Physical Therapy Protocols to Attenuate Skeletal Muscle Atrophy in Critically ill Patients: Narrative Review

Protocolos de Terapia Física para Atenuar la Atrofia del Músculo Esquelético en Pacientes Críticos: Revisión Narrativa

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SUMMARY: To describe the physical therapy protocols used in critically ill patients to attenuate skeletal muscle atrophy. We conducted a search in PubMed and Embase from inception to November 2020. Observational or experimental studies published in English or Spanish that evaluated the effect of physical therapy protocols on the attenuation of skeletal muscle atrophy in critically ill patients through muscle strength or mass measurement were considered eligible. Studies were only included if they reported a detailed description of the dosing of the interventions. Seventeen studies met the eligibility criteria. We included randomised clinical trials (n = 16) and observational studies (n = 1). The total population of the included studies was 872 critically ill patients. The studies aimed to evaluate the reliability, safety or effectiveness of neuromuscular electrical stimulation (n = 10) protocols, early mobilisation (n = 3), ergometer training (n = 2), transfers in tilt table (n = 1), and blood flow restriction (n = 1). Physical therapy protocols are part of the critically ill patient's integral management. Strategies such as passive mobilisation, in-bed and out-of-bed transfers, gait training, ergometer training, and neuromuscular electrical stimulation substantially impact critically ill patients' prognoses and quality of life after hospital discharge.

KEY WORDS: Bed Rest, Intensive Care Unit, Mechanical Ventilation, Muscular Atrophy, Physical Therapy, Rehabilitation.

INTRODUCTION

The main feature of intensive care unit-acquired weakness (ICUAW) is skeletal muscle atrophy and damage to the nerves and muscles (Kramer, 2017). ICUAW is associated with an increase in days on mechanical ventilation (MV) and hospital stay, increasing healthcare costs and the risk of mortality, and ultimately affecting patient quality of life after hospital discharge (Schreiber, Bertoni, & Goligher 2018; Kramer 2017). A period in bed (for 7–10 days) reduces skeletal muscle strength by up to 40%, mainly of the lower limbs (soleus, hamstrings, and quadriceps)(Parry et al. 2015). Skeletal muscle mass loss causes a decrease in lower extremity strength and a reduction in patients' aerobic capacity, secondary to decreased physical activity (Kortebein et al. 2008).

Skeletal muscle mass maintenance occurs by balancing two mechanisms: skeletal muscle protein synthesis and degradation pathways that involve different molecular signals (Z. A. Puthucheary et al. 2013). Critically ill patients have an imbalance in protein synthesis and degradation signalling pathway (Z. A. Puthucheary et al. 2013). The decrease in protein synthesis signalling is more pronounced in septic states, thus exacerbating the loss of skeletal muscle mass (Martindale et al. 2017). As a result of skeletal muscle disuse, oxygen-free radical production in excess causes the activation of proteases, calpains, and caspases (Powers, Smuder, & Criswell 2011). Protein catabolism exceeds protein synthesis pathway activity due to the limited availability of amino acids...
Increased sarcomere protein degradation results in impaired muscle contractile activity (Parry & Puthucheary 2015) (Fig. 1).

Several authors have reported conditions associated with skeletal muscle atrophy (Kramer 2017; Parry et al. 2015; Kortebein et al. 2008; Parry & Puthucheary 2015; Hodgson et al. 2014): bed rest, inflammatory states, sepsis, multiple organ failure, sedation, use of corticosteroids, and neuromuscular blockers (Canu et al. 2019; M. L. Dirks et al. 2016).

The absence of gravitational stimuli leads to the loss of contractile muscle proteins and reduced muscle strength, ranging from 1-5.5% per day (M. L. Dirks et al. 2016). Bed rest increases the muscle inflammation state that then promotes skeletal muscle atrophy (Topp et al. 2002; Winkelman 2009). Septic states reduce muscle mass volume, acting mainly on the protein degradation pathways, and causing a decrease in the cross-sectional area of the muscle, oxygen consumption, and contractile activity performance (Kramer 2017; Borges & Soriano 2019; Z. Puthucheary et al. 2010). Septic shock patients on MV have decreased (by 14.5%) cross-sectional area of the straight femoral stem of the quadriceps after ten days in the intensive care unit (ICU) (Borges & Soriano 2019). Additionally, a reduction (by 10.7%) in the quadriceps muscle's cross-sectional area occurs in critically ill patients, even without MV (Haaf et al. 2017). On average, 53% of patients admitted to the ICU have skeletal muscle functional deterioration or die due to acute disease episodes, whereas 32% undergo hospitalisation discharge (Dettling-Ilhenfeldt et al. 2017). Skeletal muscle contractile functioning limitations lead to an increase in prevalence of adverse events during the hospital stay and are an adverse prognostic factor for post-discharge mortality (Jutte, Erb, & Jackson 2015; Vlayen et al. 2012).

On the other hand, only 27% of ICUAW patients recover skeletal muscle mass loss at six months after hospital discharge, reaching the level of a healthy person (Ferrante et al. 2016; Dos Santos et al. 2016; Helliwell et al. 1998). Hence, there is a need for therapeutic approaches toward applying strategies that include nutritional management, suitable sedation, and early skeletal muscle mobilisation to attenuate functional motor deterioration in ICU patients (Cameron et al. 2015; Muscedere et al. 2017; Malkoç, Karadibak, & Yildrim 2009).

In this sense, recent systematic reviews with a small sample of studies have shown that exercise and neuromuscular electrical stimulation (NMES) are safe and effective intervention strategies for skeletal muscle mass and strength maintenance in critically ill patients (Anekwe et al. 2020; Trethewey et al. 2019; Doiron, Hoffmann, & Beller 2018; Valenzuela, Joyner, & Lucia 2020; Nussbaum et al. 2017). Systematic reviews, however, answer specific clinical questions and therefore, do not allow knowledge of the spectrum of possible interventions used by physical therapists for the care of critically ill patients (Thomas 2013).

Thus, this narrative review described the physical therapy protocols used in critically ill patients to attenuate skeletal muscle atrophy.

**MATERIAL AND METHOD**

**Eligibility Criteria:** Primary studies (observational or experimental) published in English or Spanish that evaluated the effect of physical therapy protocols in the prevention of skeletal muscle atrophy in sedated, intubated or awake with spontaneously breathing critically ill patients, through measurements of skeletal muscle strength or mass, were considered eligible. The included studies reported a detailed description of the dosing of the interventions. We did not include studies involving animals or healthy humans, clinical trials in which dietary supplementation was used, systematic reviews of literature, book reviews, editorials, abstracts, or conference presentations.

**Electronic Search:** Two reviewers (IC-V and MA-A) independently searched PubMed and Embase up to November 26, 2020. The search strategy combined free terms and MeSH (Table 1). Also, we manually searched the references of included articles to identify potentially relevant studies.

### Table 1. Search strategy.

<table>
<thead>
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<th>Search strategy</th>
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<tr>
<td>#1 Critical Care [MeSH] OR Critical Illness [MeSH] OR Critically ill patients OR Intensive care units [MeSH] OR ICU OR artificial respiration OR mechanical ventilation</td>
</tr>
<tr>
<td>#2 Physical Therapy Modalities [MeSH] OR Physiotherapy OR Early physical rehabilitation OR Rehabilitation OR Physical therapy OR Exercise Therapy OR early motion OR early mobilization</td>
</tr>
<tr>
<td>#3 Neuromuscular weakness OR Sarcopenia [MeSH] OR Muscle Weakness [MeSH] OR Hypotrophy OR muscle atrophy</td>
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<td>#4 #1 AND #2 AND #3</td>
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**Filters:** clinical trial, controlled clinical trial, observational study, randomized controlled trial.
Study Selection: Two reviewers (IC-V and MA-A) independently filtered the search results by title and abstract. Potentially relevant articles retrieved from the searches were reviewed in full text for inclusion. In case of disagreement, a third reviewer (GM-N) evaluated the study's inclusion or exclusion. Concordance between reviewers in selecting studies was evaluated using the Kappa statistic with SPSS version 24.0 (IBM Corp., Armonk, NY, USA).

Data Collection Process: Two reviewers (PG-V and IC-V) extracted the articles' data through a standardised form. The form considered data such as author and year, study design, patient characteristics, rehabilitation protocol, intervention control, outcome measures of skeletal muscle atrophy, and pre- and post-intervention results.
RESULTS

The search yielded 163 results, of which 17 studies met the eligibility criteria (Nakamura et al. 2019; Grunow et al. 2019; Chen et al. 2019; Silva et al. 2019; Marlow L. Dirks et al. 2015; Falavigna et al. 2014; Gruther et al. 2010; Poulsen et al. 2011; Rodriguez et al. 2012; Gerovasili et al. 2009; Zanni et al. 2010; Hickmann et al. 2018; Yosef-Brauner et al. 2015; Burtin et al. 2009; Nickels et al. 2020; Sarfati et al. 2018; Barbalho et al. 2019) (Fig. 2). The agreement between the reviewers reached a kappa value of 0.83. Randomised clinical trials (RCT; n = 16) and observational studies (n = 1) were the included study designs.

The studies aimed at evaluating the reliability, safety, or effectiveness of protocols of NMES (n = 10), early mobilisation (EM; n = 3), ergometer training (ET; n = 2), transfers in tilt table (n = 1), and blood flow restriction (BFR; n = 1). The total population of the included studies was 684 critically ill patients. Details regarding the studies and the intervention protocols are displayed in Table II.

NMES: The NMES protocols were heterogeneous in their dosage, used frequencies of 20–100 Hz with pulses of 250–400 µsec, stimulation times of 2–12 seconds, rest times of 4–20 seconds, and intensities until achieving visible or palpable contraction.

The NMES daily sessions lasted for 20–60 minutes and were applied to the limb skeletal muscles, such as the brachial biceps, quadriceps femoris, gluteus maximus, tibialis anterior, fibular longus, and hamstrings.

EM: The EM protocols were performed two times daily for approximately 30 minutes or individualised to each patient’s impairments. The interventions were heterogeneous and included passive, active-assisted mobilisations, active or passive cycling in bed or chair, bed transfers, gait training, breathing, strengthening, and balance exercises.

Other Protocols: Two studies used upper and lower extremity ET daily for at least five to six days per week. The ET sessions lasted for 20–30 minutes. We adjusted the ET intensity to the capabilities of the patients. On the other hand, two studies used a tilt table to verticalise patients daily for one hour together with standard therapy. In addition, (Barbalho et al. 2019) used BFR in comatose patients; this intervention consisted of applying a pneumatic cuff to the proximal end of the lower limb during passive mobilization (Barbalho et al. 2019).

DISCUSSION

This narrative review aimed to describe the physical therapy protocols used in critically ill patients to attenuate skeletal muscle atrophy. We synthesised the physical therapy protocols and their effects on skeletal muscle atrophy from 17 studies. Our findings indicate that NMES is the most investigated physical therapy intervention in lean muscle loss attenuation.

Despite the heterogeneity of the investigations' parameters, NMES could positively influence critically ill patients to reduce loss of strength and muscle cross-sectional areas.

EM and ET are promising interventions that need more investigations to determine their roles in preventing skeletal muscle atrophy (Garzon-Serrano et al. 2011; Gatty et al. 2020; Tadyanemhandu, van Aswegen, & Ntsiea 2021). Implementing physical therapy protocols from the first day in the ICU positively affects physical ability recovery (Morris et al. 2008).

Rehabilitation includes short-term benefits for quadriceps strength, leading to an increase in functional capacity (Burtin et al. 2009; Peiris, Taylor, & Shields 2012). Moreover, early rehabilitation reduces hospital costs as a result of a shorter ICU stay (Lord et al. 2013).

Early skeletal muscle mobilisation in the ICU might reduce hospital mortality and weaning times and preserve the muscle strength of the lower extremities and respiratory muscle strength (Miranda Rocha et al. 2017). The protocols guided by rehabilitation teams achieve favourable results in functional independence, reduction in delirium rate, and lower incidence of ICUAW (Schweickert et al. 2009). Therefore, intervention protocols need to be adjusted according to the therapeutic dose for so measure their effectiveness and the cost/benefit ratio to mitigate physical, functional and cognitive deterioration (Govindan et al. 2015). The application of physical therapy reduces the need for sedation (Needham 2008).

The immediate post-admission use of an skeletal muscle mobility protocol promotes a reduction in readmission rates after one year of hospital discharge (Morris et al. 2011). However, compared to the usual care, rehabilitation does not produce any mortality-related differences during the hospital stay or six months of hospital post-discharge (Hanekom, Louw, & Coetzee 2012). The differences seem to be due to the severity of the
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Population Characteristics</th>
<th>Inclusion Criteria</th>
<th>Intervention/Protocol</th>
<th>Comparison</th>
<th>Main Outcomes</th>
<th>Meta-Finding</th>
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<tr>
<td>NMES</td>
<td>Nakamura et al., 2019</td>
<td>RCT</td>
<td>N = 40</td>
<td>EG (n=21; 76.6 ± 11.0 years)</td>
<td>NMES: F=20 Hz; Pulse=250 sec, once a day for 20 min, duty cycle: stimulation for 5 s and 2 s pause. Rehabilitation by nurses: ROM exercise, mobilization, and mobilization, 3 times per day during 5-20 min.</td>
<td>CG: Rehabilitation by PT plus Robustex nurses.</td>
<td>Muscle strength: MRC in the UE and LE.</td>
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<tr>
<td>NMES</td>
<td>Granow et al., 2019</td>
<td>RCT</td>
<td>N=21 13.5 yrs</td>
<td>M: 7 yrs, S: 13.5 yrs</td>
<td>NMES: F=50 Hz; Pulse=350 sec, once a day for 20 mins per muscle group (M. tibialis anterior, M. triceps surae, M. vastus lateralis, posterior bight). On-time was 6 s and off-time was 2 s.</td>
<td>CM: Robustex nurses plus ROM exercise, mobilization, and mobilization, 3 times per day during 5-20 min.</td>
<td>Muscle strength: MRC in the UE and LE.</td>
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<tr>
<td>NMES</td>
<td>Chan et al., 2019</td>
<td>RCT</td>
<td>M: 55 yrs, S: 7 yrs</td>
<td>M: 55 yrs, S: 7 yrs</td>
<td>EG: NMES: F=20 Hz; Pulse=250 sec, once a day for 20 min, duty cycle: stimulation for 5 s and 2 s pause. Rehabilitation by nurses: ROM exercise, kicking rate, walking, 3 times per day during 5-20 min.</td>
<td>EG: NMES: F=20 Hz; Pulse=250 sec, once a day for 20 min, duty cycle: stimulation for 5 s and 2 s pause. Rehabilitation by nurses: ROM exercise, kicking rate, walking, 3 times per day during 5-20 min.</td>
<td>Muscle strength: MRC in the UE and LE.</td>
</tr>
<tr>
<td>NMES</td>
<td>Silva et al., 2019</td>
<td>RCT</td>
<td>M: 60 yrs, S: 13 yrs</td>
<td>M: 60 yrs, S: 13 yrs</td>
<td>NMES: F=100 Hz; Pulse=400 sec, once a day for 25 mins per muscle group (M. tibialis anterior, M. triceps surae, M. vastus lateralis, posterior bight). On-time was 5s and off-time was 25s, thus eliciting a total of 50 contractions per day, at intensity to visible contractions.</td>
<td>CG: The protocol-based physiotherapy started with a goal of passive range of motion exercise in conscious or sedated patients, followed by active and resistive exercises, muscle to the edge of the bed or a chair, standing, and walking.</td>
<td>Muscle mass: rectus femoris (RF) and tibialis anterior (TA) muscles computed tomography.</td>
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<tr>
<td>NMES</td>
<td>Doria et al., 2015</td>
<td>RCT</td>
<td>M: 67 yrs, S: 69 yrs</td>
<td>M: 67 yrs, S: 69 yrs</td>
<td>EG: NMES: F=250 Hz; Pulse=500 sec, once a day for 25 mins per muscle group (M. tibialis anterior, M. triceps surae, M. vastus lateralis, posterior bight). On-time was 5s and off-time was 25s, thus eliciting a total of 50 contractions per day, at intensity to visible contractions.</td>
<td>CG: The protocol-based physiotherapy started with a goal of passive range of motion exercise in conscious or sedated patients, followed by active and resistive exercises, muscle to the edge of the bed or a chair, standing, and walking.</td>
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<tr>
<td>NMES</td>
<td>Falavigna et al., 2014</td>
<td>RCT</td>
<td>N = 11; 54 yrs</td>
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<td>NMES: F=50 Hz; Pulse=350 sec, once a day for 20 mins per muscle group (M. tibialis anterior, M. triceps surae, M. vastus lateralis, posterior bight). On-time was 6 s and off-time was 2 s.</td>
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<tr>
<td>NMES</td>
<td>Grathner et al., 2010</td>
<td>RCT, Pilot trial</td>
<td>M: 60 yrs, S: 50 yrs</td>
<td>M: 60 yrs, S: 50 yrs</td>
<td>NMES: F=500 Hz; Pulse=500 sec, once a day for 25 mins per muscle group (M. tibialis anterior, M. triceps surae, M. vastus lateralis, posterior bight). On-time was 5s and off-time was 25s, thus eliciting a total of 50 contractions per day, at intensity to visible contractions.</td>
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<tr>
<td>NMES</td>
<td>Breeden et al., 2011</td>
<td>RCT</td>
<td>M: 66 yrs, S: 72 yrs</td>
<td>M: 66 yrs, S: 72 yrs</td>
<td>NMES: F=500 Hz; Pulse=500 sec, once a day for 25 mins per muscle group (M. tibialis anterior, M. triceps surae, M. vastus lateralis, posterior bight). On-time was 5s and off-time was 25s, thus eliciting a total of 50 contractions per day, at intensity to visible contractions.</td>
<td>CG: The protocol-based physiotherapy started with a goal of passive range of motion exercise in conscious or sedated patients, followed by active and resistive exercises, muscle to the edge of the bed or a chair, standing, and walking.</td>
<td>Muscle mass: rectus femoris (RF) and tibialis anterior (TA) muscles computed tomography.</td>
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**Table II. Summary of ICU rehabilitation protocols selected in this review.**
Coma patients, connected


**Reference Study**

**Design**

**Characteristics**

**Results**

**Main Outcomes**

**Main Findings**

**NGMS**

Rodriguez et al., 2012.

RCT

N = 56; 72 years (IQR 45–78 years)

Patient 15 yrs or older with sepsis requiring MV and a predicted 1 or more failures of organ dysfunction within 48 hours of admission to ICU.

NGMS F >1.00: Pulse-F >50; XCO_{2} and a pH < 30 mins from resuscitation by fluid bolus. APACHE II with a score ranging from 20 to 200 (p < 0.01) on admission to ICU and on line admission to ICU.

CG: Side effects body as control served as his/her own control.

Muscle volume and apparent density.

Bips (p < 0.000) and quadriceps (p < 0.003) strength were significantly higher on the stimulated side at the 1st day of NGMS. Improvements were mainly observed in knee extensors and flexors. C-statistics of 0.60 hours stimulations and administered at the 1st day of NGMS (p < 0.003), whereas no other significant differences in strength were observed in non-stimulated muscles. Number of protocols: NGMS = 0.40, 0.40, 0.40.

**NGMS**

Gonzalez III et al., 2009.

RCT

N = 26

EG (n = 13; 59 ± 23 yrs) CG (n = 13; 56 ± 19 yrs)

All patients admitted to multidisciplinary ICU connected to MV.

NGMS = 45±9 Hz, hypoxic stimulus of 60%, 12 sec and 6 sec, and on a 30 sec interval to reduce visible contractions.

CG: No intervention.

Muscle mass, quadiceps muscle thickness by ultrasonography.

Muscle strength, MVC.

**Early mobilization**

Zanin et al., 2010.

Obstet project

N = 32; 49 years (IQR 42–57 years)

Patient intubated MV for more than 4 days in the ICU.

CG: Intensive treatment group.

Without CG.

Muscle strength, MVC.

**Early mobilization**

Hollman et al., 2009.

RCT

N = 19

EG (n = 9; 59±19 yrs) CG (n = 10; 57±20 yrs)

Adolesc 4th spores connected to MV were included in the ICU due to hospitalization.

EG: Early Physiotherapy 1.

The physiotherapy sessions per day (7–7) lasting 30 minutes (1.4 hr) of continuous active-lung and bedside bad cycling followed by manual passive limbs mobilization.

CG: Conventional treatment group, received a daily physical therapy protocol.

The physical therapy protocol was the same for all patients.

Muscle fiber cross-sectional area, EG (n = 13; 59+23 yrs) vs. CG (n = 13; 56+19 yrs)

p = 0.006. However, the CSD of the right RF p < 0.05 and the CSD of the right limbs p < 0.05 was determined by the CG (CG vs. EG: 0.11–0.18 cm, 1.16–3.54 cm, p < 0.035).

**Early mobilization**

Yacoub-Bonne et al., 2015.

RCT

N = 18

EG (n = 9; 61±12 yrs) CG (n = 9; 51±14 yrs)

Patient >18 yrs.

EG: Early Physiotherapy 2.

This therapy program consisted of a two-phase protocol, with progressive muscle stimulus and which was adjusted to the patient’s condition.

CG: Conventional treatment group, received a daily physiotherapy protocol.

The physical therapy protocol was the same for all patients.

Muscle fiber cross-sectional area, EG (n = 9; 61.5±12 yrs) vs. CG (n = 9; 57±20 yrs)

p < 0.05.

**Exercise therapy**

Burlin et al., 2009.

RCT

N = 90

EG (n = 51; 56 ± 16 yrs) CG (n = 39; 57 ± 17 yrs)

Awake patients with a prolonged ICU stay of at least 7 min days.

EG: Patients in the treatment group received a session 5 days a week, using a bed exercise generator. The patient was allowed to passively and actively resist the exercise generator or control the exercise generator, without any deviation of muscle force.

CG: Received only routine physiotherapy treatment.

Without CG.

Muscle strength, isometric, MVC, and handgrip dynamometer.

**Exercise therapy**

Nichols et al., 2020.

RCT

N = 72

EG (n = 36; 56 ± 18 yrs) CG (n = 36; 56 ± 16 yrs)

Patient <65 yrs and >18 yrs.

EG: Exercise therapy plus.

CG: Standard rehabilitation plus.

Ambulation was started when considered appropriate by the medical staff.

Ambulation scores at ICU discharge were not significantly different between groups (EG 3.6–5.0; vs. CG 3.0–4.0; p = 0.011).

**Tilt Table**

Salter et al., 2018.

RCT

N = 125

EG (n = 62; 52–75 yrs) CG (n = 63; 54–75 yrs)

Patient admitted to the ICU, >18 yrs of age and MV for 3 days or more with no expectation of extubation or death in the next 24 hours.

EG: Standard rehabilitation plus.

CG: Standardized rehabilitation therapy without tilting.

MVC and muscle mass.

MVC was significantly higher in the EG than in the CG.

**Blood Flow Restriction**

Birchfield et al., 2019.

Within-subject RCT

N = 20; 69.43 yrs

Coma patients, connected to MV and admitted to the ICU.

BG: Passive mobilization plus BFR.

CG: Only passive mobilization.

Muscle mass, quadiceps muscle thickness by ultrasonography.

Leg volume, thigh circumference.

BG had a significantly lower increase in thigh circumference than the control (1.2 vs. 2.1 cm, respectively, p < 0.000).

In addition, the BFR limb had a smaller reduction in thigh circumference than the control (2.5 vs. 3.6 cm, respectively, p < 0.001).
thepathologists using a planned methodology and considering of adverse effects (Zanni et al. 2010; Hickmann et al. 2018; Yosef-Brauner et al. 2015). It should also include passive and active mobilisation of the extremities, turning exercises, sitting on the edge of the bed, physical activities with pedals, transfers from the stretcher to the wheelchair, facilitating walking, and using NMES devices (Doiron, Hoffmann, & Beller 2018). Other protocols, such as BFR (Barbalho et al. 2019), is also being used.

NMES is among the new tools used in the early rehabilitation of critically ill patients; at the same time, it applies to patients under sedation in combination with joint mobility exercises during the first days of admission to the ICU (Herzig, Maffuletti, & Eser 2015; Hodgson et al. 2012). As a result, increased muscle strength and skeletal muscle mass preservation has been reported (Routsi et al. 2010). NMES is a useful therapeutic tool, given the growing number of patients that survive the ICU and who, as a result, develop ICUAW. The preservation of skeletal muscle mass reflects the usefulness of a rehabilitation programme.

Additionally, the selection and application of stimulation must follow applicable rules in the programming, protocol, dose, and frequency to achieve optimal muscle recruitment (Nakamura et al. 2019; Grunow et al. 2019; Chen et al. 2019; Silva et al. 2019; Marlou L. Dirks et al. 2015; Falavigna et al. 2014; Gruther et al. 2010; Poulsen et al. 2011; Rodriguez et al. 2012; Gerovasili et al. 2009; Zanni et al. 2010; Hickmann et al. 2018; Yosef-Brauner et al. 2015; Burtin et al. 2009; Nickels et al. 2020; Sarfati et al. 2018; Barbalho et al. 2019). Despite NMES being a tool that has proven to be efficient in preserving muscle mass, it is not widely used in ICU units. The costs necessary to acquire NMES equipment are less than ET or tilt table equipment, so we speculate there are more studies on NMES because more of this type of equipment is available in hospitals.

It is important to note that physical therapy requirements of critically ill patients vary according to their needs for ventilatory support and clinical condition. Therefore, the physical therapy protocols used in intubated or sedated patients are different from those used in patients who remain awake in the ICU with spontaneous respiration and who may collaborate and actively participate in their therapy (Hodgson et al. 2012; Gosselink et al. 2008; Hruska 2016). The care delivered to intubated or sedated patient is greater than to awake patient; therefore, physical therapy protocols should be progressive.

EM has shown more significant beneficial effects when associated with other therapies. However, we still see physical therapists who continue to perform mobilisation in isolation in clinical practice. More studies are needed to

condition on admission (Dong 2014). Other factors include the time of intervention and clinical experience of the physical therapist (Denhey et al. 2013). Passive muscle mobilisation preserves 35% of the muscle strength of the extremity subjected to intervention compared to the disuse condition (Llano-Diez et al. 2012).

ET physical exercise is not harmful to respiratory, metabolic, or haemodynamic functions, and an intervention to improve muscle and joint function may then be recommended (Burtin et al. 2009). This issue, however, remains controversial. There is evidence that ET increases walking ability, muscle strength, and cardiovascular function in critically ill patients (Burtin et al. 2009). Other authors, however, did not report health benefits using ET (Nickels et al. 2020).

Tilt table use improves muscle recovery when associated with standard rehabilitation, compared to usual rehabilitation (Sarfati et al. 2018). A tilt table included in an EM protocol also improves transfers and walking (Sarfati et al. 2018). A study conducted in Australia reported that only 21% of physiotherapists used tilt tables more than once a week, and 40.3% mentioned using it less than once a month (Chang et al. 2004). The use of tilt tables as a therapeutic tool preserves range of motion, improves or maintains skeletal muscle strength, performs passive stretching exercises, stimulates balance, and improves cognitive function (Frazzitta et al. 2016).

The implementation of early mobility and rehabilitation protocols must be carried out by physical

Abbreviations: 1RM: One Repetition Maximum; 6MWDD: 6-Minute Walking Distance; APACHE II: Acute Physiology And Chronic Health Evaluation II; BFR: Blood Flow Restriction; CG: Control Group; CSA: Cross-sectional area; CSD: cross-sectional-diagonal; EG: Experimental group; ET: ergometer training; RT: resistance training; EVD: external ventricular drains; EQ5D-5 L: Quality of life measured; F: Frequency; FAC: Functional Ambulation Categories; FES-Cycling: Functional electrical stimulation cycling; FIM: Functional Independence Measure; FOXO1: Forkhead box protein O1; ICU: Intensive Care Unit; ICU-AW: Intensive care unit acquired weakness; IQR: Interquartile range; LE: Lower Extremities; mA: milliamper; MAFbx: Muscle atrophy F-box; MAP: Mean Arterial Pressure; MRC: Medical Research Council; mTOR: mammalian target of rapamycin; MuRF-1: Muscle ring finger-1; MV: Mechanical ventilation; NCCU: Neurocritical care unit; NMES: Neuromuscular Electrical Stimulation; Obs: observational study; OT: Occupational Therapy; PWCFT: physical working capacity of the fatigue threshold test; QF: Quadriceps femoris; RASS: Richmond Agitation Sedation Scale Score; RCT: Randomized controlled trial; Rehab: Rehabilitation; Reps: repetitions; RF: Rectus Femoralis; ROM: Range of motion; SAH: subarachnoid hemorrhage; SC: standard care; SF-36: Short Form-36 Health Survey; SOFA: Sepsis-related Organ Failure Assessment; SpO2: Peripheral oxygen saturation; UE: Upper extremities; US: Ultrasound; VM: Vastus Medialis; VL: Vastus Lateralis; vs: versus; WK: week.

*Acute <7 days; # long-term >14 days in ICU
demonstrate the effects of these therapies in isolation or combination to determine their impact on combating skeletal muscle atrophy.

**Strengths and Limitations:** By attenuating skeletal muscle atrophy in critically ill patients, one result should be a reduction in healthcare costs (reduction of days on MV and hospital stay) and a faster functional capacity recovery. This literature review summarises the physical therapy protocols most commonly used to attenuate skeletal muscle mass loss during the ICU stay and their main results.

Among the limitations, we find that due to the patients' heterogeneity of treatments and the different protocols used in the selected articles, we cannot recommend an optimal protocol to attenuate skeletal muscle atrophy in critically ill patients.

**CONCLUSION**

Physical therapy protocols are part of the critically ill patient's integral management, which allows the patient to stay physically active for a more significant portion of their time spent in the ICU. Strategies such as passive mobilisation, in-bed and out-of-bed transfers, ergometric training, gait training, and neuromuscular stimulation substantially impact the prognosis and quality of life after a critically ill patients' hospital discharge. The protocols reported in this narrative review indicate a paradigm shift in skeletal muscle rehabilitation in the ICU.

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