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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

Pablo Guerra-Vega[1,2]; Iván Cuyul-Vásquez[3]; Macarena Artigas-Arias[2,3];
Rodrigo Muñoz-Cofre[4]; Rui Curi[5,6]; Gabriel Nasri Marzuca-Nassr[2,7]

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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

[1] Unidad de Paciente Crítico, Clínica Alemana, Osorno, Chile.
[2] Programa de Magíster en Terapia Física con mención, Facultad de Medicina, Universidad de La Frontera, Temuco, Chile.
[3] Departamento de Procesos Terapéuticos, Facultad de Ciencias de la Salud, Universidad Católica de Temuco, Chile.
[4] Posdoctorado en Ciencias Morfológicas, Facultad de Medicina, Universidad de La Frontera, Temuco, Chile.
[5] Interdisciplinary Post-Graduate Program in Health Sciences, Cruzeiro do Sul University, São Paulo, Brazil.
[6] Butantan Institute, São Paulo, Brazil.
[7] Departamento de Medicina Interna, Facultad de Medicina, Universidad de La Frontera, Temuco, Chile.

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(Wollersheim *et al*. 2014; Wolfe 2018). 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-Ihnenfeldt *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 I). Also, we manually searched the references of included articles to identify potentially relevant studies.

Table I. Search strategy.

Search strategy	
#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
#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
#3	Neuromuscular weakness OR Sarcopenia [MeSH] OR Muscle Weakness [MeSH] OR Hypotrophy OR muscle atrophy
#4	#1 AND #2 AND #3
Filters:	**clinical trial, controlled clinical trial, observational study, randomized controlled trial.**

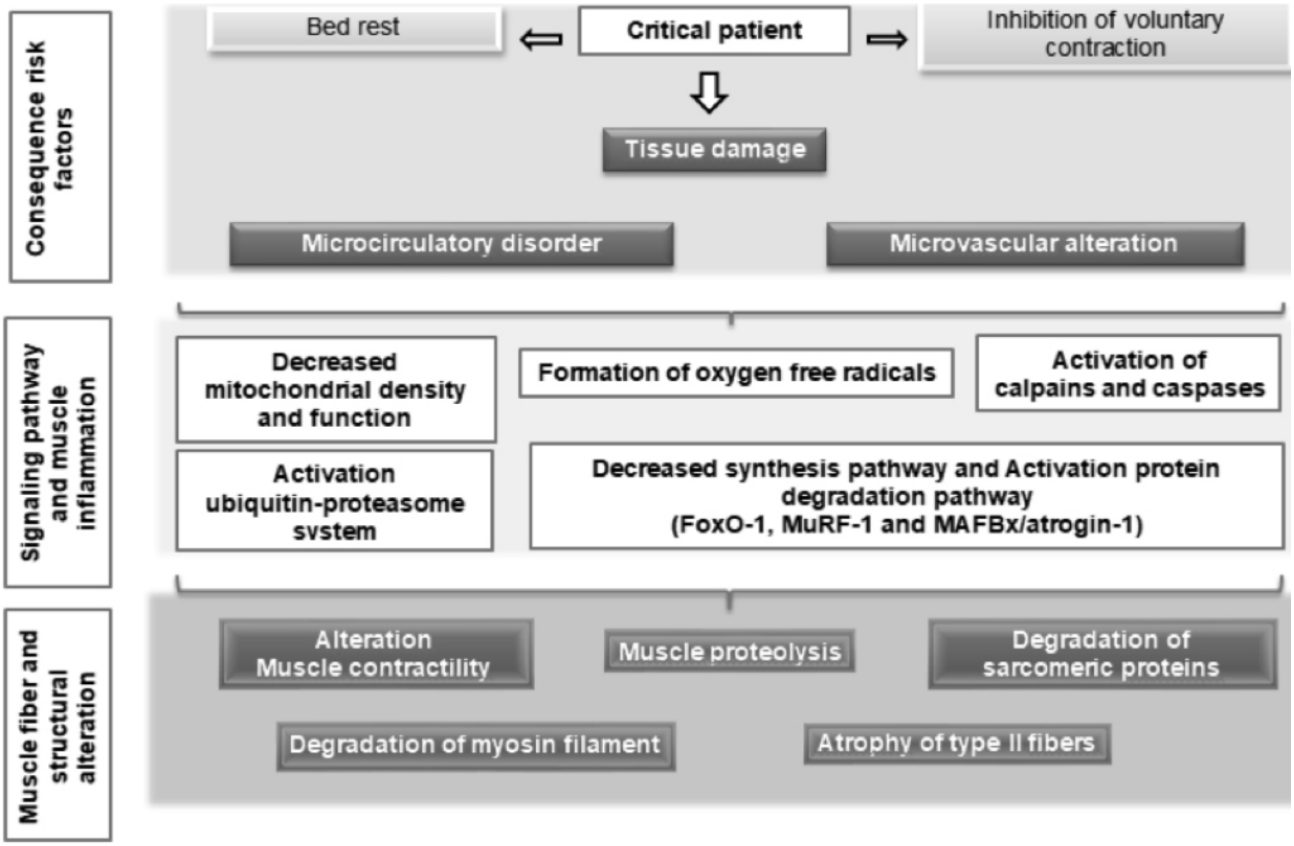

Fig. 1. Diagram of the physiopathology of skeletal muscle atrophy in critically ill patients.

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 SPPS 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.

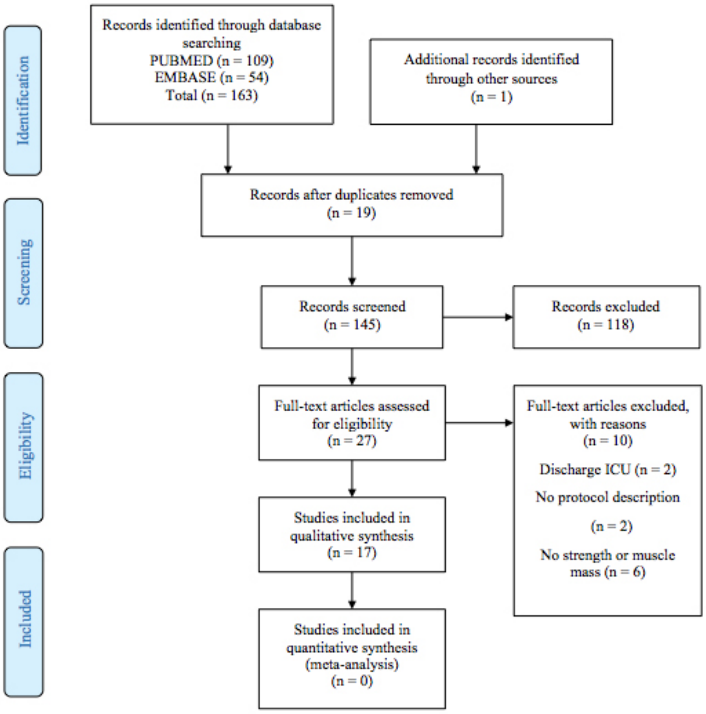

Fig. 2. PRISMA 2009 Flow Diagram.

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; 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) (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 II. Summary of ICU rehabilitation protocols selected in this review.

|	**Reference**	**Study design**	**Population characteristics**	**Inclusion Criteria**	**Intervention (Protocol)**	**Comparation**	**Main Outcomes**	**Main Findings**
NMES	Nakamura *et al.,* 2019.	RCT	N=94 EG (n=21; 76.6 ± 11.0 years). CG (n=16; 74.6 ± 13.1 years).	Patients admitted to the ICU connected to MV, sedative and analgesics	EG: NMES plus Rehab by nurses. NMES: F=20 Hz; Pulse=250 _sec, once a day for 20 min, duty cycle with stimulation for 5 s and a 2-s pause. Rehab by nurses: ROM exercise, mobilisation, and ambulation, 3 times per day during 5-20 min.	CG: Rehab by PT plus Rehab by nurses. Rehab by PT : ROM exercise, kicking stability ball, standing, ambulation exercise once a day during 20 min. Rehab by nurses: ROM exercise, mobilisation, and ambulation, 3 times per day during 5-20 min.	Femoral muscle volume: computed tomography.	For both groups, femoral muscle volume decreased significantly from day 1 to day 10 ($p<0.001$). The mean rate of muscle volume loss was 17±10.8% for the CG and 10.4%±10.1% for the EG group ($p=0.04$)
NMES	Grunow *et al.*, 2019.	Secondary analysis RCT	N=21; 53.0 years	MV patients≥ 18 years of age were included with SOFA score ≥ 9 within the first 72 h after ICU admission.	EG: NMES plus protocol-based physiotherapy. NMES: F=50 Hz; Pulse=350 _sec, once a day for 20 mins per muscle group (M. tibialis anterior, M. triceps sural, M. vastus lateralis, posterior thigh). On-time was 6/10 s and off-time was 10/15 s with a ramp of 1 s. Protocol-based PT: twice daily for 20 min.	Without CG.	Muscle strength: MRC in the UE and LE.	Muscle strength showed higher values in the upper extremities of responders vs. non-responders at ICU discharge (4.4 [4.1/4.6] vs. 3.3 [2.8/3.8] MRC score, $p=0.036$).
NMES	Chen *et al.*, 2019.	RCT	N=33 EG (n=16; 77.7 ± 14.3 years) CG (n=17; 73.8 ± 17.8)	Adults≥20 years in MV for ≥6 h/d for ≥21 d; failure to be weaned in the ICU; Medically stable (arterial blood gas pH =7.35–7.45, PaO2 ≥60 mm Hg at 40% FIO2, absence of signs and symptoms of infection, and hemodynamic stability).	EG: NMES: F=50 Hz; Pulse 400 _sec width cycling 2s on and 4 s off. Two 30-min electrical muscle stimulation sessions per day, 5 days for week for 2 weeks in VL and RF of both legs.	CG: received similar medical treatment except for the electrical muscle stimulation therapy (similar electrode placement and intervention duration, except that the stimulator power was off).	Muscle strength: MRC. Muscle volume: Leg circumference.	Significantly increased in MRC points was found in the EG group after intervention (2 [1-7] points vs. 2 [1-3.5] points, respectively, $p=0.034$). No difference in MRC points was found between baseline and post-measurement in the CG (1[1-2] points vs. 1[1-2.5] points, respectively, ($p>0.99$). Leg circumference in CG significantly decreased when compared with baseline (47.5+8.3 cm vs. 44.6+5.7 cm, respectively, $p=.004$) and remained unchanged in the EG.
NMES	Silva *et al.*, 2019.	RCT	N=60 EG (n=20; 30 years (IQR, 27-33 years) CG (n=20; 33 years (IQR, 29-37 years)	Patients of both genders, between 18 and 60_years of age, who had undergone MV for up to 24_h, following a severe traumatic brain injury, were included.	EG: NMES plus protocol-based physiotherapy. NMES: F=100Hz; Pulse=400 sec, once a day for 25 mins per muscle group (QF, hamstring, tibialis anterior, and gastrocnemius muscles). On-time was 5s and off-time was 25s, thus eliciting a total of 50 contractions per day, at intensities to visible contractions	CG: The protocol-based physiotherapy started with a global passive range of motion exercises in comatose or sedated patients, followed by active and resistive exercises, transfer to the edge of the bed or a chair, standing, and walking.	Muscle mass: rectus femoris (RF) and tibialis anterior (TA) muscles by ultrasonography. Evoked peak force: calibrated load cell attached to a platform and an electrical stimulator on the RF muscle.	After 14_days, the control group presented a significant reduction in muscle thickness of tibialis anterior and rectus femoris, mean of 0.33 mm (14%) and 0.49 mm (21%), $p<0.0001$, respectively, while muscle thickness was preserved in the NMES group. The NMES group demonstrated an increase in the evoked peak force (2.34 kg/f, $p<0.0001$), in contrast to the control group (1.55 kg/f, $p<0.0001$).
NMES	Dirks *et al.*, 2015.	RCT	N=6; 63.3±16.9 years	Patients fully sedated of 18-80 years admitted to the ICU.	EG: NMES in one leg plus SC One leg was subjected to twice-daily NMES of the quadriceps muscle for a period of 7±1 day. NMES warm-up phase (5 min, 5 Hz, 250 _sec); stimulation period [30 min, 100 Hz, 400 sec, 5s on (0.75 s rise, 3.5 s contraction, 0.75 s fall) and 10 s off] and a cooling-down phase (5 min, 5 Hz, 250 sec). Intensity level from the higher visible and palpable muscle contraction in QF. SC was not altered and passive mobilisation was performed on both legs.	CG: Sham NMES in one leg plus SC. During the NMES sessions, four electrodes and compatible cables were also applied to the control leg to standardize all procedures (representing a sham treatment). Standard medical care was not altered, and passive mobilisation was performed on both legs according to the standard care procedures.	Muscle fiber cross-sectional area (CSA): muscle biopsy + histology.	In the control leg, type 1 and type 2 muscle–fibre-CSA decreased by 16±9% and 24±7% respectively ($p<0.05$). No muscle atrophy was observed in the stimulated leg.
NMES	Falavigna *et al.,* 2014.	RCT	N=11; 34 ±17.3 years.	Patients in MV for a period of up to 48 h with absence of electrocardiographic changes, without evidence of acute myocardial infarction or arrhythmia; absence of respiratory distress signs; SpO2 of over 90%, FiO2 <60%.	EG: NMES plus Passive mobilisation in one leg. NMES on QF and the tibialis anterior, daily for 20 min. F= 50 Hz, Biphasic symmetric pulse= 400 _sec, for 9s on (including 2 s of rise time, 5 second of contraction and 2 s of fall time) and 9 s off, at intensities to visible contractions. Passive mobilisation of joints of the LE was performed. For each joint 10 mobilisations were performed throughout the arc of movement.	CG: Passive mobilisation in the contrary leg of EG. Passive mobilisation of joints of the LE was performed. For each joint 10 mobilisations were perfomed throughout the arc of movement.	Leg volume: thigh and leg circumference.	The control leg was observed of 10 cm reduction when compared to the stimulated leg one (24.7+3.1 vs. 26.4+4.0 cm; $p=0.03$).
NMES	Gruther *et al.,* 2010.	RCT. Pilot trial	N=33 *Acute EG (n=8; 52+10 years) *Acute CG (n=9; 48+12 years) #Long-term EG (n=8; 61+10 years) #Long-term CG (n=8; 64+8 years)	Men and women, all older than 19 years with severe disorders and bed resting ICU.	EG: NMES NMES was applied for a period of 4 weeks in sessions 30–60 minutes, 5 days/week. F= 50 Hz, biphasic symmetric pulses of 350 sec (stimulus regime: 8s on/24s off; 30 min/day in the first week, increased to 60 min/day in the second week) and a patient adjusted intensity to ensure a maximum tolerable tetanic contraction of the QF muscle.	CG: sham-NMES group For sham stimulation the current was only increased until the patient could feel a tingling sensation and no muscle contraction was visible or palpable.	Muscle mass: quadriceps muscle thickness by ultrasonography	Compared with acute patients, only stimulated long-term patients (+4.9%) showed a significant ($p=0.013$) increase in muscle layer thickness compared with sham-stimulated patients (–3.2%).
NMES	Poulsen *et al.* 2011.	RCT	N=8; 67 years (IQR, 64 -72 years) and 25 years (IQR, 20–29 years)	Adult diagnosed with septic shock connected to MV, sedative and admitted to the general ICU	EG: NMES plus Passive mobilisation in one leg. NMES: F=35Hz; Pulse=300 sec, once a day for 60 mins per muscle group (VM and VL,). For 9s on, on-time was 2s, contraction-time 5s and off-time was 0.5s, at intensities to visible contractions.	CG: Passive mobilisation in the contrary leg of EG.	quadriceps muscle volume: computed tomography.	During the 7-day study period, the volume of the quadriceps muscle on the control thigh decreased by 16% (4–21%, $p=0.03$) corresponding to a rate of 2.3% per day. The volume of the stimulated muscle decreased by 20 % (3–25%, $p=0.04$) corresponding to a rate of 2.9% per day ($p=0.12$ for the difference in decrease). There was no difference in muscle volume between the stimulated and nonstimulated thigh at baseline ($p=0.10$) or at day 7 ($p=0.12$).

	Reference	**Study design**	**Population characteristics**	**Inclusion Criteria**	**Intervention (Protocol)**	**Comparation**	**Main Outcomes**	**Main Findings**
NMES	Rodriguez *et al.,* 2012.	RCT	N=16; 72 years (IQR, 63-80 years)	Patients 18 years or older with sepsis requiring MV and presenting with 1 or more organ failure other than respiratory dysfunction within 48 hours of admission to ICU	EG: NMES in the same-side brachial biceps and vastus medialis. NMES: F=100Hz; Pulse=300 _sec, once a day for 30 mins per muscle group (brachial biceps and VM). Amplitude ranging from 20 to 200 V (peak to peak), on-time was 2s and off-time was 4s, at intensities to visible contractions.	CG: Side of the body contrary served as his/her own control	Muscle volume: arm and thigh circumferences. Muscle mass: biceps thickness muscle by ultrasonography Muscle strength: MRC.	Biceps (*p*= 0.005) and quadriceps (*p*= 0.034) strengths were significantly higher on the stimulated side at the last day of NMES. Improvement was mainly observed in more severe and weaker patients. Circumference of the non stimulated arm decreased at the last day of NMES (*p*=0.015), whereas no other significant differences in limb circumferences or biceps thickness were observed.
NMES	Gerovasilli *et al.,* 2009.	RCT	N=26 EG (n=13; 59±23 years) CG (n=13; 56±19 years)	All patients admitted to multidisciplinary ICU connected to MV.	EG: NMES NMES: F=45 Hz; biphasic, symmetric pulse of 400 _sec, 12 seconds on and 6 seconds off, at intensities able to cause visible contractions. Daily sessions of 55 minutes on QF and peroneous longus muscles of both LE.	CG: No intervention	Muscle mass: quadriceps muscle thickness by ultrasonography	Right RF and right vastus intermedius CSD decreased in both groups (*p*<0.05). However, the CSD of the right RF decreased significantly less in the EG (-0.11 ± 0.06 cm, -8±3.9%) as compared to the CG (-0.21±0.10 cm, -13.9±6.4%; *p*<0.05) and the CSD of the right vastus intermedius decreased significantly less in the EG (-0.10±0.05 cm, -12.5±7.4%) as compared to the CG (-0.29±0.28 cm, -21.5±15.3%; *p*<0.05).
Early mobilisation	Zanni *et al.,* 2010.	Obs. pilot project	N= 32; 49 years (IQR, 42-57 years)	Patients receiving MV for more than 4 days in the ICU.	EG: Intensive treatment group. Rehabilitation interventions were individualized to each patient's impairments and included activities such as stretching, strengthening, balance training, and functional activities.	Without CG.	Muscle strength: MRC.	Physiologic changes during rehabilitation therapy were minimal. In 53% and 79% of initial ICU assessments, muscle weakness was present in upper and lower extremities, respectively, with a decreased prevalence of 19% and 43% at hospital discharge, respectively.
Early Mobilisation	Hickmann *et al.,* 2018.	RCT	N=19 EG (n=9; 59±19 years) CG (n=10; 57±20)	Adults with septic shock connected to MV were included within the 72 hours after ICU.	EG: Early Physical Therapy. Two physiotherapy sessions per day (7/7 d) including 30 minutes (1 hr/d) of continuous passive/active leg chair/bed cycling followed by manual passive/ active limbs mobilisation.	CG: underwent a daily physiotherapy session through manual passive/ active limbs mobilisation (5/7 d).	Muscle fiber cross-sectional area (CSA): muscle biopsy + histology.	Muscle fiber cross-sectional area (_m2) was preserved by exercise (–25.8%±21.6% in CG vs. 12.4%±22.5% in EG; *p*=0.005).
Early Mobilisation	Yosef-Brauner et al., 2015.	RCT	N=18 EG (n= 9; 61.5±12 years) CG (n=9; 51.6±18 years)	Patients >18 years, conscious and able to perform simple commands, independent before the current hospitalisation. Patients required MV over 48h duration and who were expected to remain ventilated for at least 48 additional hours.	EG: intensive treatment group, were treated twice a day by a physical therapy protocol. The therapy program consisted of a three-phase protocol, with progressive levels of difficulty and which was adjusted to the patient's medical condition. The daily therapy program included respiratory (manual lung hyperinflation and bronchial suction) and functional elements, including muscle-strengthening techniques, maintaining range of motion and preventing muscle shortening (passive/active exercises, positional changes and bed mobility, including sitting until walking).	CG: conventional treatment group, received a daily custom physical therapy protocol. The physical therapy protocol was the same described in EG.	Muscle strength: MRC, maximal and handgrip dynamometer.	Significant strength improvement from first to second measurements was demonstrated for variable MRC in favor of the intensive treatment group (*p*=0.029). A trend toward increased grip strength was demonstrated for the intensive treatment group as well (*p*= 0.018)
Ergometer Training	Burtin *et al.,* 2009.	RCT	N=90 EG (n=31; 56 ± 16 years) CG (n=36; 57 ± 17 years)	Awake patients with a prolonged ICU stay of at least 7 more days.	EG: Patients in the treatment group received a session 5 days a week, using a bedside cycle ergometer. The device offers the possibility to conduct passive or active cycling at six levels of increasing resistance. The aim of each session was to have the patient cycle for 20 mins at an individually adjusted intensity level. In addition, the patients received a physical therapy protocol it was same describe in CG.	CG: Received respiratory physiotherapy adjusted to the individual needs and a standardized mobilisation session of the upper and lower extremities on 5 days per week. Passive motion was applied in sedated subjects, whereas awake patients were asked to participate actively. Intensity of the exercises was increased according to the patient's capability. Ambulation was started when considered appropriate by the medical staff.	Muscle strength: isometric quadriceps force and handgrip dynamometer.	Quadriceps force improved more between ICU discharge and hospital discharge in the treatment group (1.83 ± 0.91 $N\cdot kg^{-1}$ vs. 2.37 ± 0.62 $N\cdot kg^{-1}$, *p*=0.01) than in the control group (1.86 ± 0.78 $N\cdot kg^{-1}$ vs. 2.03 ± 0.75 $N\cdot kg^{-1}$ *p*=0.11). Handgrip force was not different between treatment and control group at ICU discharge (46± 20%pred. vs. 47±11%pred. *p*= 0.83) and at hospital discharge (51 ± 16%pred. vs. 59 ± 25%pred. *p*= 0.15).
Ergometer Training	Nickels *et al.,* 2020.	RCT	N=72 EG (n=36; 56 ± 18 years) CG (n=36 57 ± 16 years)	Patients were eligible if they were expected to be MV for more than 48 h, recruited within 96 h of their ICU admission, and expected to remain in the ICU for more than 48 h from admitted.	EG: The cycling group received routine physiotherapy interventions and they also received once daily (6 days/week) in-bed leg cycling using. Cycling sessions were delivered to passively and progressed to active or resisted exercise depending on participants' ability and level of consciousness, the exercise was at a moderate to hard level of perceived exertion. Cycling sessions were delivered for a maximum of 30 min.	CG: Received only routine physiotherapy interventions that included a daily assessment of physical and respiratory status and treatment. Physical treatments were directed to functional task achievement including; sitting, standing and mobilizing.	Muscle mass: Rectus femoris cross-sectional area (CSA) measured by ultrasound. Muscle strength: manual muscle strength and handgrip strength	There were no significant between-group differences in muscle atrophy of RFCSA at Day 10 (mean difference 3.4, 95 % CI -6.9% to 13.6%; *p*= 0.52), or for secondary outcomes: Handgrip strength (*p*= 0.85).
Tilt Table	Sarfati *et al.,* 2018.	RCT	N=125 EG (n=62; 52-73 years) CG (n=73; 54-75 years)	Patients admitted to the ICU, >18 years of age and MV for 3 days or more with no expectation of weaning on the day of selection for study eligibility.	EG: standardized rehabilitation plus Tilting. In-bed ROM exercises and out-bed mobilisation were administered 7 days per week. Passive ROM included 5 reps for each upper and lower extremity joint. Out-bed mobilisation consisted of sitting in armchair at least 2 h per day and patients were verticalized on an electrical tilt-table for at least 1 h per day. The patient was secured to the table by Velcro straps at the torso and knees and was gradually tilted from 30-60° in 10° steps. When the patient was able to stand up with assistance, rehabilitation exercises consisted in sitting in armchair, standing up and walking with assistance.	CG: standardized rehabilitation therapy without tilting. Same protocol describes in the EG without tilting.	Muscle strength: MRC Muscular recovery: was expressed as the median change in MRC score from baseline to ICU discharge.	Total mobilisation duration (median [25th-75th percentiles]) in the EG was 1,020 [580-1,695] vs 1,340 [536-2,775] minutes in the CG (*p*=0.313). MRC sum scores at ICU discharge were not significantly different between groups (EG, 50 [45-56] vs. CG, 48 [45-54]; *p*=0.555). However, the number of patients with weakness was higher in the EG at baseline (EG, 60/65 versus CG, 48/60, *p*=0.045) and muscular recovery was better in the EG (*p*=0.004).
Blood Flow Restriction	Barbalho *et al.,* 2019.	Within-patient RCT	N=20; 66±4.3 years	Coma patients, connected to MV and admitted to the ICU.	EG: Passive mobilisation plus BFR. Passive mobilisation protocol was performed with three sets of 15 knee flexion-extension movements, considering 2 seconds in the flexion phase and 2 seconds in the extension phase. BFR: The cuff was placed in the proximal thigh region and a pressure of 80% of the systolic blood pressure was applied to the patient's anterior tibial artery.	CG: Only passive mobilisation.	Muscle mass: quadriceps muscle thickness by ultrasonography Leg volume: Thigh circumference.	Despite both groups presented atrophy, the atrophy rate was lower in BFR limb in relation to the control limb (–2.1 vs. –2.8 mm, respectively, in muscle thickness; *p*=0.001). In addition, the BFR limb also had a smaller reduction in the thigh circumference than the control limb (–2.5 vs –3.6 cm, respectively; *p*=0.001).

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-diameter; 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: milliampere; 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

condition on admission (Dong 2014). Other factors include the time of intervention and clinical experience of the physical therapist (Denehy *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 therapists 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, Maffiuletti, & 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 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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GUERRA-VEGA, P.; CUYUL-VÁSQUEZ, I.; ARTIGAS-ARIAS, M.; MUÑOZ-COFRE, R.; CURI, R.; MARZUCA-NASSR, G. N. Protocolos de terapia física para atenuar la atrofia del músculo esquelético en pacientes críticos: Revisión Narrativa. *Int. J. Morphol., 40(3)*:640-649, 2022.

RESUMEN: Describir los protocolos de terapia física usados en pacientes críticos para atenuar la atrofia muscular esquelética. Realizamos una búsqueda en PubMed y Embase desde el inicio hasta noviembre de 2020. Se consideraron los estudios observacionales o experimentales publicados en inglés o español que evaluaron el efecto de los protocolos de terapia física en la atenuación de la atrofia del músculo esquelético en pacientes críticos a través de la medición de la fuerza o la masa muscular. Los estudios solo se incluyeron si informaron una descripción detallada de la dosificación de las intervenciones. Diecisiete estudios cumplieron los criterios de elegibilidad. Se incluyeron ensayos clínicos aleatorizados (n = 16) y estudios observacionales (n = 1). La población total de los estudios incluidos fue de 872 pacientes en estado crítico. Los estudios tuvieron como objetivo evaluar la confiabilidad, seguridad o efectividad de los protocolos de estimulación eléctrica neuromuscular (n = 10), movilización temprana (n = 3), entrenamiento con ergómetro (n = 2), transferencias en mesa basculante (n = 1) y restricción del flujo sanguíneo (n = 1). Los protocolos de terapia física forman parte del manejo integral del paciente crítico. Estrategias como la movilización pasiva, los traslados dentro y fuera de la cama, el entrenamiento de la marcha, el entrenamiento con ergómetro y la estimulación eléctrica neuromuscular tienen un impacto sustancial en el pronóstico y la calidad de vida de los pacientes críticos después del alta hospitalaria.

PALABRAS CLAVE: Reposo en Cama; Unidad de Cuidados Intensivos; Ventilación Mecánica; Atrofia Muscular; Terapia Física; Rehabilitación.

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Correspondence to:
Gabriel Nasri Marzuca-Nassr, PT, MSc, PhD.
Claro Solar 115,
Oficina 300, Edificio SA
Facultad de Medicina
Universidad de La Frontera
Temuco - CHILE

E- mail: gabriel.marzuca@ufrontera.cl