 5 (35.7%) received corticosteroids for a duration of 14 ⩾ days, and 7 (50%) received corticosteroids for a duration <14 days While in patients with normal EMG and nerve conduction study, 2 (40%) received corticosteroids for a duration of ⩾14 days and 3 (60%) received corticosteroids for <14 days. There was no significant relationship between corticosteroids intake and neuromuscular dysfunction proved by EMG and nerve conduction study ($P > 0.05$) (Table 3).

5.3. Relation between serum albumin level, Mg, Ca, and Ph and the neuromuscular dysfunction

Cases with normal EMG and nerve conduction study showed mean serum albumin of 2.6 g/dl (median, 2.6; range, 2.5–2.8) and in those with positive study either myopathy or peripheral neuropathy, of 2.4 g/dl (median, 2.3; range, 2–3.4). There was a statistically significant relationship between serum albumin level and neuromuscular dysfunction ($p = 0.037$). Mean of total serum Mg, total serum Ca, and serum Ph were [1.6 mg/dl (median, 1.7; range, 1.1–1.9), 7.6 mg/dl (median, 7.6; range, 7–8.1), and 3.4 mg/dl (median, 3.4; range, 3–3.6) respectively] in patients with normal EMG and nerve conduction study and [1.4 mg/dl (median, 1.4; range, 1.1–2), 7.7 mg/dl (median, 7.7; range, 7–9), and 3.4 mg/dl (median, 3.5; range, 2.2–4.1) respectively] in those with positive EMG and nerve conduction study (myopathy or peripheral neuropathy). There was no significant relationship between serum Mg, Ca, and Ph and neuromuscular dysfunction ($P > 0.05$) (Table 4).

5.4. Relation between PImax measured during PSV and neuromuscular dysfunctions proved by EMG and nerve conduction study

Cases with normal EMG and nerve conduction study showed mean PI max of −18 cm H_2O (median, −16; range, −24 to −14), while those with positive study (myopathy or peripheral neuropathy) showed mean PImax of −15 cm H_2O (median, −14.5; range, −24 to −10). There was no statistical significant relationship between the value of PImax and the presence of neuromuscular dysfunction ($P > 0.05$) (Table 5).

6. Discussion

The discontinuation or withdrawal process from mechanical ventilation is an important clinical issue.[36,37] Patients are generally intubated and placed on mechanical ventilators when their own ventilatory and/or gas exchange capabilities are outstripped by the demands placed on them from a variety of diseases. Mechanical ventilation also is required when the

Table 3 Relation between corticosteroids intake and neuromuscular dysfunction.

EMG and nerve conduction	Corticosteroid intake			Monte Carlo-Chi-Square (*P* value)	Total
	No steroids	⩾14 days duration of steroids intake	<14 days duration of steroids intake		
Normal study	0 (0%)	2 (10%)	3 (17%)	1.000	5 (27%)
Positive findings	2 (10%)	6 (32%)	7 (37%)		14 (73%)
Total	2 (10%)	8 (42%)	9 (48%)		19 (100%)

By Monte Carlo-Chi-Square test, *P* value < 0.05 represents significant difference.

Table 4 Relation between the mean values of albumin, Mg, Ca, and Ph and neuromuscular dysfunctions.

		Electromyography and nerve conduction findings		Mann–Whitney Z (*P*)
		Normal study (*n*:5)	Myopathy or peripheral neuropathy (*n*:14)	
Mean albumin g/dl	Mean ± SD	2.6 ± 0.1	2.4 ± 0.3	0.037*
	Median	2.6	2.3	
	Range	2.5–2.8	2–3.4	
Mg (mg/dl)	Mean ± SD	1.6 ± 0.4	1.4 ± 0.3	0.671
	Median	1.7	1.4	
	Range	1.1–1.9	1.1–2	
Ca (mg/dl)	Mean ± SD	7.6 ± 0.4	7.7 ± 0.5	0.963
	Median	7.6	7.7	
	Range	7–8.1	7–9	
Ph (mg/dl)	Mean ± SD	3.4 ± 0.2	3.4 ± 0.5	0.607
	Median	3.4	3.5	
	Range	3–3.6	2.2–4.1	

By Mann–Whitney-U test, *P* value < 0.05 represents significant difference. Mg: magnesium, Ph: phosphorus, Ca: calcium.
* Denotes significance.

Table 5 Showing relation between PImax and neuromuscular dysfunctions.

Mean PImax cm H_2O	EMG and nerve conduction findings		Mann–Whitney Z (*P*)
	Normal study (*n*:5)	Myopathy or Peripheral neuropathy (*n*:14)	
Mean ± SD	−18 ± 4	−15 ± 4.4	21 (0.192)
Median	−16	−14.5	
Range	−24 to −14	−24 to −10	

By Mann–Whitney-U test, *P* value < 0.05 represents significant difference.

respiratory drive is incapable of initiating ventilatory activity, either because of disease processes or drugs. As the conditions that warranted placing the patient on the ventilator stabilize and begin to resolve, attention should be placed on removing the ventilator as quickly as possible. This process is termed ''ventilator weaning'' (implying a gradual process), or ''discontinuation''. Weaning attempts that are repeatedly unsuccessful usually signify incomplete resolution of the illness that precipitated mechanical ventilation, or development of one or more new problems. All potential causes of ventilator dependency should be identified when a patient is difficult-to-wean. Then, a plan should be developed that uses a multidisciplinary team approach to correct the reversible causes of weaning failure and facilitates weaning thereafter. Failure to wean has been attributed to an imbalance between the load faced by the respiratory muscles and their neuromuscular competence. Failure to wean is usually multifactorial. The present study included 31 patients with difficult weaning from mechanical ventilation. They are screened to indentify the risk factors responsible for difficult weaning. Among the studied patients, 16 (52%) were males and 15 (48%) were female. Regarding smoking, 16 cases (52%) were non-smokers and 15 (48%) were smokers.

In revising the existing literature, PMV has been variously defined as >24 h,[38,39] >2 days,[40] >14 days,[35] or >29 days[41] of mechanical ventilation or, alternatively, the need for post-ICUs mechanical ventilator support.[42,43] In the present study, prolonged mechanical ventilation was considered as duration ⩾14 days. With follow up of our studied patients; 18 (58%) were successfully weaned and 13 (42%) failed weaning trials and finally died. Other studies found that, hospital survival for adult PMV patients in the short-term acute care (STAC) hospital setting ranges from 39% to 75%, depending on the patient population and definition for PMV.[39] and hospital survival in various non-STAC hospital settings varies from 50%

in many series[44–50] to as high as 94%, depending in part on admission criteria and likelihood of transfer to a different facility when patients become acutely ill. Difficult weaning from mechanical ventilation proved to be multifactorial.

Regarding the outcome of mechanical ventilation after correction of the detected problems; eighteen patients (58%) were successfully weaned from mechanical ventilation and thirteen (42%) failed several weaning trials and finally died. There was no significant relation between the primary diagnosis and the outcome of mechanical ventilation, ($p = 0.5$). This may be due to small sample size. Similar findings were reported by Richard et al.[51] who studied 95 patients; the cause of respiratory failure was judged to be the exacerbation of chronic obstructive pulmonary disease (COPD) (49%), pneumonia (20%), pulmonary edema (7%), surgery (11%) and others (13%). They found no statistically significant relationship between the cause of acute respiratory failure and the outcome of mechanical ventilation. In the present study, 60% of the cases with interstitial lung disease failed weaning trials and finally died. Infections were important risk factors for difficult weaning that developed in all the studied cases with interstitial lung disease either pulmonary or extra-pulmonary. Also the study revealed other factors as malnutrition in 100%, psychological problems in 80%, cardiovascular dysfunctions in 80%, electrolyte disturbances in 60%, neuromuscular dysfunctions proved by EMG and nerve conduction studies in 50% and other factors such as renal and hepatic impairment were detected in 20% of the cases. In a study adopted by Paone et al.[52] that retrospectively analyzed 34 consecutive idiopathic pulmonary fibrosis patients undergoing mechanical ventilation for acute respiratory failure, five patients (15%) survived and were discharged; one patient was still alive after 1 year. The in-hospital mortality rate observed in this study was different than Fernández-Pérez and co-workers'[53] results (85% vs. 60%), but consistent with previous observations by Fumeaux et al.[54] The cause for high mortality rate among cases with interstitial lung disease may be due to being of idiopathic pulmonary fibrosis type as they have little or no recruitable lung and may be susceptible to over-distension of the relatively intact lung when high positive end pulmonary expiratory pressure levels are used during mechanical ventilation, leading to ventilator-induced lung injury.

There were no significant relationships between the age, gender of the studied patients and the outcome and duration of mechanical ventilation ($p > 0.05$). Our observations were in accordance with the work of Richard et al.[51] who studied 95 patients with acute respiratory failure, their mean ages were 69.6 ± 9.3, 52.6% were male and 47.3% were female. They found no statistical significant relationships between the age, gender and the outcome of mechanical ventilation.

As much as overweight and weaning failure is concerned, in the present study 12 studied patients were obese (BMI $\geqslant 30$); 11 (63%) required long duration of MV $\geqslant 14$ days and 7 (47%) failed weaning trials and died at the end but there was no significant relationship between high BMI and the outcome and duration of MV ($P > 0.05$). O'Brien et al.,[55] in a secondary analysis of the data for the ARDS Network trials of mechanical ventilation, reported that the duration of mechanical ventilation was similar for overweight and obese patients compared with the normal body weight group (18.5–24.9 kg m^{-2}). Similar findings were reported by Tremblay and Bandi.[56] who looked at the effect of obesity on the length of ICU stay, which was increased, but the duration of mechanical ventilation was not.

6.1. Neuromuscular dysfunction and difficult weaning from MV

Patients receiving prolonged mechanical ventilation and other forms of critical care support commonly suffer from acquired neuromuscular disorders. Although MV may be prolonged by the occurrence of neuromuscular abnormalities, neuromuscular involvement also may be facilitated by prolonged MV. In the present work; EMG and nerve conduction study was done in 19 cases with difficult weaning. The results showed 26% with a normal picture, 63% with moderate to severe axonal sensory–motor peripheral neuropathy and 10.5% with a picture of myopathy. De Jonghe et al.[16] reported that neuromuscular weakness is a common occurrence in patients who are critically ill, developing in $\geqslant 25\%$ of patients who are in the intensive care unit (ICU) and ventilated for at least seven days. They reported, 4 independent variables associated with the occurrence of clinical motor weakness. The number of days with dysfunction in at least two organs before awakening was significantly higher in ICU acquired paresis patients than in the controls, suggesting that the duration, rather than the severity, of multiple-organ dysfunction plays a significant role in ICU acquired paresis. They found a strong association between the administration of corticosteroids and the occurrence of ICU acquired paresis. The duration of mechanical ventilation before awakening was also significantly associated with the occurrence of ICU acquired paresis. Surprisingly, female sex was found to be independently associated with a higher rate of ICU acquired paresis in their study. Regarding using maximal inspiratory pressure to assess respiratory muscle strength in the ICU, measurement of PImax is difficult and it is measured by briefly occluding the airway at end-expiratory volume. Jonathan et al. reported that neuromuscular weakness can be identified and quantified by measuring a maximal inspired pressure (should be < -30 cm H_2O).[57] In the present study measurement of maximum inspiratory pressure to the studied cases revealed that it is less negative in patients with neuromuscular disorders than those without (mean was -15 cm H_2O vs. -18 cm H_2O, respectively) yet; the difference was not statistically significant ($p = 0.192$). Concerning the relation between neuromuscular dysfunctions and the duration of MV, in the present study 50% of the cases with myopathy and 83% with polyneuropathy required a duration of mechanical ventilation $\geqslant 14$ days ($p = 0.184$). Garnacho-Montero et al.[58] evaluated septic patients receiving ventilation for at least 7 days for CIP (critical illness polyneuropathy). Patients with electrophysiologic evidence of CIP had a longer duration of mechanical ventilation than patients without (median, 34 days vs. 14 days; $p < 0.001$). This finding was explained by a longer period required for weaning and was associated with an increased length of ICU and hospital stay. Similar findings were reported in a study adopted by De Jonghe et al.[9] They evaluated ICU patients receiving ventilation for at least 7 days who were sufficiently awake to permit evaluation for ICU-acquired paresis. Of the 95 patients enrolled, 24 patients (25%) had ICU-acquired paresis. The weak patients exhibited a similarly increased period of weaning and the duration of mechanical ventilation as compared to the non-weak cohort. Regarding the effect of neuromuscular dysfunctions on the outcome of MV, in the present study, 33% of the pa-

tients with polyneuropathy failed weaning trials and finally died ($p = 0.798$). Garnacho-Montero et al.[59] studied a population of severely ill patients: septic patients with multiple organ dysfunction syndrome requiring mechanical ventilation for >10 days. Patients with CIP (Critical illness polyneuropathy) had higher in-hospital mortality rates than those without CIP (84% vs. 56.5%, $p = 0.01$). Similarly, Leijten et al.[60] found that in 50 patients receiving mechanical ventilation for >7 days, ICU mortality was higher in the CIP group (48% vs. 19%, $p = 0.03$). As much as Drug intake and its effect on the occurrence of neuromuscular dysfunction is concerned, many medications have been implicated as causes of weakness. The role of corticosteroids in CINM is particularly controversial. Corticosteroids, the most widely studied,[16,61,62] have a significant association with the development of ICU-acquired weakness. In animal models, administration of corticosteroids can produce selective muscle atrophy, particularly of fast-twitch fibers.[63] However, a thick filament myopathy identical to CIM can be best produced by combining denervation injury and corticosteroids.[64] In such an animal model, complete loss of muscle excitability was found, that was ascribed to the inactivation of fast sodium channels.[65].

In the present study 35.7% of cases with EMG and sensory–motor nerve conduction study abnormalities (myopathy or peripheral neuropathy) received corticosteroids for duration $\geqslant 14$ days (in the form of Dexamethazone in 60% and Prednisone in 40%). Statistically, there was no significant relation between the duration of corticosteroids intake and the occurrence of CINMA ($p = 1.000$). Among the studies with a multivariate analysis of risk factors for CINM, De Jonghe et al.,[16] Herridge et al.,[62] and Campellone et al.[66] concluded to a deleterious effect of corticosteroids. Whereas several data indicate that moderate doses of steroids do not prolong mechanical ventilation due to muscle weakness but are related to significantly more ventilator-free days and earlier spontaneous breathing capacity.[67]Another study showed that low-dose hydrocortisone application does not provoke impaired muscle membrane excitability, suggesting that steroid involvement in CIM development is dose dependent.[68] Concerning electrolytes disturbance as risk factors for neuromuscular dysfunctions, hypophosphatemia, hypomagnesaemia and hypocalcaemia are considered important contributing factors for myopathy and neuropathy. Phosphorus is the major intracellular anion. Approximately 85% of total body phosphorus is contained in bone. Phosphorus is used for cell membranes and is essential for adenosine triphosphate and red blood cell 2,3-diphosphoglyceric acid synthesis. It also plays a role in the regulation of glycolysis, ammonia genesis, and calcium regulation.[69] Consequently, hypophosphatemia leads to decreased oxygen delivery to tissues (including the central nervous system), and rarely to hemolysis in severe cases. Myocardial and skeletal muscle contractility also may be altered which results in symptomatic muscle weakness, respiratory failure, and difficulty in weaning from mechanical ventilation. In the present study, mean serum phosphorus was 3.4 ± 0.5 mg/dl among cases with neuromuscular dysfunctions and 3.4 ± 0.2 mg/dl among those without, there was no significant statistical relation between serum phosphorus level and neuromuscular dysfunctions, ($p = 0.607$). Asymptomatic presentation of the studied cases with neuromuscular dysfunctions may be due to near normal serum phosphorus levels. This goes in agreement with Bugg and Jones[70] who reported that symptoms of muscle weakness mostly occur in severe hypophosphatemia, defined as a serum phosphate concentration that is less than 0.32 mmol/L, but can also be present in moderate cases (0.32–0.8 mmol/L). Regarding magnesium; it is an essential cofactor of ATP reactions. This divalent cation also is involved in DNA replication and transcription, and translation of mRNA.[71] Consequently, hypomagnesaemia may have deleterious effects on energy production and protein metabolism. Serum contains only 0.3% of total body magnesium, and therefore, is a poor reflection of total stores. In addition, standard assays measure total serum magnesium; however, almost the entire ionized portion (corresponding to nearly 67% of total) is metabolically active.[72] Ionized magnesium can be measured by ion-selective electrodes; however, such analyzers are not widely available. In the present study mean of total serum Mg level was 1.6 mg/dl (median, 1.7; range, 1.1–1.9) for patients with normal EMG and nerve conduction study, and 1.4 mg/dl (median, 1.4; range, 1.1–2) for those with EMG and nerve conduction abnormalities (myopathy or peripheral neuropathy), $p = 0.671$. Dhingra et al.[73] had evaluated the effects of hypomagnesaemia on respiratory muscle strength in 11 patients admitted to the ICU with chronic obstructive pulmonary disease. They found that infusion of 6 g of magnesium increased PEmax by 24 percent and Plmax by 46 percent. Regarding calcium, the present work revealed no significant difference in serum calcium among cases with neuromuscular dysfunctions and those without (mean was 7.7and 7.6, respectively), $p = 0.963$. This study clarifies the relation between hypophosphatemia, hypomagnesaemia, and hypocalcaemia and neuromuscular dysfunctions showing that early diagnosis of electrolytes disturbances may be of help in the management of neuromuscular disorders acquired during ICU stay. Several studies have demonstrated marked increase in diaphragmatic strength immediately following repletion of Ca, Ph, and Mg, suggesting that the deficiencies impair the contractile properties of the diaphragm.[73,74] Concerning serum albumin and its relation to neuromuscular dysfunctions, in the present work mean serum albumin level was 2.4 g/dl among cases with neuromuscular dysfunction and 2.6 g/dl among those without, there was a significant relationship between hypoalbuminemia and neuromuscular dysfunction ($p = 0.037$). In agreement with our findings William E. Mitch[75] reported that low values of serum albumin are closely related to the presence of inflammation and loss of muscle mass is attributable to the activation of specific proteases. Also Nanas et al.[76] found that low serum albumin <3.5 mg/dl and mean daily serum glucose >150 mg/dl are predictive of critical illness polyneuropathy.

Any exposure to exogenous corticosteroids during the ICU stay might cause muscle weakness and possibly contribute to the duration of mechanical ventilation. In the present study, 15 patients received corticosteroids for a duration $\geqslant 14$ days; 7 (46.7%) failed weaning trials and 12 (80%) required a duration of MV $\geqslant 14$ days ($p > 0.05$). In one outcome study of survivors of ARDS, Herridge et al.[62] reported that the absence of corticosteroids was associated with a better functional outcome. Similar findings were reported by Amaya-Villar et al.[61] who observed that higher doses of steroids than those recommended for physiological replacement therapy are associated with severe myopathy that will prolong the duration of mechanical ventilation. This study together with the others gives a proof that some medications used for the management of respiratory failure may themselves be responsible for diffi-

cult weaning and prolong the duration of mechanical ventilation. So revising drug therapy used in the management of the patient in ICU during mechanical ventilation should be part of the general protocol applied for detection of the cause of difficult weaning.

The present study stresses on the importance of neuromuscular assessment in all cases with difficult weaning as this may be an important contributing factor for difficult weaning and prolonged mechanical ventilation (neuropathic or myopathic in origin). EMG and nerve conduction study may be of help for the detection of such disturbances. So, proper assessment of the neuromuscular apparatus and the management of any disorder may be a great step toward successful weaning. Evaluation of the neuromuscular factors should be put into consideration in every patient attending the ICU. Finally still there are risk factors for difficult weaning from mechanical ventilation that need to be assessed and obviously there is still scope for further investigation of difficult weaning from MV and this promises to be an exciting area of research in the future.

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