Modern Research in Inflammation, 2019, 8, 11-27
http://www.scirp.org/journal/mri
ISSN Online: 2169-9690
ISSN Print: 2169-9682

Neuromuscular Electrical Stimulation in Intensive Care Unit Patients: Integrative Review

Miriam Viviane Baron[1*], Marcus Vinicius de Mello Pinto[2], Janine Koepp[3], Cristine Brandenburg[4], Paulo Ricardo Martins[5], Amanda Corrêa dos Santos[5], Daniela Moraes[1], Carolina Gonçalves Pinheiro[6], Nathália Ken Pereira Iketani[7], Bartira Ercília Pinheiro da Costa[1]

[1]Nephrology Laboratory, Department of Postgraduate of Medicine and Health Sciences, School of Medicine, Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, Brazil
[2]Celulare Institute, Rio de Janeiro, Brazil
[3]Nursing Course, Department of Nursing and Dentistry, University of Santa Cruz do Sul, Santa Cruz do Sul, Brazil
[4]Postgraduate Program in Brazilian Education, Department of Fundamentals of Education, Federal University of Ceará, Fortaleza, Brazil
[5]School of Medicine, Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, Brazil
[6]Physiotherapy Course, Department of Physiotherapy, Vale do Salgado Faculty, Icó, Brazil
[7]Department of Physiotherapy, Dom Luiz I Hospital-Portuguese Beneficent of Belém, Pará, Brazil
Email: *miriambaron9@gmail.com

How to cite this paper: Baron, M.V., de Mello Pinto, M.V., Koepp, J., Brandenburg, C., Martins, P.R., dos Santos, A.C., Moraes, D., Pinheiro, C.G., Iketani, N.K.P. and da Costa, B.E.P. (2019) Neuromuscular Electrical Stimulation in Intensive Care Unit Patients: Integrative Review. *Modern Research in Inflammation*, **8**, 11-27.
https://doi.org/10.4236/mri.2019.82002

Received: April 28, 2019
Accepted: May 27, 2019
Published: May 30, 2019

Abstract

Intensive care units' acquired muscle weakness is present in approximately 50% of the patients. Although active muscle training can attenuate weakness, a large proportion of critical patients cannot participate in any active mobilization. Neuromuscular electrical stimulation may be an alternative strategy to reverse muscle weakness. The objective of the study was to review the scientific publications on the use of neuromuscular electrical stimulation and its parameters and the main results in patients hospitalized in intensive care units. This is an integrative review surveying studies in online databases. The studies were selected from the following descriptors: neuromuscular electrical stimulation AND parameters AND intensive care units AND muscle weakness. The inclusion criteria included articles that addressed the topic of neuromuscular electrical stimulation and the parameters used in patients admitted to intensive care units, aged 18 years or older. Exclusion criteria were studies involving animals, case reports, letters to the editor and book chapters. The search comprised articles in the Portuguese, English and Spanish languages from January 2013 to March 2019. Of the 185 articles identified, nine

met the eligibility criteria. The studies were evaluated assessing the level of evidence, and the relevant information was presented in the table and discussed. The parameters of the neuromuscular electrical stimulation employed in the studies showed positive results for the maintenance of strength and muscle mass. There was evidence of benefits in the local and systemic microcirculation, potentially mobilizing endothelial stem cells, to prevent atrophy, to reduce mechanical ventilation time and stay in intensive care unit; and when incorporated into the usual physiotherapy care, proved to be more effective than usual care. Its use is safe and viable in critically ill patients.

Keywords

Muscle Weakness, Critical Illness Polyneuropathy, Sepsis, Electric Stimulation Therapy, Physical Therapy Modalities

1. Introduction

The scientific and technological advances of the last decades have contributed to a greater survival of the critical patient, however a substantial number between 30% and 50% of these patients suffer from Intensive Care Unit Acquired Weakness (ICUAW) caused by polyneuropathy or myopathy or by a combination of these [1]. Implicit pathophysiological mechanisms include microvascular, metabolic, electrical and bioenergetic changes, relating in a complex way and resulting in muscle atrophy and/or loss of muscle strength [2].

The ICUAW manifests itself in a diffuse and symmetrical way, reaching the peripheral and respiratory skeletal muscles, with involvement of deep tendon reflexes and sensory innervation [3]. Its origin is multifactorial and the main risk factors are sepsis, prolonged immobilization, the action of drugs (corticosteroids, aminoglycosides, colistine, inotropes, vasoconstrictors and catecholamines), multiple organ failure, presence of malnutrition and parenteral nutrition (associated with hyperglycemia, hyperosmolarity and hypernatremia) [4] [5] [6]. In addition, ICUAW is associated with prolonged mechanical ventilation (MV), failure to wean, longer hospitalization, higher morbidity and mortality rates and prolonged rehabilitation, which may contribute to persistent functional disabilities and reduced quality of life [7]-[12].

The ICUAW prevention pillars involve the management of risk factors [2]. Since a large proportion of critical patients cannot participate in any active mobilization, neuromuscular electrical stimulation (NMES) may be an alternative strategy for muscle training [13]. NMES has been used in protocols of early mobilization in ICU with the objective of reversing muscle weakness, preserving muscle mass and preventing atrophy, preserving function and reducing complications and disability [13] [14] [15] [16]. In addition, studies have shown that its application is safe and viable [17] [18] [19].

The publications that involve the subject matter present methodological diversity in the use of NMES parameters in critical patients, so the research question of this study was formulated in the PICO format (P = patient population, I = intervention or area of interest, C = comparison intervention or comparison group and O = outcome) in the following way: What are the parameters of NMES used in the muscular rehabilitation of adult patients hospitalized in ICUs and the main results found?

Therefore, this study aimed to review the scientific publications on the use of NMES and investigate the parameters used in muscle rehabilitation in critically ill adult patients and their main results.

2. Method

This is an integrative review of studies. For the preparation of the present review the steps presented in Table 1 were followed.

2.1. Eligibility Criteria

We included studies that addressed the theme of NMES and the parameters used in ICU patients hospitalized with 18 years or older. Exclusion criteria were: studies involving animals, case reports, letters to the editor and book chapters.

2.2. Search Strategy

Seven databases were searched as survey sources: Public Medline (PubMed), Physiotherapy Evidence Database (PEDro), Cochrane Library, Science Direct, Scopus, Web of Science and Scientific Electronic Library Online (SciELO). The descriptors used were neuromuscular electrical stimulation AND parameters AND intensive care units AND muscle weakness. The search comprised the period from January 1, 2013 to March 31, 2019. We selected studies available in Portuguese, English and Spanish. The search for the descriptors was initially performed in Pubmed and the syntax was adjusted for each database searched. The search strategy was described in Table 2.

Table 1. Review steps.

Steps
1) Identification of the guiding question (research problem);
2) Definition of the objective of the study;
3) Selection of the sample (eligibility criteria);
4) Categorization of studies (definition of information to be extracted from articles);
5) Analysis of articles included in the review;
6) Interpretation of results;
7) Synthesis of knowledge.

Table 2. Pubmed search strategy.

Boolean Operators	Descriptors
	(neuromuscular [All Fields]) AND ("electric stimulation" [MeSH Terms]) OR ("electric" [All Fields]) AND ("stimulation" [All Fields]) OR ("electric stimulation" [All Fields]) OR ("electrical" [All Fields] AND "stimulation" [All Fields]) OR ("electrical stimulation" [All Fields])
AND	("Parameters" [Journal]) OR ("parameters" [All Fields])
AND	("intensive care units" [MeSH Terms]) OR ("intensive" [All Fields]) AND ("care" [All Fields] AND "units" [All Fields]) OR ("intensive care units" [All Fields])
AND	("muscle" [All Fields] AND "weakness" [All Fields]) OR ("muscle weakness" [All Fields] OR "muscle weakness" [MeSH Terms])
AND	(("2013/01/01" [PDAT]: "2019/03/31" [PDAT]) AND "humans" [MeSH Terms])

2.3. Selection of Studies

After the full search, two reviewers independently assessed the titles and abstracts of the studies. Those articles that did not provide sufficient information in the abstract were read in full. After selection by title and abstract, reviewers reviewed the articles in full text. Disagreements between reviewers were resolved by consensus. Data extraction was performed using a standardized form.

2.4. Analysis of the Level of Evidence in the Studies

The hierarchy of evidence proposed by Oxford Center Evidence-Based Medicine [20] was also used by researchers in previous integrative review [21] to determine the level of evidence, according to the type of study. The hierarchy of evidence is described in **Table 3**.

2.5. Summary of Information

To organize and summarize the information of the study findings and prepare the database, the following items were considered: sample (subjects) and characteristics of the studies, objectives, type of study, level of evidence, parameters employed and main results.

2.6. Analysis of the Data

Data analysis was performed in a descriptive and qualitative way and presented in the form of tables.

3. Results

3.1. Selection of Studies

First, 185 articles were identified, and after the removal of the duplicates and reading of the titles and abstracts, 19 articles were considered potentially relevant and read in full. After reading the studies, ten were excluded, detailing the justifications. The reviewers identified 9 articles that met the eligibility criteria. **Figure 1** shows the flowchart of the studies.

The studies' description is detailed in **Table 4**.

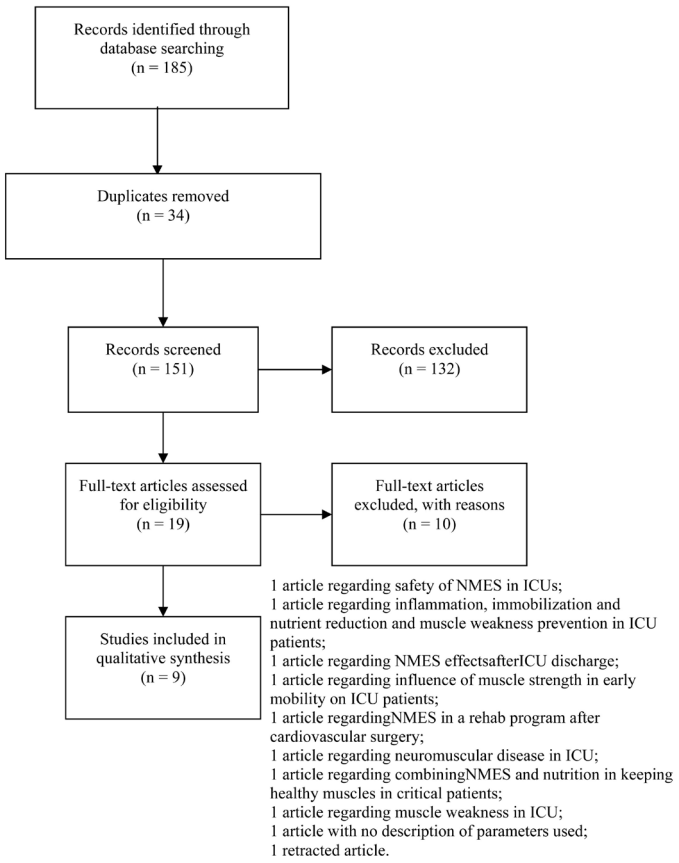

Figure 1. Flowchart of the study.

Table 3. Level of evidence of the studies.

Level of evidence	Source of evidence
Level 1A	Evidence from systematic reviews and meta-analyzes of comparable clinical trials. Well-delineated randomized controlled trials with relevant clinical outcome.
Level 1B	Evidence based on randomized controlled trials with narrow confidence intervals.
Level 1C	Evidence of "all or nothing" results. Case-control study.
Level 2A	Evidence resulting from a homogeneous systematic review of cohort studies (with comparison groups and control variables).
Level 2B	Evidence based on cohort studies with poor quality of randomization, control or without long follow-up, cross-sectional cohort study.
Level 2C	Evidence of research results (observation of therapeutic results or clinical evolution).
Level 3A	Evidence resulting from homogeneous systematic review of case studies with control group.
Level 3B	Evidence based on case studies with control group.
4	Evidence from case and series reports without case-control definition.
5	Evidence from the opinion of authorities or experts. Review of non-systematic literature.

Table 4. Description of selected articles.

Author/Year	Type of study	Sample/ Characteristics	Objective	Used parameters	Main results	Evidence level
Maffiuletti *et al*., 2013 [19]	RCT systematic review	8 RCTs published between 2009 and 2012. ICU patients of both genders, aged between 48 and 72 years. Of the 172 patients 74 (NMES) and 76 (CG) and 22 patients received NMES on one side of the body and the contralateral one was the control.	To assess the effectiveness of NMES to prevent weakness and loss of muscle mass in critically ill patients compared to usual care.	Duration of the protocol: between 7 days and 6 weeks. MG: gluteus, quadriceps, hamstrings, fibularis long us and biceps. F: between 8 - 100 Hz; I: between 15 - 47 mA (evoking visible muscle contraction); T: 250 - 400 μs; Ton: between 2 - 12 s; Toff: between 4 - 24 s; TA: 25 to 60 min/day; P: symmetrical biphasic rectangular.	The NMES added to the usual physiotherapy care proved to be more effective than just the usual care to prevent ICUAW.	1A
Angelopoulos *et al*., 2013 [22]	Pilot randomized prospective Study	Group 1-SIRS or sepsis with diagnosis of three to five days on the day of the NMES session. Group 2-with diagnosis of ICUAW. Both sexes with average age = 59 years. Patients randomized to HF (17) and MF (14) protocol. NMES of 30 min on both LL.	To compare changes in systemic and local microcirculation during a single session of HF and MF NMES.	Single 30 min application MG: vast lateral and medial, long fibular. HF group = F: 75 Hz, T: 400 μs, Ton: 5 s, Toff: 21 s. MF group = F: 45 Hz, T: 400 μs, Ton: 5 s, Toff: 12 s. Employed HF and MF with biphasic symmetrical trapezoidal pulses.	A single NMES session produces changes in local and systemic microcirculation. The medium and high frequency currents were equally effective.	2B
Williams *et al*., 2013 [23]	Systematic review of randomized trials and observational prospective trials	8 studies on NMES without date limit for the research. Of these 357 ICU patients were randomized to receive NMES on one side of the body and the other served as control. And 10 patients were randomized to receive 2 treatment periods for each patient.	Investigate the evidence of the effects of NMES in severe patients.	Duration of protocol: between 4 days up to 4 weeks or discharge from ICU. MG: biceps brachii, vastus lateralis and medialis, fibularis long us, quadriceps, rectus femoris. F: between 1.75 - 100 Hz; I: between 0 - 120 mA (evoking visible muscle contraction); T: 250 - 400 μs; Ton: between 2 - 12 s; Toff: between 4 - 24 s; TA: 30 to 60 min/day.	NMES has potential advantages in improving muscle strength, reducing MV time, and length of stay in ICU. However, the heterogeneity of the included studies shows that the evidence is inconclusive about the efficacy of NMES in critically ill patients.	2A
Wageck *et al*., 2014 [18]	Systematic review with meta-analysis	9 (RCT and quasi-randomized) published between 1986 and 2013. ICU patients of both sexes over 18 years of age. Of the 274 patients, 139 (CG) and 135 (IG) who received NMES in UL and LL.	To investigate the application and effects of NMES in ICU patients.	Duration of the protocol: between 7 days and 5 weeks or until extubation or discharge from ICU. MG: quadriceps, posterior thigh, vastus medial and lateral, inguinal, fibular and biceps. F: between 1.75 - 100 Hz; I: from palpable and visible to tetanic contraction. T: 300 - 400 μs; Ton: between 2 - 12 s; Toff: between 4 - 24 s; TA: 30 to 60 min.	NMES presents positive results for the maintenance of strength and muscle mass in critically ill patients in ICU.	1A

Continued

Segers *et al*., 2014 [13]	Cohort prospective study	50 patients of both sexes and with more than 18 years hospitalized in ICU between 3 to 5 days. NMES in both LL.	To investigate the safety and viability of NMES in critically ill patients.	Application of 25 min and 5×/week. MG: quadriceps of the thigh. 5 min heating and after protocol = F: 50 Hz, I: 0 - 80 mA, T: 300 - 500 μs, Ton: 8 s. Toff: 20 s. The intensity and pulse were adjusted until a visible or palpable contraction was obtained.	NMES is a safe intervention to be administered at the ICU. Patients with sepsis, edema and vasopressors use present less adequate contraction.	2B
Kho *et al*., 2015 [24]	Randomized pilot clinical trial with blinded-results evaluation	34 patients of both sexes and with average age of 55 years. Recruited in three ICUs between 6/2008 and 3/2013 who were in MV within the first week of ICU stay and who could make independent transfer from the bed to the chair before hospital admission. Randomized 16 patients for NMESG and 18 for SIG.	To evaluate whether patients in MV who receive NMES and habitual rehabilitation versus simulated NMES intervention and habitual rehabilitation present higher strength of LL at hospital discharge.	Duration of the protocol: up to 45 days. NMESG = 60 min/day bilaterally in the quadriceps of the thigh, anterior tibial and gastrocnemius. Used pulsed current, balanced, asymmetrical and biphasic rectangular wave with 2 s ramp and ramp inactivity < 1 s and 50 Hz. Quadriceps protocol = T: 400 μs, Ton: 5 s and Toff: 10 s. Anterior and gastrocnemius tibial protocol = T: 250 μs, Ton: 5 s and Toff: 5 s. The intensity was gradually increased until a visible contraction was achieved. SIG = current amplitude 0 mA.	NMES in critically ill patients and in MV did not significantly improve leg strength at hospital discharge.	1B
Stefanou *et al*., 2016 [25]	Randomized prospective trial	32 patients, of both sexes, with mean age of 58 years with MV and sepsis admitted to ICU. They were randomized to two protocols of NMES in LL, one group of AF and another MF. Blood samples were analyzed by flow cytometry before and after application of the protocol.	To explore the role of NMES in the mobilization of ESC in hospitalized ICU patients in MV and sepsis.	The sessions took an average of 7.6 days. Application of 30 min + 10 min warm-up and recovery. MG: vastus lateral, medial and fibular long bilaterally. Both protocols used symmetrical biphasic trapezoidal pulses. T: 400 μs, ramp up 1.5 s and descent of 0.8 s. AF = F: 75 Hz, Ton: 6 s and Toff 21 s. MF = F: 45 Hz, Ton: 5 s and Toff 12 s. The intensity was gradually increased until reaching total contraction.	NMES of MF and HF has the potential to mobilize ESC in patients with MV and sepsis admitted to ICU.	2B

Continued

Burke *et al*., 2016 [26]	Systematic review and meta-analysis	12 studies (11 RCTs and 1 control case) evaluated 449 ICU patients. The patients had a mean age between 34 and 72 years of age.	To evaluate the evidence on the efficacy of NMES compared to usual care in ICU.	Duration of the protocol: between 7 to 30 days or until extubation, discharge from the ICU or until the patient was able to voluntarily move the limbs or achieve a muscle strength score in 4 of 5. MG: quadriceps, anterior tibial, triceps sural, biceps brachii. F: between 35 - 100 Hz; I: 15 mA - 150 mA and some studies up to visible contraction, up to the maximum tolerated level and one study until producing pain. T: 200 - 400 μs; RT: 30 to 60 min.	This review provides evidence that NMES increases muscle strength and shows potential benefit for joint range of motion, muscle atrophy, MV outcomes, and limited activities in the critical patient.	1A
Silva *et al*., 2017 [17]	Prospective observational study	11 critically ill male patients with a mean age of 39 years and receiving MV in ICUs, received NMES in bilateral LL. Before and after the application of the protocol blood samples were collected and analyzed.	To evaluate the safety and viability of an NMES protocol based on neuromuscular excitability and applied to various muscle groups.	The sessions took place for three consecutive days. Based on chronaxie and rheobase evaluated daily the NMES protocol was performed with a total of 45 min. MG = maximum gluteus and gastrocnemius (15 min bilateral and simultaneous application). Tibialis anterior and hamstrings (15 min simultaneously). Thigh quadriceps (15 min bilaterally). T: same as chronaxie. F: 100 Hz, Ton: 5 s and Toff: 5 s. The intensity was standardized and corrected from the highest visible contraction. P: rectangular bipolar.	The protocol employed was safe and feasible. The differences in neuromuscular excitability between different muscle groups and patients demonstrated the possibility of using customized protocols based on chronaxie.	2C

RCT = Randomized Clinical Trial; ICU = Intensive Care Unit; NMESG = neuromuscular electrical stimulation group; CG = Control Group; NMES = neuromuscular electrical stimulation; MG = Muscle Group; F = frequency; Hz = hertz; I = intensity; mA = miliamperes; T = Time of pulse; μs = microseconds; Ton = time on; s = seconds; Toff = time off; TA = time of application; min = minutes; P = pulse; ICUAW= Intensive Care Unit Acquired Weakness; SIRS = Systemic Inflammatory Response Syndrome; HF = High frequency; MF = Mid frequency; LL = Lower Limbs; IG = Intervention Group; UL = Upper Limbs; SIG = Simulated Intervention Group; MV = Mechanical Ventilation; ESC = Endothelial Stem Cells.

3.2. Level of Evidence

In the evaluation of the level of evidence, based on the evidence hierarchy [20] it was observed that three (33.3%) studies presented high level of evidence (1A) [18] [19] [26], followed by one (11.1%) study with evidence (1B) [24], one (11.1%) study with evidence (2A) [23] and three (33.3%) studies with evidence (2B) [13] [22] [25] and one (11.1%) study with evidence (2C) [17].

3.3. Complications and Diseases Diagnosed

There were 1420 patients included across the nine articles that met the eligibility criteria. The most common complications and diseases at the ICU admission or during ICU hospitalization were sepsis, chronic obstructive pulmonary disease (COPD), trauma, neurological problems, cancer and postoperative complications [19]; post-cardiac surgery, gastrointestinal/hepatic disorders, respiratory failure, post-organ transplantation, post-thoracic surgery, hematologic and oncologic disorders among others [13]; polytrauma, pancreatitis, postoperative abdominal and sepsis [17]; sepsis or systemic inflammatory response syndrome (SIRS) [22]; sepsis, respiratory failure, gastrointestinal disorders and others [24]; sepsis, septic shock among others [23]; mixed pathologies, COPD, sepsis, septic shock, post traumatic brain injury coma and stroke [26]; sepsis, cardiovascular disease, respiratory disease, liver disease, renal disease, diabetes mellitus, haematological/anticoagulation disease [25]; sepsis, septic shock, polytrauma, cardiovascular disease, trauma and neurological disease, stroke, transplantation, pneumonia, cancer, respiratory failure and post-surgery [18].

3.4. Beginning of the Protocol

Patients started the NMES protocol shortly after ICU hospitalization [17]. In the review conducted by [23], the authors report variations at the beginning of treatment with the NMES, and half (4) studies reported onset within 48 h of ICU admission. In review of [18] the initiation of NMES treatment in the studies began after 48 hours of hospitalization.

The initiation of NMES treatment occurred between day 3 and 5 after admission to the ICU in the study [13], in the presence of sepsis for a period longer than 72 h and with MV at the time of enrollment in the study [25], in patients with diagnosis of sepsis or SIRS for a minimum of 3 and a maximum of 5 days on the day of the session [22], in patients with MV for at least one day and at least two more days predicted of hospitalization [24].

In the review of [26] five studies started treatment within 3 days after admission to ICU and two studies involving COPD patients initiated NMES between 12 and 30 days post admission. One study varied the start of treatment with an acute intervention group, initiating treatment within one week after admission and a long-term intervention group after 2 weeks. In a systematic review [19] the beginning period of NMES protocols was not described.

3.5. Local and Systemic Effects of NMES

Among the studies selected, two studies explored the effects of NMES on systemic microcirculation [22] [25] and the others investigated the local effects of NMES and were grouped according to their objectives. Researchers investigated the effects of NMES on critically ill patients [18] [23]; the safety and feasibility of NMES in critically ill patients [13] [17]; assessed the efficacy of NMES in relation to the usual care in patients in ICU [19] [26]; evaluated patients in MV who

received NMES and usual rehabilitation versus simulated intervention and usual rehabilitation [24].

4. Discussion

4.1. Main Findings

This integrative review, based on the evidence from the nine articles analyzed, found that the NMES parameters used in muscle rehabilitation in adult and critically ill patients are divergent in most studies. The heterogeneity in the parameters employed may have occurred due to the different methodologies used in the studies to answer different research questions. In addition, the NMES parameters may have been defined based on the personal preferences of the researchers, the reasoning in other studies or the limitation of the maximum current intensity available in some electrical stimulation devices. However, the results using the different parameters show positive effects on the maintenance of strength and muscle mass (supported by two systematic review studies with meta-analysis), as well as on local and systemic microcirculation.

4.2. Evidence for Clinical Practice

Of the nine studies evaluated, three presented level of evidence (1A), followed by one study of evidence (1B), one study (2A), three studies (2B) and one study (2C), showing that most articles included in this review present robust data for the clinical practice of evidence-based physical therapy within the ICU environment. These evidences are based on two articles of systematic review of randomized clinical trial (RCT) and observational studies and of two systematic reviews with meta-analysis; of two prospective, randomized studies, one RCT, and two non-randomized prospective cohort studies with no control group.

4.3. Sepsis and ICUWA

Sepsis was the most prevalent diagnosis observed in the present review. Sepsis remains the leading cause of death in ICUs [2]. In addition, the major risk factors for the development of ICUAW have been widely reported and include association with high disease severity on admission, sepsis, SIRS, multiple organ failure, prolonged immobilization, hyperglycemia, as well as advanced age [2] [16] [27].

4.4. Timing of the Start of Study Protocols

In this review we observed that the protocols started at different times during ICU patients' hospitalization, depending on the objectives of each study. One of the systematic reviews did not describe the timing of initiation of protocols included studies [19]. The other studies began their protocols in periods that ranged from immediately after ICU admission up to 30 days of hospitalization [13] [17] [18] [19] [22] [23] [24] [25] [26]. According to [26] patients diagnosed with severe diseases rapidly develop ICUAW and therefore it is suggested to

start NMES in the acute phase of the disease. An electrophysiological study [28] of peripheral nerves in critically ill patients demonstrated abnormalities in the first days of ICU admission and up to 13 days in all patients evaluated. Of the 28 patients with abnormal electrophysiological signs, in 10 patients, the amplitude of nerve action potential decreased progressively over 3 days, and in 18 patients it fell abruptly within 24 hours. These data support the NMES acute onset recommendation.

4.5. Parameters of NMES and Local Effects

For the description of the parameters employed and the main results, we group the studies according to the similarity of objectives. Two articles aimed to investigate the effects of NMES in severe patients, and the parameters employed varied between studies [18] [23]. The systematic review [18] showed that NMES can maintain or increase muscle mass, strength and volume, reduce MV time and weaning time, and decrease muscle breakdown in critically ill patients in ICU. Within this review, two studies allowed a meta-analysis of NMES effects on femoral quadriceps strength and showed a significant effect in favor of NMES in the Medical Research Council Scale presenting mean differences of 0.77 points ($p = 0.02$; 95% CI: 0.13 - 1.40). The systematic review of [23] also showed benefits of NMES on muscle strength preservation, decreased MV time, and shorter ICU stay. However, the authors report methodological heterogeneity of the studies and suggest future studies with high methodological quality to provide more evidence.

In this sense, new evidence was presented in a current study. Exploratory and randomized interventional exploration with critical patients in MV and diagnosis of sepsis and ICUAW employed the use of NMES and/or whole body vibration, in addition to a protocol of physiotherapy of individualized approach daily (intervention group) in comparison with the protocol of conventional physiotherapy of early mobilization (control group). After 15 days of intervention, surgical muscle biopsy and molecular analysis by blinded evaluators was performed. The myocyte cross-sectional area of the intervention group was significantly higher (type I + 36%, type IIa + 49%, type IIb + 65%, $p < 0.001$ for all) compared to the control group (type I + 10%, type IIa + 13%, type IIb + 3%, $p < 0.001$ for all). This increase was accompanied by regulated gene expression for myosin heavy chains (fold change median [IQR]: MYH1 2.3 [1.1 - 2.7], MYH2 0.7 [0.2 - 1.8]; MYH4 5.1 [2.2 - 15.3]) indicating that the muscle protein synthesis pathway was activated, probably due induced by muscle activation [16].

The authors [13] [17] evaluated the feasibility and safety of different protocols. In the study of [13] there were no significant changes in cardiovascular and respiratory parameters (cardiac frequency, respiratory frequency, blood pressure and SpO^2) and there was no damage to the skin, showing that the protocol is safe. Regarding viability, the researchers showed that "responder" patients should achieve an effective contraction (type 4 or 5, on a scale of 1 - 5) in 75% of the sessions. The results showed that 50% of the patients obtained adequate con-

tractions. However, univariate analysis revealed that edema in lower limbs ($p < 0.001$), sepsis ($p = 0.008$), admission to clinical ICU ($p = 0.041$), and treatment with vasopressors ($p = 0.011$) were all associated with reduced contractions. The study of [17] showed no significant changes in central venous oxygen saturation ($ScvO^2$) and serum lactate ($p = 0.23$ and $p = 0.8$). Thus this study demonstrated that NMES did not provoke deleterious changes in the balance between supply and oxygen consumption. There was also no significant change in creatine phosphokinase (CPK) levels, used to evaluate indirect muscle damage on the three days of evaluation: 470 (±270) IU/L and 455 (±240) IU/L ($p > 0.99$). There was a significant difference between the maximum gluteal chronaxie: 550 (±150) microseconds versus quadriceps: 300 (±90) microseconds; Quadriceps: 300 (±90) microseconds and anterior tibial: 540 (±160) microseconds, respectively ($p = 0.005$ and $p = 0.005$). Eighty-four (85%) of the total of 99 sessions were completed and muscle contractions were present in 100% of the time. There were no adverse effects with NMES. Therefore, these two studies showed that the applied NMES protocols were safe and feasible. According to [25] the absence of clinically significant side effects in terms of cardiac, hemodynamic and muscle damage further evidence the role of NMES as a safe and viable intervention in ICU patients.

The researchers [24] [26] presented different protocols and parameters in the comparison of NMES versus usual rehabilitation. In the study of [24] the muscle strength of lower limbs was evaluated by blind evaluators the attribution of randomization. The authors found that critically ill and other patients undergoing MV who received NMES when compared versus a simulation group, found no significant improvement in leg strength at hospital discharge ($p = 0.07$) between groups. Among the secondary outcomes, the NMES-versus-simulation group showed a significant difference in the distance walked [514 (389) vs. 251 (210) feet $p = 0.05$] and in the increase in lower limb muscle strength [5.7 (5.1) vs. 1.8 (2.7), $p = 0.019$]. One of the limitations of the research was early termination due to the slow recruitment and termination of funding. For this reason the results may be insufficient to detect a true difference between the groups. The systematic review by [19] has provided evidence that concur with the above findings regarding the inclusion of NMES therapy to usual care as more effective than the usual treatment in the prevention of ICUAW. These results are also supported by systematic review with meta-analysis performed by [26] which supports NMES to preserve muscle strength using a fixed effects model [n = 146; standardized mean difference 0.93 (0.51, 1.35) $p = 0.0002$].

4.6. Parameters of NMES and Effects on Microcirculation

Two studies investigated the effects of high frequency (HF) and mid-frequency (MF) NMES on the local and systemic microcirculation of critical patients with a diagnosis of sepsis. The parameters employed were similar, with a minimum difference only in the time of action and rest of the pulse (HF = Ton: 5 s and Toff: 21 s and MF = Ton: 5 s and Toff: 12 s) and (Toff: 21 s and MF = Ton: 5 s

and Toff: 12 s) [25].

In a study of [22] using the HF protocol, the peripheral microcirculatory parameters presented results such as: thenarO^2 consumption rate from 8.6 ± 2.2 to 9.9 ± 5.1 (%/minute) ($p = 0.08$), endothelial reactivity of 2.7 ± 1.4 for 3.2 ± 1.9 (%/second) ($p = 0.04$) and vascular reserve from 160 ± 55 to 145 ± 49 (seconds) ($p = 0.03$). In the MF protocol: O^2 the nar consumption rate from 8.8 ± 3.8 to 9.9 ± 3.6 (%/minute) ($p = 0.07$), endothelial reactivity from 2.5 ± 1.4 to 3.1 ± 1.7 (%/second) and vascular reserve from 163 ± 37 to 144 ± 33 (seconds) ($p = 0.001$). In the vastus lateralis muscle, the mean O^2 consumption rate during the HF protocol was 61 ± 9 (%/minute) while in the MF protocol it was 69 ± 23%/minute ($p = 0.5$). The blood lactate level showed a moderate increase in both protocols and CPK levels did not increase after the NMES session. The minimum amplitude in oxygen saturation (StO^2) increased slightly after the use of NMES, showing also that these changes correlate well with the muscle contraction force. In this study it was observed that a single session of NMES of HF or MF affected the local and systemic microcirculation of the muscle. The study [25] that used HF and MF protocols and similar parameters showed that a single NMES session increased endothelial stem cell (ESC) count in patients with sepsis. In general, $CD34^+$, $CD133^+$, $CD45^-$ ESC increased from 13.5 ± 10.2 to 20.8 ± 16.9 and $CD34^+$, $CD133^+$, $CD45^-$, $VEGFR2^+$ESC from 3.8 ± 5.2 to 6.4 ± 8.5 cells/10^6 (mean ± SD, $p < 0.05$). ESC $CD34^+$, $CD45^-$, $VEGFR2^+$ also increased from 16.5 ± 14.5 to 23.8 ± 19.2 cells/10^6 (mean ± SD, $p < 0.05$). ESC mobilization occurred with the use of both NMES protocols and was not affected by septic disease severity ($p > 0.05$). The authors concluded that NMES is effective in mobilizing ESC and is indicative of the potential for endothelium restoration in critically ill patients.

NMES seems to have a short-term systemic effect on peripheral microcirculation and acute microcirculation activation capacity, as observed by the increased rate of oxygen consumption and reperfusion [29]. A randomized, controlled clinical trial is underway to elucidate the possible beneficial effects of NMES, evaluated by the mobilization of ESC in patients with septic shock. This study will explore the potential use of NMES as a preventive and rehabilitative tool in critical patients in septic shock [30].

4.7. Limitations and Clinical Implications

Limiting factors in the present study refer to the methodological quality of some studies that present a small sample size, absence of random allocation and control group to compare groups. One study pointed out that slow recruitment of patients and the termination of funding for research led to its early termination and may have influenced the results of the research and the size of the effect [24]. In addition, some authors do not state in full the parameters used in their studies, and do not report possible damages caused by the use of these parameters. These factors compromise the reproducibility of protocols in clinical practice and future research. Another limitation is that the design of most studies al-

lowed monitoring of the effects of NMES only in the short term, implying that repeated application of NMES might be necessary to maintain the results. In addition, some authors have shown that patients' characteristics (sepsis, edema, vasopressors and hospitalization in medical ICU) may prevent adequate muscle contraction and therefore it is important to understand that not all patients will respond in a similar way to stimulation [13], therefore influencing the results.

Despite the heterogeneity of the parameters used to answer different research questions and the peculiar characteristics of critical patients, NMES showed potential positive effects for its use in clinical practice in critically ill patients. Studies show positive results for the maintenance of muscle strength and mass and benefits in the amplitude of joint movement, in the prevention of muscle atrophy and in the reduction of MV time, being an important resource for the maintenance/recovery of the skeletal muscle system in critically ill patients. This reflects in the reduction of complications and costs related to length of stay in ICU [18] [19] [23] [26], implying quality of life for the patient.

However, the optimal parameters for NMES use have not yet been elucidated, but the studies (randomized controlled clinical trials) in this area have advanced and it is believed that new evidence will contribute to reinforce the positive role of NMES and its parameters in the context of ICUs [30] [31].

4.8. Recommendations for Future Research

Future clinical trials should evaluate the efficacy and safety of different NMES parameters as performed in the studies [22] [25], however longer time periods studies are needed. And they should investigate the clinical implications of the results on different subpopulations of critical patients in order to identify optimal parameters for the prevention of ICUAW.

5. Conclusions

The NMES optimal parameters for the muscular rehabilitation of critically ill patients have not yet been elucidated, and this may be due to the different methodologies used in the studies to answer different research questions. In addition, the NMES parameters can be defined in protocols based on researchers' preferences, which is justified by personal experience in previous research, based on other studies, as well as due to the limitations that some electrical stimulation devices present with respect to the maximum available current intensity.

In the present review, the different NMES parameters used in the studies showed positive results for keeping strength and muscle mass. It also showed benefits: in the local and systemic microcirculation with the potential to mobilize ESC; in the amplitude of joint movement; in the prevention of atrophy; in the reduction of the length of the MV; in the time of permanence in the ICU, and when incorporated into the usual physiotherapy care, it proved to be more effective than usual care. In addition, studies have shown that its use is safe and viable in critically ill patients.

Acknowledgements

This study was funded in part by the Coordination of Improvement of Higher Level Personnel—Brazil (CAPES)—Finance Code 001 and by the National Council of Scientific and Technological Development—Brazil (CNPq)—Doctorate GD.

Conflicts of Interest

Authors declare not having any conflict of interest regarding this article.

References

[1] Apostolakis, E., Papakonstantinou, N.A., Baikoussis, N.G. and Papadopoulos, G. (2015) Intensive Care Unit-Related Generalized Neuromuscular Weakness Due to Critical Illness Polyneuropathy/Myopathy in Critically Ill Patients. *Journal of Anesthesia*, **29**, 112-121. https://doi.org/10.1007/s00540-014-1875-x

[2] Hermans, G. and Van den Berghe, G. (2015) Clinical Review: Intensive Care Unit Acquired Weakness. *Critical Care*, **19**, 274. https://doi.org/10.1186/s13054-015-0993-7

[3] França, E.É.T., Ferrari, F., Fernandes, P., Cavalcanti, R., Duarte, A., Martinez, B.P., Aquim, E.E. and Damasceno, M.C.P. (2012) Fisioterapia em Pacientes Críticos Adultos: Recomendações do Departamento de Fisioterapia da Associação de Medicina Intensiva Brasileira. *Revista Brasileira de Terapia Intensiva*, **24**, 6-22. https://doi.org/10.1590/S0103-507X2012000100003

[4] Koukourikos, K., Tsaloglidou, A. and Kourkouta, L. (2014) Muscle Atrophy in Intensive Care Unit Patients. *Acta Informatica Medica*, **22**, 406-410. https://doi.org/10.5455/aim.2014.22.406-410

[5] Abdelmalik, P.A. and Rakocevic, G. (2017) Propofol as a Risk Factor for ICU-Acquired Weakness in Septic Patients with Acute Respiratory Failure. *The Canadian Journal of Neurological Sciences*, **44**, 295-303. https://doi.org/10.1017/cjn.2016.424

[6] Zorowitz, R.D. (2016) ICU-Acquired Weakness: A Rehabilitation Perspective of Diagnosis, Treatment, and Functional Management. *Chest*, **150**, 966-971. https://doi.org/10.1016/j.chest.2016.06.006

[7] Hermans, G., De Jonghe, B., Bruyninckx, F. and Van den Berghe, G. (2008) Clinical Review: Critical Illness Polyneuropathy and Myopathy. *Critical Care*, **12**, 238. https://doi.org/10.1186/cc7100

[8] Kramer, C.L. (2017) Intensive Care Unit-Acquired Weakness. *Neurologic Clinics*, **35**, 723-736. https://doi.org/10.1016/j.ncl.2017.06.008

[9] Horn, J. and Hermans, G. (2017) Intensive Care Unit-Acquired Weakness. In: *Handbook of Clinical Neurology*, Vol. 141, Elsevier, Amsterdam, 531-543. https://doi.org/10.1016/B978-0-444-63599-0.00029-6

[10] Supinski, G.S., Morris, P.E., Dhar, S. and Callahan, L.A. (2017) Diaphragm Dysfunction in Critical Illness. *Chest*, **153**, 1040-1051. https://doi.org/10.1016/j.chest.2017.08.1157

[11] Maestraggi, Q., Lebas, B., Clere-Jehl, R., Ludes, P.O., Chamaraux-Tran, T.N., Schneider, F., Dienmusch, P., Geny, B. and Pottecher, J. (2017) Skeletal Muscle and Lymphocyte Mitochondrial Dysfunctions in Septic Shock Trigger ICU-Acquired Weakness and Sepsis-Induced Immunoparalysis. *BioMed Research International*, **2017**, Article ID: 7897325. https://doi.org/10.1155/2017/7897325

[12] Harvey, N.R. and Stanton, M.P. (2017) Intensive Care Unit-Acquired Weakness: Implications for Case Management. *Professional Case Management*, **22**, 72-78.

[13] Segers, J., Hermans, G., Bruyninckx, F., Meyfroidt, G., Langer, D. and Gosselink, R. (2014) Feasibility of Neuromuscular Electrical Stimulation in Critically Ill Patients. *Journal of Critical Care*, **29**, 1082-1088. https://doi.org/10.1016/j.jcrc.2014.06.024

[14] Baron, M.V., Lisboa, L.C. and Cardoso, D. (2016) Fisioterapia Motora na Unidade de Terapia Intensiva: Revisão Integrativa. *Revista Inspirar—Movimento & Saúde*, **9**, 6-11. https://www.inspirar.com.br/revista/fisioterapia-motora-na-unidade-de-terapia-intensiva-revisao-integrativa

[15] Trethewey, S.P., Brown, N., Gao, F. and Turner, A.M. (2019) Interventions for the Management and Prevention of Sarcopenia in the Critically Ill: A Systematic Review. *Journal of Critical Care*, **50**, 287-295. https://doi.org/10.1016/j.jcrc.2019.01.008

[16] Wollersheim, T., Grunow, J.J., Carbon, N.M., Haas, K., Malleike, J., Ramme, S.F., Schneider, J., Spies, C.D., Mardian, S., Mai, K., Spuler, S., Fielitz, J. and Weber-Carstens, S. (2019) Muscle Wasting and Function after Muscle Activation and Early Protocol-Based Physiotherapy: An Explorative Trial. *Journal of Cachexia, Sarcopenia and Muscle*. https://doi.org/10.1002/jcsm.12428

[17] Silva, P.E., Babault, N., Mazullo, J.B., de Oliveira, T.P., Lemos, B.L., Carvalho, V.O. and Durigan, J.L.Q. (2017) Safety and Feasibility of a Neuromuscular Electrical Stimulation Chronaxie-Based Protocol in Critical Ill Patients: A Prospective Observational Study. *Journal of Critical Care*, **37**, 141-148. https://doi.org/10.1016/j.jcrc.2016.09.012

[18] Wageck, B., Nunes, G.S., Silva, F.L., Damasceno, M.C.P. and de Noronha, M. (2014) Application and Effects of Neuromuscular Electrical Stimulation in Critically Ill Patients: Systematic Review. *Medicina Intensiva*, **7**, 444-454. https://doi.org/10.1016/j.medin.2013.12.003

[19] Maffiuletti, N.A., Roig, M., Karatzanos, E. and Nanas, S. (2013) Neuromuscular Electrical Stimulation for Preventing Skeletal-Muscle Weakness and Wasting in Critically Ill Patients: A Systematic Review. *BMC Medicine*, **11**, 137. https://doi.org/10.1186/1741-7015-11-137

[20] Phillips, B., Ball, C., Sackett, D., Badenoch, D., Straus, S., Haynes, B. and Dawes M. (1998) Oxford Centre for Evidence-Based Medicine—Levels of Evidence (2009). CEBM. https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009

[21] Pedrosa, K.K.A., Oliveira, I.C.M., Feijão, A.R. and Machado, R.C. (2015) Enfermagem Baseada em Evidências: Caracterização dos Estudos no Brasil. *Cogitare Enfermagem*, **20**, 733-741. http://docs.bvsalud.org/biblioref/2016/08/1128/40768-166899-1-pb.pdf

[22] Angelopoulos, E., Karatzanos, E., Dimopoulos, S., Mitsiou, G., Stefanou, C., Patsaki, Kotanidou, A., Routsi, C., Petrikkos, G. and Nanas, S. (2013) Acute Microcirculatory Effects of Medium Frequency versus High Frequency Neuromuscular Electrical Stimulation in Critically Ill Patients—A Pilot Study. *Annals of Intensive Care*, **3**, 39. https://doi.org/10.1186/2110-5820-3-39

[23] Williams, N. and Flynn, M. (2014) A Review of the Efficacy of Neuromuscular Electrical Stimulation in Critically Ill Patients. *Physiotherapy Theory and Practice*, **30**, 6-11. https://doi.org/10.3109/09593985.2013.811567

[24] Kho, M.E., Truong, A.D., Zanni, J.M., Ciesla, N.D., Brower, R.G., Palmer, J.B. and Needham, D.M. (2015) Neuromuscular Electrical Stimulation in Mechanically Ventilated Patients: A Randomized, Sham-Controlled Pilot Trial with Blinded Outcome Assessment. *Journal of Critical Care*, **30**, 32-39. https://doi.org/10.1016/j.jcrc.2014.09.014

[25] Stefanou, C., Karatzanos, E., Mitsiou, G., Psarra, K., Angelopoulos, E., Dimopoulos, S., Gerovasili, V., Boviatsis, E., Routsi, C. and Nanas, S. (2016) Neuromuscular Electrical Stimulation Acutely Mobilizes Endothelial Progenitor Cells in Critically Ill Patients with Sepsis. *Annals of Intensive Care*, **6**, 21. https://doi.org/10.1186/s13613-016-0123-y

[26] Burke, D., Gorman, E., Stokes, D. and Lennon, O. (2016) An Evaluation of Neuromuscular Electrical Stimulation in Critical Care Using the ICF Framework: A Systematic Review and Meta-Analysis. *Clinical Respiratory Journal*, **10**, 407-420. https://doi.org/10.1111/crj.12234

[27] Godoy, M.D.P., Costa, H.L.L.S., Neto, A.E.S., Serejo, A.L.C., Souza, L.C., Kalil, M.R., Kalil, R.F.M., Monteiro, L.F., Souza, O.G., Freitas, M.R.G., Bastos, V.H., Novellino, P.N., Matta, A.P. and Orsini, M. (2015) Fraqueza Muscular Adquirida na UTI (ICU-AW): Efeitos Sistêmicos da Eletroestimulação Neuromuscular. *Revista Brasileira de Neurologia*, **51**, 2447-2573. https://revistas.ufrj.br/index.php/rbn/article/view/3109/Fraqueza%20muscular%20adquirida%20na%20UTI%20%28ICU-AW%29%3A%20efeitos%20sist%C3%83%C2%AAmicos%20da%20eletroestimula%C3%83%C2%A7%C3%83%C2%A3o%20neuromuscular

[28] Latronico, N., Fagoni, N. and Gobbo, M. (2017) Neuromuscular Electrical Stimulation in Critically Ill Patients. *Essentials of Neuroanesthesia*, **46**, 771-781. https://doi.org/10.1016/B978-0-12-805299-0.00046-4

[29] Gerovasili, V., Tripodaki, E., Karatzanos, E., Pitsolis, T., Markaki, V., Zervakis, D., Rousti, C., Roussos, C. and Nanas, S. (2009) Short-Term Systemic Effect of Electrical Muscle Stimulation in Critically Ill Patients. *Chest*, **136**, 1249-1256. https://doi.org/10.1378/chest.08-2888

[30] Lago, A.F., Oliveira, A.S., Souza, H.C.D., Silva, J.S., Basile-Filho, A. and Gastaldi, A.C. (2018) The Effects of Physical Therapy with Neuromuscular Electrical Stimulation in Patients with Septic Shock: Study Protocol for a Randomized Cross-Over Design. *Medicine*, **97**, e9736. https://doi.org/10.1097/MD.0000000000009736

[31] Baron, M.V. and Pinheiro da Costa, B.E. (2018) Neuromuscular Electrical Stimulation in the Prevention of Pressure Ulcer in the Posterior Region of the Pelvis of ICU Patients: A Randomized Controlled Trial of Efficacy and Safety. Registro Brasileiro de Ensaios Clínicos—ReBEC. http://www.ensaiosclinicos.gov.br