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REVIEW ARTICLE

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EFFECTIVENESS OF REHABILITATION INTERVENTIONS IN ADULTS WITH MULTI-ORGAN DYSFUNCTION SYNDROME: A RAPID REVIEW

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Background: **Multiple organ dysfunction syndrome, defined as altered organ function in critically ill patients, is a possible consequence of COVID-19. Investigating the current evidence is therefore crucial in this pandemic, as early rehabilitation could be effective for the functioning of patients with multiple organ failure. This rapid review assesses the effectiveness of rehabilitation interventions in adults with multiple organ dysfunction syndrome.**

Methods: **A rapid review was conducted including only randomised control trials, published until 30 November 2020. All databases were investigated and the results synthesized narratively, evaluating the risk of bias and quality of evidence in all included studies.**

Results: **A total of 404 records were identified through database searches. After removal of duplicates 346 articles remained. After screening, 3 studies (90 participants) met the inclusion criteria. All studies reported positive effects of neuromuscular electrical stimulation on muscle mass preservation compared with no treatment or standard physiotherapy.**

Conclusion: **The lack of evidence on the effectiveness of rehabilitation interventions does not allow any firm conclusion to be drawn. Neuromuscular electrical stimulation might be a possible rehabilitation intervention to prevent muscle volume loss and improve function in patients with multiple organ dysfunction syndrome. However, further studies are needed to support these preliminary findings.**

Key words: multiple organ failure; rehabilitation; rapid review.

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LAY ABSTRACT

This paper synthesizes the current evidence on the effects of rehabilitation interventions in patients with multi-organ dysfunction syndrome. The results show that neuromuscular electrical stimulation may be a feasible treatment to prevent muscle mass loss and increase upper and lower limb strength in this population. Following multi-organ dysfunction syndrome people frequently experience new or worsened disabilities. Therefore, it is relevant to provide the clinician with the best current evidence on treatment that could be applied in the acute phase, in order to enhance the recovery of these patients. This is even more applicable while the COVID-19 pandemic is raging globally, as multi-organ dysfunction syndrome is one of the worst possible consequences of the disease.

Multiple organ dysfunction syndrome (MODS) is defined as altered organ function in an acutely ill patient (1). MODS usually involves 2 or more organ systems among the respiratory, cardiovascular, renal, hepatic, gastrointestinal, haematological, endocrine, and central nervous system (2). Once the syndrome has developed, there is no effective therapy for modulating the inflammatory response and reducing the severity of MODS. Therefore, treatment is focused on prevention and treating individual organ dysfunction as it develops, and supportive measures are required (3).

The survival of critically ill patients is frequently associated with significant functional impairment and reduced health-related quality of life (4). Although the pathophysiology of MODS is not entirely understood, the dysregulated immune response to critical illness plays a central role in determining the severity of the disease (3). MODS can be classified as primary (immediately after several specific traumas, such as extensive injuries of tissues, hypoxia and the ischaemia-reperfusion syndrome) or secondary (end-stage of a systemic inflammatory response syndrome, commonly involving sepsis) (5). The clinical course of MODS is divided by the Sequential Organ Failure Assessment (SOFA) score system into 4 stages, according to the degree of dysfunction of 6 organ systems (respiration, coagulation, liver, cardiovascular, central nervous system, renal). The SOFA score is instrumental in predicting the outcome (6). Independent of the initial score, an increase in SOFA during the first 48 h in the intensive care unit (ICU) predicts a mortality rate of at least 50% (7). The first clinical objective in MODS is always patient survival. Having assured survival, the objective shifts into improvement in as much as possible of health-related quality of life, reducing any organ dysfunction, and preventing all the possible sequelae of MODS or a long period of hospitalization (8). Therefore, rehabilitation interventions could cover an essential role in the accomplishment of functional recovery.

MODS is one of the worst possible manifestations of COVID-19, along with respiratory failure, neuro-

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logical symptoms, septic shock, or a combination of all of these (9). To date, there is no effective treatment for COVID-19, except for supportive care, including oxygen and mechanical ventilation. As with MODS, severely ill patients with COVID-19 require a lengthy period of hospitalization and experience a massive alteration in their life (10). Due to the similarities, rehabilitation interventions for MODS could also help manage patients with COVID-19. Therefore, a rapid review of rehabilitation interventions for MODS could be highly relevant in the current pandemic, because it is a form of knowledge synthesis that accelerates the process of conducting a traditional systematic review, to produce evidence for stakeholders in a resource-efficient manner under pandemic circumstances (11).

This rapid review assessed the effectiveness of rehabilitation interventions on functional outcomes in adults with MODS.

METHODS

A rapid review of rehabilitation interventions in adults with MODS was performed. The review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (12) and the Interim Guidance from the Cochrane Rapid Reviews Methods Group (13). The protocol was registered on PROSPERO (CRD42020222599).

Selection criteria

Type of study. The review included only randomized controlled trials (RCTs) addressing the effects of rehabilitation interventions in patients with multiple organ failure.

Population. Considering the high variability in the definition of MODS in epidemiology and in the clinical outcomes in diverse healthcare settings, the review included studies involving adults with 2 or more organ dysfunctions diagnosed with SOFA (14).

Interventions. The review included studies addressing rehabilitation interventions, defined according to the classificatory items relevant to rehabilitation defined by Cochrane Rehabilitation (15): "all interventions provided or prescribed by rehabilitation professionals to enable people with disabilities to attain, or maintain, their maximum independence; all the interventions provided by rehabilitation professionals to prevent secondary health conditions or complications arising from a primary health condition, and all physical modalities, manual therapies, exercise therapies, prosthetic and orthotic interventions and adaptive technologies for disabilities". Interventions aiming to maintain or prevent worsening of the clinical condition, such as electrical stimulation or patient positioning, were also included. Pharmacological or surgical interventions were not considered rehabilitation approaches and were therefore excluded.

Comparator(s). The review included studies that compared the rehabilitation interventions with any other type of intervention or with no intervention.

Outcomes. Considering the complexity and heterogeneity of outcomes related to the improvement in MODS in a rehabilitation context, it was decided to categorize the primary outcomes according to the International Classification of Functioning, Disability and Health (ICF) (16), as follows:

- Primary outcomes:
  - Body functions: mobility and muscle power (e.g. Medical Research Council scale); functions of cardiovascular, haematological, respiratory, metabolic and endocrine systems.
- Secondary outcomes:
  - Mortality rate reduction, medical complications' risk mitigation, and prevention of worsening of symptoms.
  - Quality of life: e.g. Short Form 36 (SF-36) questionnaire.

Search strategy and screening

The search was performed by an information specialist (SGL) on 30 November 2020 in the following databases: PubMed, Embase and Cochrane Central Register of Controlled Trials in the Cochrane Library, using the following key words: "rehabilitation interventions", "multi-organ dysfunction syndrome, adult" and "randomized controlled trial". The full search strategy is shown in Table I. A review author (EP) screened the title abstracts and full-text articles, with conflict resolution performed by another review author (CA). The review excluded conference abstracts, conference proceedings, abstracts, protocol stages, pilot or cross-over designs and full-text articles in non-English languages.

Assessment of risk of bias in included studies

The risk of bias in included randomized controlled trials was assessed using the Cochrane "Risk of Bias" tool, described in the Cochrane Handbook for Systematic Reviews of Interventions (17). The tool was applied to the included studies for each outcome, by 1 author (EP), and a second author (SGL) verified her judgements. Any disagreements were solved by consensus or by consultation with the third review author (CA).

The following domains were assessed: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), other sources of bias. Each domain of the studies was classified as "low risk", "high risk" or "unclear risk"', and the bias of individual items was evaluated as described in the Cochrane Handbook for Systematic Reviews of Interventions (17). For performance bias (blinding of participants and personnel) and detection bias (blinding of outcome assessment), the risk of bias was evaluated only for the primary outcome.

Summary of findings and assessment of the certainty of the evidence

A "Summary of findings" table was proposed using standard Cochrane methodology to present results for each outcome (18). The GRADE approach was used to assess the body of evidence's certainty to all outcomes of interest. A single review author (EP) applied GRADE and the second review author (MP) verified all judgements and added rationales for judgements to footnotes.

Data extraction

One review author (EP) extracted data on study characteristics using Microsoft Excel before comparing findings. A predetermined data form was used to extract the features of the selected papers, including:

- Report characteristics (year, authors, title and journal)
- Study design (location, groups and number of participants)
- Intervention characteristics (type, dose, intensity and frequency)

Table I. Search strategy

Database	Search strategy
PubMed	"Multiple Organ Failure"[Mesh]
	"Multiple Organ Dysfunction Syndrome"[tiab] OR "Multiple Organ"[tiab] OR "multi-organ"[tiab] OR MODS[tiab] OR "organ failure*"[tiab]
	#1 OR #2
	"Rehabilitation"[Mesh]
	rehabilitat*[tiab]
	"Physical Therapy Modalities"[Mesh]
	"Physical Therap*"[tiab] OR physiotherap*[tiab]
	"Exercise Therapy"[Mesh]
	Exercise*[tiab]
	"Electric Stimulation Therapy"[Mesh]
	"Electrical Stimulation"[tiab] OR "Electric stimulation"[tiab] OR Electrotherap*[tiab]
	"Patient Positioning"[Mesh] OR "Moving and Lifting Patients"[Mesh]
	patient[tiab] AND (moving*[tiab] OR positioning*[tiab] OR repositioning*[tiab] OR lifting*[tiab] OR Handling*[tiab])
	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
	"randomized controlled trial"[pt]
	"controlled clinical trial"[pt]
	randomized[tiab]
	placebo[tiab]
	"clinical trials as topic"[mesh: noexp]
	"randomly"[tiab]
	"trial"[ti]
	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
	animals [mh] NOT humans [mh]
	#22 NOT #23
	#3 AND #14 AND #24
Embase (via Embase.com)	'multiple organ failure'/exp OR 'multiple organ': ti,ab,kw OR 'multi-organ': ti,ab,kw OR mods: ti,ab,kw OR 'organ failure*': ti,ab,kw
	'rehabilitation'/exp OR rehabilitation: ti,ab,kw OR rehabilitat*: ti,ab,kw
	'physiotherapy'/exp OR 'physiotherapy': ti,ab,kw OR 'physical therapy'/exp OR 'physical therapy': ti,ab,kw OR physiotherap*: ti,ab,kw OR 'physical therap*': ti,ab,kw
	'exercise'/exp OR exercise*: ti,ab,kw
	'electrostimulation'/exp OR 'electrotherapy'/exp OR 'electrical stimulation': ti,ab,kw OR 'electric stimulation': ti,ab,kw OR 'electrotherap*': ti,ab,kw
	'patient positioning'/exp OR 'patient lifting'/exp OR (patient: ti,ab,kw AND (moving*: ti,ab,kw OR positioning*: ti,ab,kw OR repositioning*: ti,ab,kw OR lifting*: ti,ab,kw OR handling*: ti,ab,kw))
	#2 OR #3 OR #4 OR #5 OR #6
	'randomized controlled trial'/de
	'controlled clinical trial'/de
	random*: ti,ab,tt
	'randomization'/de
	'intermethod comparison'/de
	placebo: ti,ab,tt
	(compare: ti,tt OR compared: ti,tt OR comparison: ti,tt)
	((evaluated: ab OR evaluate: ab OR evaluating: ab OR assessed: ab OR assess: ab) AND (compare: ab OR compared: ab OR comparing: ab OR comparison: ab))
	(open NEXT/1 label): ti,ab,tt
	((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)): ti,ab,tt
	'double blind procedure'/de
	(parallel NEXT/1 group*): ti,ab,tt
	(crossover: ti,ab,tt OR 'cross over': ti,ab,tt)
	((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)): ti,ab,tt
	(assigned: ti,ab,tt OR allocated: ti,ab,tt)
	(controlled NEAR/8 (study OR design OR trial)): ti,ab,tt
	(volunteer: ti,ab,tt OR volunteers: ti,ab,tt)
	'human experiment'/de
	Trial: ti,tt
	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
	(((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database or databases)): ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled': ti,ab,tt OR 'randomized controlled': ti,ab,tt OR 'randomly assigned': ti,ab,tt))
	('cross-sectional study'/de NOT ('randomized controlled trial'/de OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled': ti,ab,tt OR 'randomized controlled': ti,ab,tt OR 'control group': ti,ab,tt OR 'control groups': ti,ab,tt))
	('case control*': ti,ab,tt AND random*: ti,ab,tt NOT ('randomised controlled': ti,ab,tt OR 'randomized controlled': ti,ab,tt))
	('systematic review': ti,tt NOT (trial: ti,tt OR study: ti,tt))
	(nonrandom*: ti,ab,tt NOT random*: ti,ab,tt)
	'random field*': ti,ab,tt
	('random cluster' NEAR/4 sampl*): ti,ab,tt
	(review: ab AND review: it NOT trial: ti,tt)
	('we searched': ab AND (review: ti,tt OR review: it))
	'update review': ab
	(databases NEAR/5 searched): ab
	((rat: ti,tt OR rats: ti,tt OR mouse: ti,tt OR mice: ti,tt OR swine: ti,tt OR porcine: ti,tt OR murine: ti,tt OR sheep: ti,tt OR lambs: ti,tt OR pigs: ti,tt OR piglets: ti,tt OR rabbit: ti,tt OR rabbits: ti,tt OR cat: ti,tt OR cats: ti,tt OR dog: ti,tt OR dogs: ti,tt OR cattle: ti,tt OR bovine: ti,tt OR monkey: ti,tt OR monkeys: ti,tt OR trout: ti,tt OR marmoset*: ti,tt) AND 'animal experiment'/de)
	('animal experiment'/de NOT ('human experiment'/de OR 'human'/de))
	#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40
	#27 NOT #41
	#1 AND #7 AND #42
CENTRAL (via Cochrane Library	("Multiple Organ Dysfunction Syndrome" OR "multiple organ failure" OR "Multiple Organ" OR "multi-organ" OR MODS OR (organ NEXT failure*)): ti,ab,kw
	(Rehabilitation OR rehabilitat* OR physiotherapy OR physiotherap* OR (physical NEXT therap*) OR exercise OR exercise* OR "Electrical Stimulation" OR "Electric stimulation" OR Electrotherap* OR (patient AND (moving* OR positioning* OR repositioning* OR lifting* OR Handling*))): ti,ab,kw
	#1 AND #2 – in Trials

- Comparator characteristics (type, dose, intensity and frequency)
- Outcomes assessed and measures
- Numerical data for outcomes of interest (effect size between groups and statistical significance).

Differences of opinion regarding study characteristics and methodological limitations of the studies were resolved by consensus with the second review author (SGL).

Data synthesis

Given the heterogeneity of the included studies' comparisons and outcomes, meta-analysis was not performed. Consequently, the results have been synthesized narratively and reported at the study level.

RESULTS

A total of 404 papers were identified through the database search, and 346 remained after removal of duplicates. After screening by title and abstract, 17 full-text articles were evaluated for eligibility. Three studies (90 participants) ultimately met the inclusion criteria for assessing the study question. Fig. 1 reports details of the screening process.

The 3 included studies (19–21) were RCTs with 90 critically ill patients with MODS, measured using the SOFA score, admitted to the intensive care unit (ICU) for at least 48 h. These studies aimed to prevent the loss of muscle mass and to improve muscle strength and functional outcomes in critically ill patients with MODS during their period of hospitalization before and after awakening, using neuromuscular electrical stimulation (NMES), alone or in combination with whole-body vibration (WBV), added to no treatment or usual care, such as early protocol-based physiotherapy.

Gerovasili (19) included 26 patients (13 per group) with admission scores of Acute Physiology and Chronic Health Evaluation (APACHE) II of 13 or higher. SOFA mean admission scores were 10 and 8 for NMES and control groups, respectively. This study compared daily NMES session simultaneously implemented on quadriceps muscles of both lower extremities, with control intervention for 7 days after admission to preserve muscle mass loss. They assessed the results with ultrasound, measuring the cross-sectional diameter (CSD) of the quadriceps muscles at baseline and end of treatment (7/8 days after the assessment). The duration of sessions was 55 min, including 5 min of warm-up and 5 min of recovery.

Rodriguez (20) included 14 intubated patients with baseline APACHE II and SOFA scores of 20 (interquartile range (IQR) 18–27) and 10 (IQR, 9–12), respectively. This study compared NMES applied on one side of the brachial biceps and vastus medialis with the other side. The authors evaluated the level of muscle strength after awakening and on the last day of treatment. NMES intensity was gradually increased until the achievement of 1 of these 3 outputs: visible contraction of the muscle mass, pain onset, or maximal tool intensity stimulation. Each session lasted 30 min.

Finally, Wollersheim (21) included 50 participants (33 intervention, 17 control) with sepsis at admission and a me-

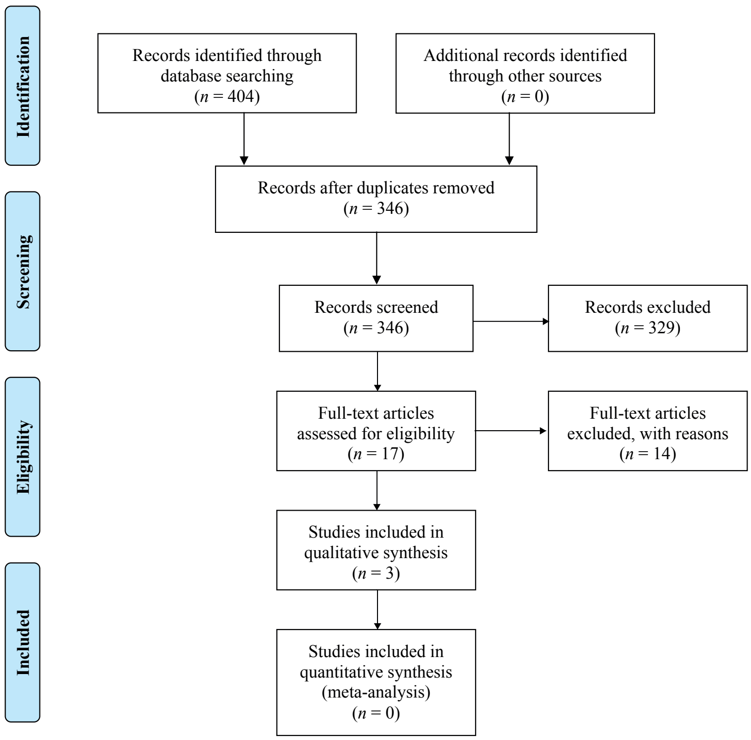

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of the study.

dian SOFA score of 14. This study compared NMES and (not better specified in the original study) WBV in addition to early protocol-based physiotherapy applied twice a day. The aim was to improve muscle strength and physical performance at first awakening and ICU discharge. NMES was performed bilaterally on 8 muscle groups for 20 min; WBV was performed daily for 20 cycles. The study also performed a molecular analysis, but these results were not reported, due to the aim of the current systematic review. Full details of the study are reported in Table II.

Risk of bias in included studies

Fig. 2 provides an overview of the risk of bias for the considered domains.

Random sequence generation (selection bias)

Two studies (19, 20) did not provide enough information about the sequence generation process. Another study (21) reported the method of random sequence generation with sealed opaque envelopes.

Allocation concealment (selection bias)

Two studies (19, 21) did not provide enough information on the concealment method to permit assessment of whether the allocation sequence was concealed. One study (20) reported the allocation side selection randomized method: to balance previous minor muscle strength and mass differences between sides, the authors used sealed envelopes according to cerebral dominance.

Blinding of participants and personnel (performance bias)

Blinding of participants and providers was not possible for any study (19–21) because of the physical nature of the interventions. No studies reported whether data analysts were blinded to the treatment allocation.

Blinding of outcome assessor (detection bias)

None of the studies (19–21) provided sufficient information about the blinding of outcome assessor, but the outcome measured was objective and, consequently, unlikely to be influenced by the lack of blinding.

Incomplete data outcome (attrition bias)

Two studies (19, 20) reported dropouts and loss to follow-up. Data from these participants were excluded from the analysis in either study. Another study (21) reported no missing data to follow-up into the clinical analysis.

Selective reporting

One study (19) did not report all outcome measures mentioned in the registered protocol. Two other studies (20, 21) reported insufficient information to permit any judgement of risk of bias.

Effects of interventions

All studies (19–21) compared intervention with no treatment or standard physiotherapy, and reported positive effects of NMES on muscle mass measurements and strength.

Gerovasili (19) showed that the CSD of quadriceps muscles (rectus femoris and vastus intermedius) decreased significantly less in the NMES group than in the control group. Considering the right side, the CSD values of rectus femoris were –0.11±0.06 cm (−8±3.9%) in the NMES group and –0.21±0.10 cm (–13.9±6.4%) in the control group ($p=0.009$ for the absolute and $p=0.029$ for the relative difference); corresponding values of vastus intermedius were –0.10±0.05 cm

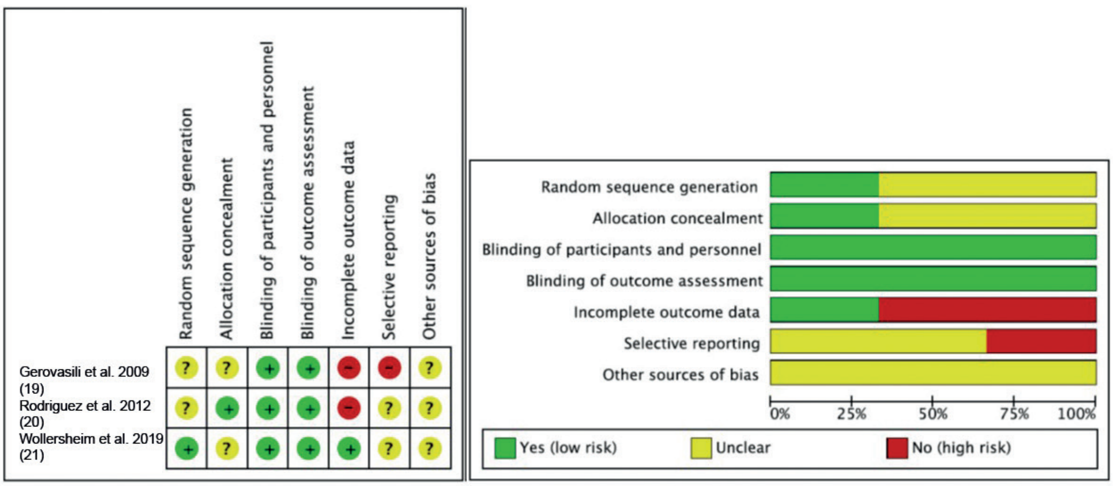

Fig. 2. Methodology quality summary.

Table II. Characteristics of included studies

Study	Title	Number of participants	Population	Intervention	Comparison	Outcomes	Outcome measures	Participants analysed, *n*	Statistical significance	Effect size between groups
Gerovasili et al. 2009 (19)	Electrical muscle stimulation preserves the muscle mass of critically ill patients: a randomised study	49	Adult patients with an APACHE II admission score of 13 or higher and an ICU stay of more than 48 h	Daily EMS sessions of both lower extremities	NR	Preservation of muscle mass	CSD right rectus femoris evaluated with US	26	SS $p=0.009$	EMS group −0.11±0.06 cm. Control group −0.21±0.10 cm.
							CSD right vastus intermedius evaluated with US		SS $p=0.034$	EMS group: −0.10±0.05 cm. Control group: −0.29±0.28 cm.
							CSD left rectus femoris evaluated with US		NS $p=0.07$	EMS group: −0.13±0.10 cm. Control group: −0.19±0.16 cm.
							CSD left vastus intermedius evaluated with US		SS $p=0.018$	EMS group: −0.09±0.05 cm. Control group: −0.22±0.26 cm.
Rodriguez et al. 2012 (20)	Muscle weakness in septic patients requiring mechanical ventilation: a protective effect of transcutaneous neuromuscular electrical stimulation.	32	Adult patients with sepsis requiring MV and presenting 1 or more organ failure and an ICU stay of more than 48 h	Two daily sessions of NMES only applied to the muscles of 1 side of the body	No treatment	Quadriceps muscle strength after awakening	Medical Research Council (MRC) scoring system	28	SS $p=0.025$ at awakening SS $p=0.034$ on the last day of NMEs	NMES group: at awakening 3 (2–3), on the last day of NMES 3 (3–4). Control group: at awakening 2 (2–3), on the last day of NMES 3 (2–3).
						Biceps muscle strength after awakening	Medical Research Council (MRC) scoring system		SS $p=0.014$ at awakening SS $p=0.005$ on the last day of NMES	NMES group: at awakening 3 (2–4), on the last day of NMES 4 (3–4). Control group: at awakening 3 (1–4), on the last day of NMES 3 (2–4).
						Arms circumferences	Measured at the middle line every 48 h using a 7.5-MHz lineal ultrasound transducer		NS $p=0.615$	NMES group: −1.3cm (−1.9–0) cm. Control group: −1.00 cm (IQR, −2.50 to 0.00 cm). (From enrolment to the last day of NMES)
						Thigh circumference	Measured at the middle line every 48 h using a 7.5-MHz lineal ultrasound transducer		NS $p=0.979$	NMES group: −0.4cm (−1.5–1.8) cm. Control group: 0.9 cm (−1.0–1.9) cm. (From enrolment to the last day of NMES)
						Biceps thickness	Measured on the short-axis view from the superficial fat muscle interface to the humerus using a 7.5-MHz lineal ultrasound transducer		NS $p=0.290$	NMES group: 0 (−2–2). Control group: 0 (−3–0). (From enrolment to the last day of NMES).
Wollersheim et al. 2019 (21)	Muscle wasting and function after muscle activation and early protocol-based physiotherapy: an explorative trial	50	Mechanically ventilated patients ≥18 years of age with sepsis-related MODS indicated by a sepsis-related organ failure assessment (SOFA) score ≥9 within the first 72 h after ICU admission were eligible for enrolment	Muscle activating measures (NMES and whole-body vibration (WBV)) in addition to protocol-based physiotherapy	Protocol-based physiotherapy	Muscle strength	Medical Research Council (MRC) score	50	NS $p>0.05$	MRC median [IQR]. At awakening, control 3.0 [2.7–3.4]; intervention 3.0 [2.1– 3.8]. At ICU discharge, control 3.9 [3.3–4.0]; intervention 3.6 [2.8–4.0]. At 12-month follow-up, control 5.0 [4.3–5.0]; intervention 4.8 [4.3–5.0].
						Muscle strength	Handgrip dynamometry		NS $p>0.05$	NR
						Muscle strength	6 min-walking test		NS $p>0.05$	NR
						Physical ability	Functional Independence Measure (FIM)		NS $p>0.842$	NR

APACHE II: Acute Physiologic Assessment and Cronic Health Evaluation; ICU; Intensive Care Unit; EMS: Electrical Muscle Stimulation; NR: Not Reported; CSD: Cross Sectional Diameter; US: Ultrasound; SS: Statiscal Significance; NS: Non Significance; V: Mechanical Ventilation; NMES: Neuro-Muscolar Electrical Stimulation; MRC: Medical Research Council;MODS: Multiple Organ Dysfunction Syndrome; SOFA score: Sequential Organ Failure Assessment score; WBV: Whole-Body Vibration; FIM: Functional Independence Measure; CI: Confidence Interval.

(–12.5±7.4%) and –0.29±0.28 cm (–21.5±15.3%), respectively. The absolute and relative difference in CSD were statistically significant (p=0.034 and p=0.05, respectively). Considering the left side, the absolute difference in the CSD of the rectus femoris was significantly less in the NMES group than in the control group (–0.13±0.10 vs –0.19±0.16 cm, p=0.07) and the absolute difference in the CSD of the vastus intermedius was significantly less in the NMES group than in the control group (–0.09±0.05 vs –0.22±0.26 cm, p=0.018). The relative difference in the CSD of both muscles was minor in the NMES group compared with the control group; however, results were not statistically significant (–11.7±11.5% vs –13.5±11.5%, p=0.331; and –11.6±7.5% vs −14±21%, p=0.167, respectively).

Rodriguez (20) reported that the difference between stimulated and non-stimulated side circumferences remained unchanged over the first 8 days of treatment with NMES before the awakening. Also, the difference in biceps thickness did not significantly differ from the baseline during the whole treatment period. After awakening, both biceps and quadriceps' muscle strength were statistically higher on the stimulated side respect of non-stimulated side (p=0.009). Seventy-one percent of patients showed marked weakness on non-stimulated muscles, while their stimulated side showed enough strength to move against gravity at the end of treatment.

Wollersheim (21) reported a significant muscle weakness in patients before awakening. Muscle strength and functional mobility did not differ significantly between intervention and control groups at ICU discharge. However, muscle strength showed a significant increase for the control (p=0.008), intervention (p=0.009), and usual physiotherapeutic practise group (p=0.036) from the first awakening until discharge, with no difference between the groups at either time-point. Compared with common physiotherapeutic practise, the function outcome showed no significant improvement in the control or in the intervention group. At the 12-month follow-up visit, muscle strength and functional independence measure (FIM) scores returned to normal values in both groups independently of the study intervention.

The overall quality of evidence was low, due to high risk of bias and the imprecision of the small number of included studies (3) and participants (90) (see Supplementary Tables SI–SIII[1]).

DISCUSSION

This rapid review investigated the effectiveness of rehabilitation interventions to improve functional outcomes in critically ill patients with MODS. The results show that NMES may be a potential preventive and rehabilitative intervention to preserve the muscle mass of the lower extremities, reduce muscle weakness, and improve muscle strength and function outcome in critically ill patients with MODS.

Muscle weakness is a frequent complication of MODS, and is associated with high morbidity and mortality (22). It involves functional and structural alterations in both muscles and nerves, and muscle atrophy can occur early during hospitalization (23). Critically ill patients with MODS undergo a state of hypermetabolism, characterized by increased energy expenditure, associated with increased protein loss (24). The immobilization caused by this health condition has damaging effects on skeletal muscles in healthy subjects and critically ill patients (23). Therefore, it is crucial to contain MODS sequelae, reducing the recovery period and increasing the capability to preserve and strengthen muscle mass in patients with complete or relevant functional impairments (25). Reducing duration of immobilization with early mobilization is recommended in international guidelines because it improves safety, intensity, and degree of mobility (26).

Compared with patients receiving standard physiotherapy, quadriceps strength at hospital discharge improved in long-stay patients receiving passive or active exercise training using a bedside ergometer (25). Passive range-of-motion exercises in unresponsive patients, progressing to active range-of-motion exercises, bed mobility, sitting upright, transfer training, and eventually walking, can improve functional status and health-related quality of life in these patients (27). Therefore, rehabilitation interventions might deliver tangible improvements in several aspects in the recovery from MODS and other pathologies causing similar impairments, such as COVID-19.

Quality of evidence

There are several potential sources of bias in this review: selection bias, attrition bias and selective reporting were common to all studies. These critical issues regard patient selection process, differences between participants who leave or continue the study, particularly between study groups (28), and missing protocol registration (29). Review outcomes were rated as low-quality using the GRADE system. Indeed, poor reporting of methods increased the risk of bias, and the small number of included studies and participants contributing to each outcome increased imprecision. All these methodological issues can lead to overestimation of intervention effects (30).

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[1]http://www.medicaljournals.se/jrm/content/?doi=10.2340/16501977-2846

CONCLUSION

NMES may be a potential rehabilitation intervention for preventing muscle volume loss and improving muscle strength and function in critically ill patients with MODS. However, no firm conclusion can be drawn, due to a lack of evidence on the effectiveness of rehabilitation interventions in improving or maintaining the clinical condition in critically ill patients with MODS. Further studies, with adequate sample size and methodological rigour, are needed to investigate the effectiveness of this approach and to support these preliminary findings. Moreover, other studies on other possible interventions are also needed.

REFERENCES

1. Gourd NM, Nikitas N. Multiple organ dysfunction syndrome. J Intensive Care Med 2020; 35: 1564–1575.
2. Mizock B. The multiple organ dysfunction syndrome. Dis Mon DM 2009; 55: 476–526.
3. Murray MJ, Coursin DB. Multiple organ dysfunction syndrome. Yale J Biol Med 1993; 66: 501–510.
4. Gosselink R, Needham D, Hermans G. ICU-based rehabilitation and its appropriate metrics. Curr Opin Crit Care 2012; 18: 533–539.
5. Balk RA. Pathogenesis and management of multiple organ dysfunction or failure in severe sepsis and septic shock. Crit Care Clin 2000; 16: 337–352, vii.
6. Jones AE, Trzeciak S, Kline JA. The Sequential Organ Failure Assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation. Crit Care Med 2009; 37: 1649–1654.
7. Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 2001; 286: 1754–1758.
8. Hotchkiss RS, Moldawer LL, Opal SM, Reinhart K, Turnbull IR, Vincent J-L. Sepsis and septic shock. Nat Rev Dis Primer 2016; 2: 16045.
9. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: a review. Clin Immunol Orlando Fla 2020; 215: 108427.
10. Shang Y, Pan C, Yang X, Zhong M, Shang X, Wu Z, et al. Management of critically ill patients with COVID-19 in ICU: statement from front-line intensive care experts in Wuhan, China. Ann Intensive Care 202; 1: 73.
11. Tricco AC, Garritty CM, Boulos L, Lockwood C, Wilson M, McGowan J, et al. Rapid review methods more challenging during COVID-19: commentary with a focus on 8 knowledge synthesis steps. J Clin Epidemiol 2020; 126: 177–183.
12. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement. PLoS Med 2009; 6: e1000097.
13. Garritty C, Gartlehner G, Kamel C, King VJ, Nussbaumer-Streit B, Stevens A, et al. Cochrane Rapid Reviews. Interim Guidance from the Cochrane Rapid Reviews Methods Group. Mar 2020. [Cited 2021 Feb 11]. Available from: https: //methods.cochrane.org/rapidreviews/sites/methods.cochrane.org.rapidreviews/files/public/uploads/cochrane_rr_-_guidance-23mar2020-final.pdf.
14. Vincent J-L, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 1996; 22: 707–710.
15. Levack WMM, Rathore FA, Pollet J, Negrini S. One in 11 Cochrane reviews are on rehabilitation interventions, according to pragmatic inclusion criteria developed by Cochrane Rehabilitation. Arch Phys Med Rehabil 2019; 100: 1492–1498.
16. Garritty C, Gartlehner G, Kamel C, King VJ, Nussbaumer-Streit B, Stevens A, Hamel C, Affengruber L. Cochrane Rapid Reviews. Interim Guidance from the Cochrane Rapid Reviews Methods Group. Mar 2020. [Cited 2021 Feb 11]. Available from: https: //apps.who.int/classifications/icfbrowser/.
17. Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated Feb 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook. [Cited 2021 Feb 12]. Available from: /handbook/current/chapter-08.
18. Schünemann HJ, Higgins JPT, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated Feb 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook. [Cited 2021 Feb 12]. Available from: /handbook/current/chapter-14.
19. Gerovasili V, Stefanidis K, Vitzilaios K, Karatzanos E, Politis P, Koroneos A, et al. Electrical muscle stimulation preserves the muscle mass of critically ill patients: a randomized study. Crit Care Lond Engl 2009; 13: R161.
20. Rodriguez PO, Setten M, Maskin LP, Bonelli I, Vidomlansky SR, Attie S, et al. Muscle weakness in septic patients requiring mechanical ventilation: protective effect of transcutaneous neuromuscular electrical stimulation. J Crit Care 2012; 27: 319.e1–8.
21. Wollersheim T, Grunow JJ, Carbon NM, Haas K, Malleike J, Ramme SF, et al. Muscle wasting and function after muscle activation and early protocol-based physiotherapy: an explorative trial. J Cachexia Sarcopenia Muscle 2019; 10: 734–747.
22. Bednarik J, Lukas Z, Vondracek P. Critical illness polyneuromyopathy: the electrophysiological components of a complex entity. Intensive Care Med 2003; 29: 1505–1514.
23. Hermans G, Van den Berghe G. Clinical review: intensive care unit acquired weakness. Crit Care Lond Engl 2015; 19: 274.
24. Plank LD, Connolly AB, Hill GL. Sequential changes in the metabolic response in severely septic patients during the first 23 days after the onset of peritonitis. Ann Surg 1998; 228: 146–158.
25. Morris PE, Goad A, Thompson C, Taylor K, Harry B, Passmore L, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. Crit Care Med 2008; 36: 2238–2243.
26. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med 2018; 46: e825–e873.
27. Burtin C, Clerckx B, Robbeets C, Ferdinande P, Langer D, Troosters T, et al. Early exercise in critically ill patients enhances short-term functional recovery. Crit Care Med 2009; 37: 2499–2505.
28. Nunan D, Aronson J, Bankhead C. Catalogue of bias: attrition bias. BMJ Evid-Based Med 2018; 23: 21–22.
29. Saric F, Barcot O, Puljak L. Risk of bias assessments for selective reporting were inadequate in the majority of Cochrane reviews. J Clin Epidemiol 2019; 112: 535–538.
30. Armijo-Olivo S, Dennett L, Arienti C, Dahchi M, Arokoski J, Heinemann AW, et al. Blinding in rehabilitation research: empirical evidence on the association between blinding and treatment effect estimates. Am J Phys Med Rehabil 2020; 99: 198–209.